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RESEARCH ARTICLES

AUTHOR GUIDELINES

Global Medical and Health Communication is a journal that publishes medical and health scientific articles published every 4 (four) months. Articles are original research that needs to be disseminated and written in English.

The submitted manuscript must be an article that has never been published, and the author must ensure that all co-authors have agreed by signing a statement on the seal. For original research, we accept the study which is last then 7 (seven) years when the manuscript is submitted. The manuscript is an original article free from plagiarism. When the article is published in another journal then in the next journal, the article will be disallowed.

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Table title is the typed center, font size 11 pt, bold, initial letter of each word written with a capital letter, except conjunctions. The titles are numbered and written on top of the table. Example: Table 3 *Neisseria gonorrhoeae* Resistance to 8 Types of Antimicrobials in 20 Specimens. Table, no vertical dividing line, and there are only three horizontal borderlines. Created tables in sequence two spaces from the text. Table descriptions and abbreviations are placed in the table description, not on the table title.

Typed center figure title with 11 pt font size, bold, numbered according to the appearance in the text and typed under the image. The source of the cited image and or table should be added to references if it is not the author's work.

Figures (graphs, diagrams, and photos) and tables besides being written in place, are also made separately on other text pages with sufficient sharpness and darkness. A maximum number of tables and or images are 6 (six) pieces. Figures are sent in black and white or colored format when required, uploaded to the Supplementary File(s) are in high-resolution jpeg, jpg, or png formats.

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Content and Format Articles

The article contains results of original research in the field of basic medical or applied, and health. The article format consists of Title, Introduction, Methods, Results, Discussion, Conclusion(s), Conflict of Interest, Acknowledgments, and References.

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The abstract is typed using 12 pt font size and one space. The abstract is written in one paragraph, one space, a maximum of 250 words, and should describe the entire contents of the article. The abstract should be suitable for the format of introduction, methods (contain method, place, and time of the study), results, discussion, and conclusion. Abstract be equipped with keywords consisting of 3–5 words.

Introduction

The introduction begins with the general background of the study in a brief maximum of one paragraph. Then, load the State of the Art (a brief review of literature or previous studies, 1–2 paragraphs) to justify/strengthen the statement of novelty or significance or scientific contribution or originality of this article and try to have references to articles from journals of the last 10 years that strengthen the justification for originality or contributions.

Before writing the purpose of the study, there must be a clear and explicit Gap Analysis or statement of gaps (originality) or a statement of the contribution of novelty (novelty statement), or the unique difference of this research compared to previous studies, also in

terms of the importance of whether or not the research was conducted.

Methods
Methods contain the material under study, and the way described briefly by the order of operation as well as the location and time of the study. Explain statistical methods in detail. Consideration of ethical issues is included. If the protocol has been approved then the ethical clearance/approval letter number and the health research ethics committee must be written.

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The result is the core of scientific writing. This section presents data and information that will be used as the basis of the conclusion and is even expected to get a new theory. In results, listed the tables and or images, graphics, photos to explain and abbreviate the description should be given; numbered according to their appearance in the text. Results of the study and discussion should be written separately.

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Discussion of the article reveals, explains, and discusses the results of the study with an analysis by the research design, interpretation, and explanation of its synthesis. Also, the results obtained are compared with the results of previous research of others. Suggestions are also written here.

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The conclusion is submitted by the results obtained by the researcher and written briefly and clearly in two or three sentences in one paragraph.

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All authors must make a formal statement at the time of submission indicating any potential conflict of interest that might constitute an embarrassment to any of the authors if it were not to be declared and were to emerge after publication. Such conflicts might include but are not limited to, shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product.

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Zhang B, Kunde D, Tristram S. *Haemophilus haemolyticus* is infrequently misidentified as *Haemophilus influenzae* in diagnostic specimens in Australia. Diagn Microbiol Infect Dis. 2014;80(4): 272–3.

Books and Other Monographs
Editor as Author
Nriagu J, editor. Encyclopedia of environmental health. Michigan: Elsevier BV; 2011.

Organization as Author
World Health Organization. Guideline: neonatal vitamin A supplementation. Geneva: WHO Press; 2011.

Chapter in Book
Miller LG. Community-associated methicillin resistant *Staphylococcus aureus*. In: Weber JT, editor. Antimicrobial resistance. Beyond the breakpoint. Basel: Karger; 2010. p. 1–20.

Conference Proceeding
Nicholai T. Homeopathy. Proceedings of the Workshop Alternative Medicines; 2011 November 30; Brussels Belgium. Brussels: ENVI; 2011.

Journal Article from Internet
King P. *Haemophilus influenzae* and the lung (*Haemophilus* and the lung). Clin Transl Med. 2012;1:10 [cited 2015 August 15]. Available from: https://clintransmed.springeropen.com/articles/10.1186/2001-1326-1-10.

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RESEARCH ARTICLE

Stakeholder Insights on Malaria Elimination Strategies in Pangandaran, West Java: a Qualitative Analysis

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Abstract

Indonesia has launched a determined effort to eliminate malaria by 2023, focusing on Java and Bali. Despite these efforts, Pangandaran in Java still faces malaria cases. This study aims to meticulously delve into the intricacies of the malaria elimination program's implementation while conducting a comprehensive evaluation of its effectiveness. Structured interviews were conducted with key stakeholders responsible for the malaria program in Pangandaran to extract invaluable insights. The study, carried out in November 2022, followed qualitative research with narrative analysis to reveal nuanced narratives from the participants. Findings from this rigorous analysis revealed a harmonious alignment between the malaria control program in Pangandaran and the Indonesian Ministry of Health guidelines. The strategy to combat malaria vectors in Pangandaran included mosquito net distribution, strategic larvicide application, and educational campaigns like Malaria Awareness Society (MASAMA). The expectation is that the current effective control program will resonate within the Pangandaran community, ultimately leading to the realization of the 2023 elimination target.

Keywords: Elimination, malaria, Pangandaran, qualitative

Introduction

Malaria is an acute infectious disease caused by the *Plasmodium* parasite, transmitted to humans through the bites of female *Anopheles* mosquitoes. There are 400 species of *Anopheles* mosquitoes, and 30 of them act as vectors for malaria. Malaria transmission is intricately linked to environmental factors, where climate, temperature, and suitable breeding sites play pivotal roles. *Anopheles* mosquitoes, the primary vectors for malaria, thrive in warm, humid conditions and breed in stagnant water, such as ponds and swamps. Altitude, vegetation, and human activities further influence transmission dynamics. Climate-related changes, urbanization, and land use alterations can impact malaria's distribution and intensity. Mosquitoes undergo a four-stage life cycle comprising the egg, larva, pupa, and adult stages, varying durations for each stage across species. Typically, eggs are laid in water and hatch within days, influenced by environmental factors like temperature and humidity. Larvae, or wrigglers, reside in water, feeding on organic matter, and undergo molting over one to two weeks. Pupae, or tumblers, represent a non-feeding stage lasting one to four days, during which larvae transform into adult mosquitoes. The adult stage, with varying lengths of life depending on the species, commences as pupae emerge as winged mosquitoes, breaking the water's surface. A comprehensive understanding of the mosquito life cycle is imperative for effective prevention measures, including eliminating or treating standing water where mosquitoes breed.[1]

According to the World Malaria Report, there were 229 million reported cases of malaria and 409,000 deaths in 2019, compared to 228 million cases and 411,000 deaths in 2018. Children under the age of five were the most vulnerable group, accounting for 67% of all malaria-related deaths worldwide in 2019. The burden of malaria remains exceptionally high in the African region, where 94% of all malaria-related deaths occurred

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in 2019. Six countries, namely Nigeria (23%), the Democratic Republic of Congo (11%), the Republic of Tanzania (5%), Burkina Faso (4%), Mozambique (4%), and Niger (4%), accounted for approximately half of all global malaria-related deaths.[2]

While regions in the Eastern Mediterranean, West Pacific, Americas, and Southeast Asia also reported cases and deaths due to malaria, Southeast Asia has witnessed a remarkable 74% reduction in malaria cases over the past two decades, from 23 million cases in 2000 to 6.3 million in 2019. Incidence and mortality have declined by 78% and 74%, respectively. India has played a significant role in this reduction. Sri Lanka reported zero cases in 2015, and Timor Leste achieved the same in 2018 and 2019. Indonesia has also made progress, with malaria cases dropping from 1.1 million in 2015 to 658,000 in 2019.[1]

Despite these improvements, malaria remains a significant concern in Indonesia, particularly in regions with tropical and sub-tropical climates. Efforts to eliminate malaria continue, even amid the COVID-19 pandemic. While several districts and cities in Indonesia have achieved malaria-free status, specific areas, including Pangandaran, Garut, Sukabumi, and Tasikmalaya in West Java,[3] continue to grapple with endemic malaria. Numerous factors contribute to this ongoing challenge, such as geographical conditions, budget constraints, infrastructure limitations, insufficient workforce capacity in quantity and quality, coordination across sectors, community empowerment, and limited public awareness.[4]

Based on reported cases as of December 2022, seven individuals were identified as *P. vivax* malaria sufferers. Epidemiological investigations conducted by the Pangandaran Health Office indicated that these cases were imported. In contrast to 2021, when no malaria cases were reported, malaria resurfaced in the Pangandaran area in 2022, primarily due to factors related to malaria transmission risks. Hence, continuous evaluation of malaria elimination efforts is essential in malaria-endemic regions. The Indonesian government has instituted a malaria elimination program outlined in the Minister of Health of the Republic of Indonesia's Decree No. 293/MENKES/SK/IV/2009, dated April 28, 2009, to achieve a malaria-free and healthy society by 2030. This study aims to conduct an in-depth examination of the complexity of the implementation and evaluate the efficacy of the malaria elimination program. This undertaking is significant for Indonesia, a nation facing persistent challenges related to endemic malaria. In 2023, Indonesia initiated a comprehensive malaria elimination program, specifically emphasizing West Java's regions. The success of the existing control program, accepted by the Pangandaran community, is expected to lead to the realization of the 2023 elimination target.

Methods

In our research, a qualitative approach was adopted for distinct reasons. This methodology was selected because it facilitates a thorough exploration and understanding of complex phenomena, specifically those associated with malaria control and elimination initiatives. The qualitative approach is particularly adept at capturing participants' perspectives, experiences, and narratives, making it well-suited for generating context-specific and rich data that can significantly contribute to the evaluation of malaria control programs.[5]

This research framework combines program evaluation, policy analysis, and qualitative research to assess the malaria elimination program in Pangandaran comprehensively. In the triangulation process, the entire research team's involvement is fundamental for ensuring a rigorous and reliable analysis. Every research team member actively participates in the data analysis, and each individual's contribution is precious. The collaborative effort ensures that diverse perspectives and knowledge from each team member are integrated into the analysis, enriching the overall understanding of the data.

The evaluation of malaria control and elimination activities in the Pangandaran district was conducted following the Activity Stages Elimination of Malaria indicators outlined in the Republic of Indonesia Decree of the Minister of Health No. 293/MENKES/SK/IV/2009. Participants were selected meticulously using a purposeful sampling technique, which deliberately targets individuals who meet specific criteria deemed relevant to the research. In this instance, the requirements centered around individuals associated with malaria control and elimination programs within the Pangandaran regency area.

The selected informants met the stipulated

criteria for the Pangandaran regency area, ensuring that the information acquired was characterized by clarity, detail, and communicability. The study is an in-depth interview with two informants with different categories of participants: (1) the program manager responsible for the health program at the district level and (2) the implementer operating at the sub-district. The first informant is a male and works at the Health Office as a sub-coordinator for the prevention and control program of infectious diseases in Pangandaran. The second informant is a male at the Health Office of Pangandaran Sub-district. Before the interviews, explicit informed consent was obtained from each participant, following a thorough explanation of the purpose and significance of the interview activity. Detailed records were maintained throughout these interviews, ensuring the accuracy of the data and functioning as a mechanism for validating the evaluation of malaria control and elimination program activities.

The study was executed in the Pangandaran district, within the West Java province, in November 2022. The perspectives shared by the informants guided data interpretation, offering insights into the concepts and theories that could best elucidate the findings obtained from the field. This systematic approach facilitated the identification of challenges present in the area, thereby making a substantial contribution to the comprehensive assessment of the efficacy of malaria control efforts. The interviews were recorded, transcribed, and coded to facilitate a thorough data analysis.

Results

Malaria remains a prevailing health concern within the Pangandaran district as the region continues to grapple with its classification as a malaria-endemic area. In the year 2019, data from the Province of West Java, encompassing districts including Pangandaran, Tasikmalaya, Garut, and Sukabumi, revealed that these areas exhibited a low prevalence of malaria, characterized by an annual parasite index (API) of less than 1. However, this favorable overall status only extends uniformly to Pangandaran, which still faces significant challenges associated with malaria transmission.

Official health records from the Pangandaran region emphasize the persistent presence of malaria within its borders. This data identifies five villages in the district categorized as having a low endemicity for malaria and one with a medium endemicity. These classifications offer crucial insights into the region's enduring complexities of malaria transmission and endemicity. It is imperative to recognize the gravity of these findings, as they underscore the imperative for ongoing efforts in malaria control and prevention within Pangandaran. Despite strides made in some areas of West Java, Pangandaran's distinct challenges necessitate the implementation of tailored strategies and interventions to address the enduring issue of malaria endemicity effectively. This comprehensive analysis establishes a pivotal groundwork for the formulation and execution of targeted public health initiatives designed to mitigate the impact of malaria within the district.

"Various species of the sundaicus *mosquito are highly prevalent in the area. In the past, stagnant swamps posed significant challenges, particularly at night. However, this situation has improved, and stagnant swamps are no longer the primary concern. Instead, our principal issue pertains to land excavation. Whenever issues related to land excavation arise, we diligently report them to the relevant village and district authorities. It is essential to note that the concept of land ownership concerning excavation has evolved. Historically, many excavation sites were left abandoned, resulting in unclear or unclaimed ownership." (Informant)*

"Certainly, for accurate identification, we must examine mature mosquitoes. Attempting to identify them during their larval stage can be quite challenging. It becomes problematic when trying to distinguish one Anopheles *species from another, especially when they belong to different species. However, it's worth mentioning that the public health center in the Kalipucang area has made significant strides in mosquito identification. They have identified several species, including* Anopheles birostris, barbirostris, sundaicus, javanicus, *and* maculatus. *Among these, the most prevalent* Anopheles *species in Pangandaran is the* sundaicus, *primarily because it thrives in brackish water habitats." (Informant)*

In the Pangandaran area, it should be noted that there are numerous abandoned fish ponds.

These ponds are acknowledged as potential breeding grounds for mosquitoes, as explained by one of the informants:

"Even if there are fish ponds with closed surfaces, the possibility of mosquito breeding remains high. In areas like Kalipucang, Cibuluh, Banjarharja, and Tunggilis, numerous abandoned fish ponds belong to the local community but are often far from residential areas. For instance, an individual may own a pond in Hamlet A while residing in Hamlet B, leading to neglect. Consequently, these ponds are left unused, becoming breeding grounds for mosquitoes. As a result, such incidents are prevalent, causing ponds to become overgrown with moss and algae." (Informant)

The management of malaria in the Pangandaran district has been effectively carried out, encompassing program implementation, innovative measures, and community empowerment in malaria treatment. As one informant stated:

"If it comes to malaria, we must eliminate it because we aim for a certification. We have introduced an innovative approach known as 'Waiter Beautiful and Gorgeous Gogon' to control the vector.' This approach involves a community movement called 'Germas Gogon,' where we collectively clean and clear lagoons. The 'Waiter Beautiful' part involves strategically releasing fish, such as mujair and head fish, into these lagoons." (Informant)

Lagoons are potential habitats for developing vector mosquitoes within the Pangandaran area, where malaria cases have been documented. Sustaining control measures, including larvicide applications, documentation of lagoon ownership, and facilitating fish donations from various regions, is imperative. The informant provided this information.

"Every month, larvicides are applied to these lagoons, resulting in a noticeable decrease in the larvae population due to the larvicide treatments conducted in the previous month. This practice has proven effective, especially considering these lagoons were previously not under any ownership management. Comprehensive data on lagoon ownership is now available. Historically, the fish introduced into these lagoons originated from Pamotan before being donated by various organizations, including the KKP, Fisheries Regency Pangandaran, and PPKL Jakarta." (Informant)

"Indeed, larvicides are applied monthly as a preventive measure due to the persistent presence of malaria cases in the area. The nature of these breeding sites tends to change with the seasons; during dry periods, the breeding sites become more confined, whereas during the rainy season, they expand. NA conveyed this information from public health center." (Informant)

Additionally, malaria elimination is actively pursued through various programs initiated by several public health centers, which demonstrate a diligent effort. Nonetheless, there are challenges in sustaining this elimination, which continue to result in significant malaria cases. This insight is based on information provided by informants from the Department of Health and public health centers.

*"No, the "*Si Cantik dan Gogon*" program is an innovative initiative introduced by the public health center in Kalipucang. Currently, the program at the* puskesmas *level is highly active. The challenge we face is that we have yet to achieve malaria elimination; therefore, we do not hold the certification for elimination. Maintaining this certification is particularly challenging because elimination efforts are not solely focused on vector control or targeting endemic areas; instead, elimination involves addressing specific cases. All vectors pose significant obstacles to this endeavor."*

"Furthermore, maintaining the elimination status is complex due to the need for inter-sectoral coordination. Nevertheless, we are grateful that Kalipucang is taking prompt action, and we are working on existing regulations and directives from the district, including perbup, perda, and perdes, to address this issue." (Informant)

"In reality, we must acknowledge that due to the endemic nature of malaria, the residents in this area have developed a level of immunity, and they tend to consider malaria as a common occurrence. This perception has been formed because, for several years, there were no

reported cases of malaria. However, some cases have been reported again this year, indicating that the threat of malaria is still present." (Informant)

The *puskesmas* and the local health office in the Pangandaran district have intensified malaria elimination programs. Their goal is to elicit a more substantial response from the community and anticipate the implementation of another health program to achieve 100% malaria elimination.

"We are fortunate that the community's cooperation extends beyond just addressing malaria; it includes other diseases like dengue. The community is now prepared for the PSN (a movement to eradicate mosquito breeding sites by practicing 3M Plus), and this heightened awareness is crucial. If malaria cases resurge, the community must be well-informed about the measures and challenges." (Informant)

The community must understand how to manage malaria effectively. However, control measures must continue to be enforced to eliminate malaria successfully, particularly in Pangandaran. The community is encouraged to remain vigilant even if malaria cases have decreased and are urged not to let their guard down.

"Furthermore, it's worth noting that people tend to become more complacent when a disease re-emerges. It presents a challenge for us as we strive to educate the community. While people may want to understand, getting them to act accordingly can still be challenging." (Informant)

The evaluation activities are ongoing and are conducted by the *puskesmas* and the health office. These activities involve monitoring reported cases and coordinating with healthcare services. Presently, surveillance is primarily passive, meaning that health officers respond when the community reports a case. From 2015 to 2019, malaria cases were endemic in this district. However, from 2020 to 2022, there has been a decreasing trend in imported and indigenous cases in this region.

"So, if there is any disease, it is rapidly brought to the nearest healthcare facility from their home." (Informant)

In addition to monitoring cases, some districts in the Pangandaran region have engaged cadre members' support in monitoring and evaluation activities. With the assistance of cadre members, reports of persistent malaria cases have been effectively managed.

"It's true that not all villages are fully prepared. For instance, there is one village with four hamlets. Have all four hamlets been thoroughly checked? Not yet, but we rely on cadre members to provide information for our visits and inspections. Cadre members play a crucial role in making this process more efficient. It would be quite challenging without cadre members as we would need to navigate through various complexities. Information is readily available when cadre members are involved, making the inspection process smoother." (Informant)

"Furthermore, cadre members in the community show greater dedication, which significantly contributes to our efforts." (Informant)

Furthermore, a map indicating deployment locations in this region is accessible at each health center.

"Yes, the map can be obtained at the Kalipucang Health Center, and they are more than willing to share it." (Informant)

Discussion

The successful elimination of malaria in the District of Pangandaran faces ongoing challenges in reducing cases, particularly in health centers within the district. Despite progressing to a stage of low endemicity with no local transmission recorded in 2022, comprehensive efforts related to malaria control are still in the process of full implementation. As outlined in the Republic of Indonesia Minister of Health Decree No. 293/MENKES/SK/IV/2009, critical indicators for malaria elimination include the discovery and management of cases, prevention and control of risk factors, epidemiological surveillance, communication and education, and the enhancement of human resources.[5] Observational endeavors are concentrated on ensuring that locations with ongoing malaria transmission

are identified, along with pinpointing at-risk populations. It includes monitoring vectors and assessing their vulnerabilities to devise targeted interventions.[6]

According to the World Health Organization (WHO), several inhibiting factors in malaria elimination include a lack of supervision, regulation, and community knowledge.[7] This is substantiated by data from the 2013 *Riskesdas*, which underscores the necessity for enhanced monitoring, evaluation, and the bolstering of cross-sector participation in malaria treatment—additionally, identified various factors related to elimination activities, encompassing community knowledge, engagement, and participation, particularly in the private sector.[8] The support of technology information utilization in managing standardized drug supply at primary healthcare facilities is another crucial aspect. In the Pangandaran district, multiple vector control activities have been undertaken and continue to improve. These include distributing mosquito nets, using larvicides, ongoing community education, and establishing the *Masyarakat* Awareness of Malaria (MASAMA) program to minimize the resurgence of malaria transmission in the region. Furthermore, based on interviews with informants, the health service, in collaboration with health centers in the Pangandaran area, routinely conducts monitoring activities in lagoons, which serve as transmission sites for malaria. Specific endemic target areas have been identified with the elimination program in the Republic of Tanzania. An approach targeting communities at higher risk of malaria transmission is encouraged, involving interventions such as the distribution of mosquito nets, mosquito vector control through indoor residual spraying (IRS), and the management of malaria cases through the provision of appropriate medication doses.[4,9]

The management of malaria programs, including coordination among provinces, districts, and health centers, must be integrated with the Ministry of Health's program, with support from UNICEF and WHO. The role of both public and private sector organizations becomes crucial in the malaria elimination efforts.[10] Policy development in the health sector can be effective when it is well-structured and supported by valid and comprehensive evidence.[11] Kader Maideen et al.,[12] adopting a "one health" approach, which involves collaboration between the health sector and other fields, is believed to be one of the strategies for accelerating malaria elimination efforts. Furthermore, Marhaban et al.[13] assert that malaria management involves the treatment of patients and vector control. It is because various factors, such as changes in ecosystem areas, the consequences of deforestation, shifting climates, and the development of settlements or urban areas influence malaria.

The prevention of malaria in Pangandaran district involves coordination among the Department of Health, health centers, and various community stakeholders. Educating the public about malaria is crucial, enabling them to distinguish it from other vector-borne diseases and learn how to handle it properly. Reports from Columbia have shown that knowledge and practices related to malaria prevention have improved after implementing interventions like counseling and distributing educational materials such as books, booklets, t-shirts, and audio-visual media.[14–16] Nevertheless, it is crucial to acknowledge that the understanding of malaria among the general population may vary from that of individuals who have personally experienced the disease. Typically, those who have suffered from malaria have a better understanding of how to manage and treat the disease.[17] Additionally, the basic health research (*riset kesehatan dasar, Riskesdas*) results conducted in 2013 in various regions of Indonesia indicate that effective treatment has yet to be widely achieved due to inappropriate treatment-seeking behavior. In six malaria-endemic provinces (Bengkulu, Maluku, North Maluku, East Nusa Tenggara, Papua, and West Papua), people still obtain malaria treatment from stalls and pharmacies.[18]

Similar to Indonesia, the country of Zanzibar is also actively engaged in malaria prevention efforts. These efforts include the use of mosquito nets treated with insecticides, indoor residual spraying (IRS), and health promotion campaigns.[19] These activities are driven by concerns and fears within the public regarding the potential resurgence of malaria within their territory, especially during the rainy season, and the introduction of cases from other regions or through imports. Successful implementation of these programs has led to the City of Sabang becoming a prosperous city with significant progress in eliminating malaria. Several key factors have contributed to this success, including the accurate discovery and management of valid malaria cases, mitigating

risk factors, effectively monitoring malaria epidemiology and outbreak control, improved cross-sector communication and cooperation, enhanced public information and education, and increased human capacity.[13] Furthermore, a decline in malaria cases has also been observed in the village of Tetel in Purbalingga regency, where implementing village regulations has played a crucial role in educating the local community about malaria elimination. These educational activities encompass health village meetings, group recitations at mosques, community gatherings, and integrated health service posts (*pos pelayanan terpadu*, *posyandu*). Public participation, with active individuals serving as team supervisors, has been instrumental in reporting individuals with malaria symptoms.[20–24] This participatory approach is consistent with the routine practices in Pangandaran involving local cadres. Ultimately, with efficient control measures and the active involvement of the community, the malaria elimination program in various areas of Pangandaran holds promise for success. As long as these efforts are relevant to local malaria vectors and accepted by the community, the goal of eliminating malaria in West Java can be realized.

Conclusions

Activity surveillance in the district area Pangandaran already properly proven in malaria cases in 2019 to 2022 decreased. Cooperation cross-sector did, but the role of the public in activity elimination must be improved. The successful elimination of malaria not only from society; therefore, an increase in HR quality must continue with the enhancement of the quality of human resources in the Pangandaran district and cooperation between the public, and the giver policy expected the following regions to become a region with success elimination of malaria.

Conflict of Interest

The authors declare that they have no competing interests.

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RESEARCH ARTICLE

Smoking Habit and Coffee Consumption with Gastritis Incidence Rate at Productive Ages

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Abstract

Gastritis is a disease caused by an inflammation of the mucous and submucosal lining of the stomach. Several studies show that there is an influence of smoking habit and coffee consumption on gastritis incidence rate. The study was to determine the correlation between smoking habit and coffee consumption toward gastritis at productive ages. The research is an analytical observational study with a cross-sectional design conducted in Makale Health Center, South Sulawesi, in February 2020. Required data was gathered by conducting guided interviews using a questionnaire that includes age range, sex, and education level. Brinkman Index was used to measure smoking habits, coffee consumption, and gastritis questionnaire. Data was analyzed using a chi-square test with a significance level of p=0.05. From a total of 115 respondents, there are 69.6% included in the age range of 26–35 years old, 58.3% have mild smoking habits, 56.5% have severe coffee consumption, and 85.2% are suffering from gastritis. There is a relation between smoking habit (p=0.029) and coffee consumption (p=0.003) with gastritis (p<0.05). The conclusion is that there is a relationship between smoking habits, coffee consumption, and gastritis incidence.

Keywords: Coffee, gastritis, productive age, smoking

Introduction

Gastritis is a common disease that often occurs in everyone and is a health problem with a high prevalence. Lifestyle is an essential factor in the occurrence of gastritis.[1,2] Gastritis is an inflammation of the mucous and submucosal lining of the stomach, which can be caused by several factors, such as smoking, coffee drinking, and drug consumption, such as aspirin or NSAID.[3]

The incidence of world gastritis is around 1.8–2.1 million of the population every year. Based on research conducted by the World Health Organization, gastritis incidents occurred highly in the USA (47%), India (43%), Canada (35%), and China (31%). Based on data from the Ministry of Health of the Republic of Indonesia (2019), 40.8% of gastritis incidents occur in Indonesia.[1,4] Gastritis patient prevalence is often found in the age range of 20 to 44 years old. Research conducted by the University of Medicine and Pharmacy Tîrgu-Mureş mentioned that gastritis prevalence in people with coffee consumption and smoking habits often occurred in those who are 30 to 49 years old.[5]

Smoking is one of many modern lifestyles that are not only found in adults but also in children and young adults. According to the 5th Indonesian Family Life Survey (IFLS-5) data, the percentage of smoking in Indonesia was 58%, with 95% dominated by males with an average age of 19 years old. Most (48%) choose kretek filtered as the preferred cigarette.[6]

Smoking habits can cause gastric disturbance because nicotine in cigarettes will pucker and disrupt blood vessels in the stomach, which will further cause irritation that triggers excessive increase of gastric acid production.[7]

Another factor that influences gastritis occurrence is consuming coffee/caffeine. Long-term and high-frequency caffeine consumption (>3 glasses a day) will accelerate gastric acid production that would irritate the mucosa. When mucosa in the stomach is irritated, hydrochloride acid (HCl) diffusion towards the mucosa will disrupt mucosa and eliminate its ability to protect the stomach from HCl and pepsin auto digestion.[3,5,8,9] Research conducted by Ilham

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et al.[10] stated that the caffeine compound in coffee can accelerate gastric acid production stimulation and cause gastritis. However, a different result was published by Novitasary et al.,[11] which said that there is no relationship between coffee consumption and gastritis, which is highly dependent on the type of coffee, where in this research, the subjects consume more instant coffee with a lower caffeine compound than ground coffee beans. Research by Cheng et al.[12] said that there is a relationship between smoking habit and gastritis, but contrary research by Novitasary et al.,[11] Hairuddin et al.,[13] and Khandelwal et al.,[14] which said that there is no relationship between smoking habit and gastritis occurrence because there are factors with stronger influence on gastritis such as consumption habit and stress.

Based on the description above, the authors are interested in researching the relationship between smoking habits and coffee consumption and gastritis incidence rates at productive ages, which can further identify the contributing factors to preventive and curative sources of gastritis.

Methods

This research is a type of observational analytical study using a cross-sectional design. This study searched for a relationship between smoking habits and coffee consumption with gastritis incidence rate in Makale Health Center, South Sulawesi, conducted in February 2020. Subjects were men and women aged 26–45 years at the study site. Subjects in this study were taken through simple random sampling on subjects by the inclusion criteria, namely men or women aged 26–45 years, have smoking habits and coffee consumption, are not taking NSAIDs and aspirin, and are willing to sign informed consent. Determination of sample size is done by using an infinite-finite population formula with a significance level of 95% from 1.96, and with gastritis prevalence in Indonesia of 40.8%[1] where the measurement accuracy is 0.05 and 115 subjects are willing to participate in this study.

Data collection was collected through questionnaire filling that gathers information regarding identity (name, age, sex, and education level), Brinkman index questions to measure the number of cigarettes consumed in a day multiplied by length of smoking habit in a year with valuation category of light between 0–199, medium between 200–599, and heavy >600.[15] The questionnaire also measures the length and frequency of coffee consumption practiced by the subjects with categories of light with a frequency of ≤3 glasses/day and heavy with a frequency of >3 glasses/day.[16] A gastritis questionnaire was also included to measure the perceived gastritis symptom complaints with a valuation of ≥12 and <12 for non-gastritis complaints.[2]

The Research Ethics Committee of the Faculty of Medicine, Universitas Trisakti, Jakarta, has already approved this research, with approval number 11/KER-FK/1/2019.

Results

Univariate analysis was used to determine the frequency distribution of respondents' characteristics in terms of age, sex, education level, smoking habits, coffee consumption, and gastritis events of the research subjects.

Table 1 suggests that most subjects in the Makale Health Center were aged between 26 and 35 years (69.6%), with a slightly higher proportion of males (56.5%) than females. Eighty subjects (69.6%) had a high level of education, 67 subjects (58.3%) could be considered to have a mild smoking habit, and 65 subjects (56.5%) are known to consume coffee to a significant extent.

Table 1 Characteristic Data

Variables	n=115 (%)
Age (years)	
26–35	80 (69.6)
36–45	35 (30.4)
Gender	
Male	65 (56.5)
Female	50 (43.5)
Level of education (years)	
Low (<9)	35 (30.4)
High (≥9)	80 (69.6)
Smoking habit	
Mild (<200)	67 (58.3)
Moderate (200–599)	45 (39.1)
Severe (>600)	3 (2.6)
Coffee consumption	
Mild (≤3)	50 (43.5)
Severe (>3)	65 (56.5)
Gastritis occurrences	
Gastritis	98 (85.2)
Non-gastritis	17 (14.8)

In the assessment of the incidence of gastritis, it was found that 98 subjects (85.2%) had gastritis.

Bivariate analysis with a chi-square test was used to determine the relation between socio-demographic factors (age, sex, and level of education), smoking habits, and coffee consumption on the incidence of gastritis at the age of 26–45.

Table 2 shows that gastritis occurrence is found more in people in the age group of 26–35 years old with 68 subjects (59.1%), and from chi-square statistical test result, it is revealed that there is no significant relation between age group and gastritis incidence rate in subjects of 26–45 years of age (p=0.921). As many as 55 subjects (47.8%) are male with gastritis, which is slightly higher than female subjects. This shows that there is no significant difference between the two sexes. Based on the chi-square statistical test result, a value of p=0.836 was obtained. Based on that, we can conclude no significant relation exists between sex and gastritis incidence rate in subjects at productive ages. In groups with higher education levels, there are 66 subjects (57.4%) that suffer from gastritis, which is more than the one with lower education. In this group, the chi-square statistical test result shows a value of p=0.214, which means no relation exists between education level and gastritis incidence rate in subjects at productive age.

On a bivariate result of the smoker group, authors combine moderate and severe smokers because there are only three subjects who are heavy smokers. The result obtained shows that the light smokers group suffers more gastritis incidence with 53 subjects (46.1%). On the chi-square test result, a value of p=0.029 was obtained, which means a relationship exists between smoking habits and the incidence rate of gastritis in subjects at a productive age. As for the coffee consumption variable, gastritis incidence was found more in heavy coffee consumers, with 61 subjects (53%). The chi-square test result shows a value of p=0.003, which means that there is a relationship between coffee consumption and gastritis incidence. The results indicated that the subjects consuming more coffee can increase the incidence of gastritis at a productive age.

Discussion

In this research, demographic characteristics (age, sex, and education level) are unrelated to the gastritis incidence rate in subjects aged 26–45. Gastritis tends to happen at a younger age due to uncontrolled eating patterns caused by daily activity.[1,17] The results by Feyiza and Woldeamanuel[3] showed younger aged 18–28

Table 2 Bivariate Relation between Demographic Characteristics, Smoking Habits, and Coffee Consumption with Gastritis Incidence Rate at Productive Ages

Variables	Gastritis Occurrence				p[c]
	Gastritis		Non-gastritis		
	n=98	%	n=17	%	
Age (years)					
26–35	68	59.1	12	10.4	0.921
36–45	30	26.1	5	4.3	
Gender					
Male	55	47.8	10	8.7	0.836
Female	43	37.4	7	6.1	
Level of education (years)					
Low (<9)	32	27.8	3	2.6	0.214
High (≥9)	66	57.4	14	12.2	
Smoking habit					
Mild	53	46.1	14	12.2	0.029*
Moderate–severe	45	39.1	3	2.6	
Coffee consumption					
Mild	37	32.2	13	11.3	0.003*
Severe	61	53	4	3.5	

Note: [c]chi-square statistical test, *significance p<0.05

years (57.5%) tend to suffer gastritis because they don't know about good health behaviors, but according to Khandelwal V et al.,[14] those aged 14–25 years and 36–45 years has more tend to be gastritis. However, gastritis can also occur in older subjects because of several factors such as age increase, degenerative process, *Helicobacter pylori* infection, and NSAID drug usage.[18] The research by Putri et al.[17] concluded that gastritis is found more in females because females tend to lower their weight by managing food consumption frequency, size, and type, which would lead to gastritis. This statement was also made by Yunanda et al.[19] Women also tended to have gastritis due to lack of rest,[3] but some studies said the opposite.[14] The research by Liu et al.[20] revealed that gastritis risk factors depend on each country's economics, education, and health problems. Sipponen and Maaroos[21] also say that the prevalence of gastritis is increasing in line with the increasing age in developed countries. Still, other statements say that 50% of the prevalence of gastritis occurs in young age groups and even in childhood in developing countries. The research by Wulandari et al.[22] said that education level does not have any relationship with gastritis because both education levels can suffer from gastritis. A low education doesn't mean a low knowledge level because it can be obtained from non-formal education, such as information and personal experience, as their future references.[23] Still, Umasugi et al.'s[4] research said that a lack of education could cause a lack of behavior regarding gastritis prevention.

This research shows that there is a relation between smoking habits and gastritis incidence rate at productive ages. The mechanism of smoking influence on the mucosa is by stimulating HCl and pepsinogen, reducing pancreatic bicarbonate flow, removing the protective mucus layer, disturbing epithelial repair, microcirculation disruption, reducing gaster's motility and decreasing prostaglandin E2.[5,24] Smoking can lower prostaglandin synthesize in gastric mucosa and lower barrier function on stomach.[5] Smoking has various factors, such as reactive oxygen species, peroxynitrite, peroxynitrite, free radicals, and other reactive compounds that can cause oxidative stress, impacting endothelial function. This inflammation reaction will continue to occur and further lead to gastritis.[5,12] Smokers who have smoked for more than two years could increase gastric acid secretion and lower gastric pH.[24] This research had similar findings by Cheng et al.,[12] where a smoking lifestyle could lead to gastritis. Still, some had different conclusions, which said there's no relationship between smoking habit and gastritis because there are other stronger influencing factors that might lead to gastritis occurrence, which are eating patterns and stress.[11,14,25]

This research showed a relation between coffee consumption and gastritis incidence rate at productive ages. Coffees are available in several forms. The chemical composition of coffee depends on green beans and roasted and brewed coffee. The green coffee beans depend on roasting, which can cause a Maillard reaction. This reaction can produce coffee acrylamide and reduce free chlorogenic acids and antioxidant forms. Meanwhile, roasted coffee consists of many components, and some effects are antioxidant, anti-inflammatory, antifibrotic, and antiproliferative. Coffee brewing also influenced the coffee composition. It depends on coffee solubilization in hot or cold water, separation of the water extract from the coffee ground, and water absorption. A recent study showed that hot and cold brew coffees have essential differences in total antioxidant capacity. But, whatever your coffee's methods, its components will affect your body.[8] The caffeine compound in coffee stimulates the secretion of HCl and gastrin through G cells, which are present in the gaster and duodenum but don't expedite gastric emptying.[9,10] Increased gastric acid secretion can increase the possibility of dyspepsia, gastritis, ulcers, and gastroesophageal reflux disease.[9] Caffeine can stimulate the central neural system and increase stomach activity to produce gastrin hormones in the stomach and pepsin, which are acidic, leading to irritation and stomach mucosa erosion.[8,26] Caffeine can accelerate acid production in gaster and produce excess gas, which can cause bloating.[27] This result is similar to the one Mahmoud et al.[18] conducted, which shows a significant association between gastritis and drinking coffee. The opposite study by Novitasary et al.[11] showed that the respondents rarely or not excessively drink coffee. Our body can absorb caffeine wholly and rapidly (95% within 45 minutes), and plasma levels increase within 30–60 minutes.[28] The International Agency for Research on Cancer also said there is evidence that coffee consumption helps reduce incidents of certain cancers, like colon, prostate, endometrium, melanoma, and liver.[8] Based on

International Food Information Council data, the safe consumption of coffee within the moderate range is up to 400 mg of caffeine per day or 3–5 cups per day for healthy adults.[28] Regarding this research, which reveals that most of the subjects consumed >3 glasses of pure coffee per day (black coffee), although every individual experiences different effects, it would risk them to contract gastritis. This result is the same with Santoso,[27] who said drinking coffee for an extended period and continuously with more than three glasses per day can irritate mucosa gaster, leading to gastritis and recurrence of gastritis.

The limitation of this research is that endoscopy examination is not used for gastritis diagnosis due to resource limitations. Therefore, the authors are unable to exclude gastritis contributors due to *Helicobacter pylori* infection or other irritant exposure.

Conclusion

Smoking behavior and coffee consumption are related to the incidence rate of gastritis at productive ages in Makale Health Center, South Sulawesi.

Conflict of Interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Evaluating Risk Factors for Early-onset Neonatal Sepsis

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Abstract

Neonatal sepsis is a systemic infection that occurs in infants at 28 days of life and is a significant cause of morbidity and death in newborns. Early-onset neonatal sepsis (EONS) occurs within 72 hours after birth and is often associated with infections contracted before or during childbirth. The study aims to evaluate the risk factors of EONS. The study design was a case-control retrospective observational study that evaluated the medical records of neonates who were admitted to the neonatal care unit of Al Islam Hospital Bandung from January 2020 to December 2022. This study assessed the impact of independent variables such as gestational age, birth weight, premature rupture of membrane (PROM), miconeal amniotic fluid, APGAR score of 5 minutes, and the mother's white blood cell count elevation (>15,000/µl). The logistic regression analyses were employed to analyze the data. The logistic regression analyses were employed to analyze the data. The study included 3,103 neonates, of whom 124 met the inclusion criteria. Thirty-nine patients (31.35%) were diagnosed with sepsis, while 85 patients (68.55%) did not have sepsis. Based on bivariate analysis, EONS was significantly linked to low birth weight (p=0.027, 95% CI=0.184 to 0.902, OR=2.455), PROM (p=0.000, 95% CI=4.359 to 26.582, OR=10.764), and the mother's white blood cell count elevation (p=0.002, 95% CI=1.560 to 7.622, OR=3.448). On multivariate analysis, the risk factors were significantly associated (p<0.05), which had an influence of 38.4% on EONS (Nagelkerke R square=0.384). In conclusion, the risk factors for EONS were low birth weight, PROM, and elevation of white blood cell count in the mother, which increased by 38.4% with EONS.

Keywords: Early-onset neonatal sepsis, risk factors

Introduction

Neonatal sepsis is a clinical condition characterized by a systemic illness accompanied by bacteremia within the first month of a newborn's life.[1] It arises when pathogens invade and proliferate in the bloodstream, causing systemic infection and releasing toxins that can lead to severe health complications and neonatal mortality.[2] Neonatal sepsis is further categorized into early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS). EONS occurs within 72 hours after birth and is often associated with infections contracted before or during childbirth. On the other hand, LONS typically manifests 72 hours after birth and is commonly attributed to hospital-acquired infections or infections acquired within the community.[1–3]

Neonatal sepsis contributes significantly to morbidity and mortality among newborns, posing a significant health concern.[4] The estimated incidence of early-onset sepsis (EOS) in the United States was between 0.77 and 0.98 cases per 1,000 live births.[1] According to Shane et al.'s[5] study, the incidence of neonatal sepsis varies across different regions. In South Asia, the total incidence of culture-positive sepsis was 15.8 per 1,000 live births,[6] while in sub-Saharan Africa, it ranges from 6–21 cases per 1,000 live births.[7] The Middle East and North Africa region report an incidence of 1.8–12 cases per 1,000 live births, and in the Americas and Caribbean, it is reported as 2.9 cases per 1,000 live births.[7] In specific hospital settings, the incidence of neonatal sepsis can vary. At Dr. Cipto Mangunkusumo National Central General Hospital in Jakarta, from December 2006 to July 2007, neonatal sepsis with positive blood cultures was reported at 6.4%.[8] Similarly, at Sanglah Hospital Bali, from January 2010 to December 2010, neonatal sepsis

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was 5%, with a death rate of 30.4%.[9]

Diagnosing neonatal sepsis can present challenges due to the subtle and varying early signs of sepsis at different gestational ages.[10] Several risk factors contribute to developing neonatal sepsis, such as low birth weight, delivery in unsafe or unclean environments, prolonged rupture of membranes exceeding 18 hours, maternal fever, chorioamnionitis, prolonged labor, and perinatal asphyxia. Clinical symptoms of neonatal sepsis are often nonspecific, and although blood culture is the gold standard for diagnosis, it does not yield immediate results. Additionally, some infants may have received antibiotics before the blood culture, further complicating an early diagnosis.[11] Therefore, timely identification of sepsis in neonates is crucial, as the condition can progress rapidly and sometimes result in fatality.[10] This study aims to identify the risk factors associated with the development of EONS among patients delivered or referred to the neonatal care unit of Al Islam Hospital, Bandung.

Methods

The study design was a case-control retrospective observational study that evaluated the medical records of neonates who were admitted to the neonatal care unit of Al Islam Hospital Bandung from January 2020 to December 2022. A purposive sampling technique was used for participant selection. The inclusion criteria were neonates suspected of having bacterial sepsis with a gestational age of >26 weeks. Neonates with significant congenital abnormalities or syndromes (e.g., Down syndrome) and incomplete data were excluded. The data of all neonates diagnosed with suspected sepsis were reviewed, and sample characteristics such as sex, gestational age, birth weight, mode of delivery, parturient, and outcome were collected.

The sample population was divided into two groups: sepsis (proven and probable sepsis) and non-sepsis (suspected infection), which were analyzed between these two groups to assess the impact of independent variables including gestational age (GA), birth weight (BW), premature rupture of membranes (PROM), meconium amniotic fluid, APGAR score of 5 minutes, and the mother's white blood cell count elevation (>15,000/µl). Logistic regression analyses were employed to analyze the data. The collected data were presented in a distribution tabulation, and statistical analysis was performed using a computer-assisted statistical package (SPSS version 12.0). Chi-square and logistic regression analyses were employed to analyze the data. The calculation of risk factors involved calculating odds ratios and 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

Diagnosing neonatal sepsis is based on risk factors, clinical findings, and laboratory data. The maternal and neonatal risk factors (EONS) assessed were gestational age <37 weeks, birth weight <2,500 grams, APGAR score <7 on the fifth minute (low APGAR scores), premature rupture of membranes >18 hours before birth, maternal body temperature >38°C intrapartum, the mother's white blood cell count elevations (>15,000/µl), and greenish-thick-and-foulsmelling amniotic fluid in the first 72 hours after birth.

Laboratory examinations include the following: blood cell examination, immature to total RA, value of C-reactive protein, and microbial blood culture. The total white blood cell count was obtained using the Mindray BC 5300 auto hematology analyzer and corrected for nucleated red blood cells. Differential counts were performed on Giemsa smears, and about 200 cells were counted. Hematology sepsis markers confirmed sepsis based on the following: (a) total white blood cell (WBC) count: <5,000/µl, >25,000/µl at birth, >30,000/µl 12–24 h, >21,000/µl day two onwards; (b) platelet count <150,000/µl; (c) immature to a total PMN ratio >0.120; and (d) value of C-reactive protein >6.0 mg/l. Bacteria in blood cultures with clinical and laboratory evidence of sepsis have been proven to have sepsis. Probable sepsis was defined as signs or symptoms of neonatal sepsis supported by two or more septic markers but without evidence of bacteria in the blood culture. Suspected infection was defined as the presence of risk factors for neonatal infection without any signs or symptoms of clinical sepsis.[8]

Results

Based on the data, the number of neonate births at Al Islam Hospital Bandung from January 2020 to December 2022 was 3,103 infants, with the number of neonates who met the inclusion and exclusion criteria in this study being 124 neonates. The diagnosis of sepsis was in 39 patients

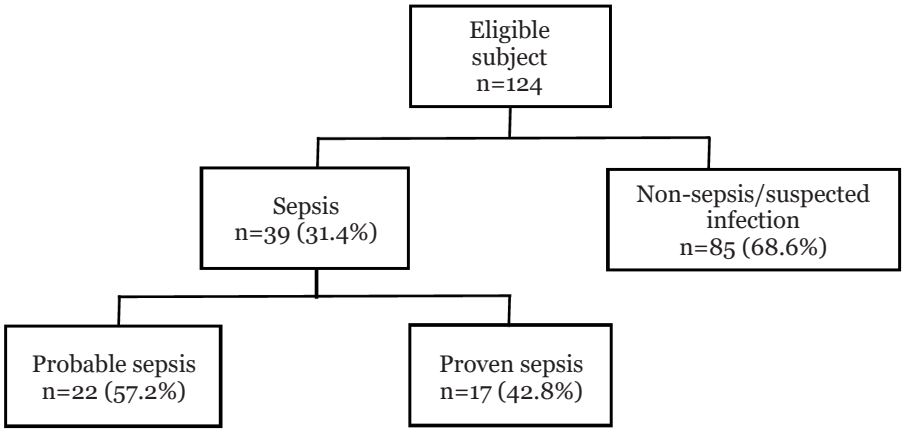

Figure Research Subject Distribution Schema

(50.8%) and no sepsis in 85 patients (49.2%). The incidence of EONS at Al Islam Hospital Bandung during the study was (39/3,103; 1.26%), and the mortality rate during the study was 18/124; 14.5%. Most deliveries were performed spontaneously (79, 63.7%). Most infants had a gestational age over 37 weeks (41, 33.1%) with a mean gestational age of 33.895 (SD=4.213). The birth weight majority were 1,500–2,499 grams (40, 32.25%) and more than 2,500 grams (40, 32.25%), with a mean birth weight of 2,012.22 (SD 884.71) grams—Table 1.

Based on the results of this study (Figure), 39 neonates met the inclusion criteria (sepsis), consisting of probable sepsis 22 (57.2%) and proven sepsis 17 (42.8%). The most common bacteria found were *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*.

Table 2 shows that based on bivariate analysis, the factors that were significantly associated with the occurrence of early-onset sepsis at Al Islam Hospital Bandung were LBW (p=0.027, 95% CI=0.184 to 0.902, OR=2.455), PROM more than 18 hours (p=0.000, 95% CI=4.359 to 26.582, OR=10.764), and the mother's white blood cell count elevation (>15,000/µl, p=0.002, 95% CI=1.560 to 7.622, OR=3.448). Meanwhile, other risk factors did not have a significant influence on the occurrence of EOS, such as gestational age <37 weeks (p=0.094, 95% CI=0.892 to 4.326, OR=1.964), meconium amniotic fluid (p=0.111, 95% CI=0.853 to 4.688, OR=2.000), and a 5-minute APGAR score <7 (p=0.372, 95% CI=0.578 to 4.341; OR=1.583).

Multivariate analysis results are shown in Table 3. The maternal factors significantly associated with bacterial EONS were premature rupture of membranes >18 hours (OR=0.096, 95% CI=0.036 to 0.255, p=0.000) and leukocytosis in the mother >15,000 (OR=0.283, 95% CI=0.112 to 0.718, p=0.008). The neonatal factors associated with bacterial EONS were BW (OR=1.358, 95% CI=0.196 to 9.427, p=0.757) and GA (OR=1.493, 95% CI=0.213 to 10.460, p=0.687). We decided on multivariate analysis that the risk factors were significantly associated (p-value<0.05), where all risk factors had an influence of 38.4% (Nagelkerke's R square=0.384) on early-onset neonatal sepsis.

Discussion

This research shows that the incidence of EONS at Al Islam Hospital Bandung is 1.26% of cases from 3,103 subjects. This incidence rate is higher than the report by Lusyati and Sauer[13] at Harapan Kita Hospital, Jakarta, around 1.4 cases per 1000 population, but still lower than the research by Suwarna et al.[14] at Dr. Hasan Sadikin General Hospital, Bandung, where the incidence of early-onset neonatal sepsis in 2018–2019 was 8.1% from 5,224 subjects. In our study, 17/124 (42.8%) subjects had bacterial-positive blood cultures, and 22/124 (57.2%) had probable sepsis. This research shows that positive blood cultures are higher than the research by Fitriana et al.[12] at Mohamad Hossein Hospital Palembang (42.8% vs 9.3%), but still lower than the research by Sianturi et al.[15] at Adam Malik Hospital, Medan (42.8% vs 66.1%). Meanwhile, Giannoni et al.,[16] in a previous study, identified blood culture-proven sepsis, 20% of whom had EONS and 62%

Table 1 Characteristics of Subjects

Variables	Sepsis		Non-sepsis		Total	
	n=39	50.8%	n=85	49.2%	n=124	100%
Gender						
Male	19	48.7	29	34.1	48	38.7
Female	20	51.3	56	65.9	76	61.3
Type of pregnancy						
Singleton	37	94.9	77	90.6	114	91.9
Gemeli	2	5.1	8	9.4	10	8.1
Mode of delivery						
Spontaneous	25	64.1	54	63.5	79	63.7
Caesarian section	13	33.3	30	35.3	43	34.7
Vacuum extraction	1	1.6	1	1.2	2	1.6
Birth weight (grams)						
Means (SD)	2,012.22 (884.71)					
<1,000 (extremely low BW)	6	15.4	8	9.4	14	11.3
1,000–1,499 (very low BW)	7	17.9	23	27.1	30	24.2
1,500–2,499 (low BW)	8	20.5	32	37.6	30	32.25
≥2,500	18	46.2	22	25.9	40	32.25
Gestational age (weeks)						
Means (SD)	33.895 (4.213)					
26–29+6 (very early preterm)	8	20.5	18	21.2	26	21.0
30–33+6 (early preterm)	6	15.4	28	32.9	34	27.4
34–36+6 (late preterm)	8	20.5	15	17.6	23	18.5
≥37 (term)	17	43.6	24	28.2	41	33.1
Parturient						
Primipara	15	38.5	27	31.8	42	33.9
Multipara	24	61.5	58	68.2	82	66.1
Mortalitas						
Dead	18	46.2	18	21.2	36	29.0
Alive	21	53.8	67	78.8	88	71.0

of whom had late-onset neonatal sepsis.

The mortality rate for neonatal sepsis in this study was 14.5%, much higher than other studies such as those by Lim et al.[17] at Chang Gung Memorial Hospital, China, where the case fatality rate in neonatal sepsis patients was 7.0% (11/158). In Indonesia, RSCM Jakarta reported that neonatal sepsis mortality was 14.18%.[9] Similar results were reported at Moewardi Hospital Surakarta, which found that the neonatal sepsis mortality rate was 40%.[18] Various factors can explain differences in mortality rates in neonatal sepsis between countries. Including economic, geographic, and social-racial factors, using ventilators and incubators, and exposure to different microorganisms and antibiotics.[4] While advancements in neonatal intensive care have decreased the impact of EONS among full-term infants, the risk of EONS and its consequences remains high for preterm infants. Additionally, very-low-birth-weight (VLBW) infants are susceptible to late-onset (healthcare-associated) sepsis.[4] Among infants born at 37 weeks gestation or more, the incidence of EONS is approximately 0.53 cases per 1,000 live births. However, in the preterm population, the incidence is significantly higher at 3.7 cases per 1,000 live births (seven times higher). Among VLBW infants, the incidence escalates to approximately 11 cases per 1,000 live births (20 times higher).[1]

Birth weight and mortality showed significant differences in the characteristics of the sepsis and non-septic groups. Neonates with birth weight <2,500 grams were found in 36 patients (57.14%) with a p-value of 0.003, similar to research by Suwarna et al.[14] at Dr. Hasan Sadikin General Hospital, Bandung, where there was a significant relationship between birth weight <2,500 grams

Table 2 Risk Factors for Early-onset Sepsis (Bivariate Test)

Variables	EOS		No EOS		OR	95% CI		p
	n=39	%	n=85	%				
Gestational age (weeks)								
<37	22	58.4	61	66.9	1.964	0.892	4.326	0.094
≥37	17	43.6	24	33.1				
Birth weight (grams)								
<2,500	21	53.8	63	74.1	2.455	0.184	0.902	0.027*
≥2,500	18	46.2	22	25.9				
Premature rupture of membranes (hours)								
<18	15	38.5	74	87.1	10.764	4.359	26.582	0.000*
≥18	24	61.5	11	12.9				
Meconeal amniotic fluid								
No	26	66.7	68	80.0	2.000	0.853	4.688	0.111
Yes	13	33.3	17	20.0				
APGAR score 5 minutes								
>7	6	15.4	19	22.4	1.583	0.578	4.341	0.372
≤7	33	84.6	66	77.6				
Mother's white blood cell (/µl)								
<15,000	14	35.9	56	65.9	3.448	0.156	7.622	0.002*
≥15,000	15	64.1	29	34.1				

Note: EOS: early-onset sepsis, *significance p<0.05

and the incidence of neonatal sepsis (p-value 0.001). Neonates weighing <2,500 grams have a 1.42 times higher risk of experiencing neonatal sepsis compared to babies weighing the same or more than 2,500 grams. This is because babies with low birth weight are mostly born prematurely, have difficulty eating, lose heat quickly, have low glucose levels, and are at greater risk of experiencing hypoglycemia. Apart from physiological factors, neonates with low birth weight are closely related to other risk factors for neonatal sepsis, such as a history of maternal infection, premature rupture of membranes >24 hours, prematurity, and asphyxia.[1,4]

Based on bivariate analysis in this study, the following were significantly associated with the occurrence of EONS: LBW (p=0.027, 95% CI=0.184 to 0.902, OR=2.455), PROM (p=0.000, 95% CI=4.359 to 26.582, OR=10.764), and the mother's white blood cell count elevation (p=0.002, 95% CI=1.560 to 7.622, OR=3.448), with a multivariate analysis, with an influence of 38.4%. A case-control study in Tanzania found the following maternal risk factors to be associated with bacterial EONS: chorioamnionitis (OR=1.9), HIV (OR=2.9), premature rupture of membranes >18 hours (OR=2.8), cloudy amniotic fluid (OR=3.2), foul-smelling amniotic fluid (OR=4.2), and vaginal examination during the delivery process (OR=5.9). The neonatal risk factors associated with EONS were <37 weeks gestational age (OR=1.5), newborn weight risk (OR=1.5),

Table 3 Risk Factors for Early-onset Sepsis (Multivariate Test)

Variables	B	S.E	Wald	OR	95%CI		p
BW	0.306	0.988	0.096	1.358	0.196 to	9.427	0.757
GA	0.401	0.993	0.163	1.493	0.213 to	10.460	0.687
PROM	−2.344	0.498	22.121	0.096	0.036 to	0.255	0.000
Leukocytosis	−1.262	0.475	7.060	0.283	0.112 to	0.718	0.008
Constant	1.738	0.510	11.604	5.683			0.001

Note: EOS: early-onset sepsis, *significance p<0.05

fetal distress (OR=1.6), and perinatal asphyxia (OR=6.7).[19] In Utomo's[20] study, it was found that risk factors with a significant relationship included low birth weight, premature gestational age, SC birth, and meconium amniotic fluid p-value <0.05. Babies with low birth weight and premature birth are at risk of immunodeficiency, thereby predisposing them to sepsis. LBW and premature conditions also tend to require invasive procedures and close monitoring, so there is a risk of nosocomial infections, which can lead to sepsis.

Premature rupture of membranes carries the risk of "prolonged leakage" of amniotic fluid, thereby increasing the risk of ascending bacterial infection from the urinary tract, proven by the presence of leukocytosis. Microorganisms from the vagina can infect the amniotic sac ascendingly, resulting in infection of the baby in utero.[21,22] The results of this study are similar to the research of Shifera et al.,[22] where it was found that PROM had a significant relationship with neonatal sepsis, especially in PROM >18 hours; the incidence of sepsis was five times higher. Meanwhile, in Fitriana et al.'s[12] study at Mohamad Hossein Hospital Palembang, Suwarna et al.'s[14] study at Hasan Sadikin General Hospital Bandung, and Wilar et al.'s[23] study at Kandau Hospital Manado, premature rupture membranes >18 hours were significantly associated with bacterial early onset sepsis (OR=4.46, 95% CI=1.35 to 14.71, p=0.008), (OR=1.69, 95% CI=1.27 to 2.25, p=0.001), and (OR=1.41, 95% CI=1.24 to 1.59, p=0.002), respectively. However, in Utomo's[20] study, there was no correlation between premature membrane rupture and sepsis. Some factors may contribute to this finding, such as the patient's history and the fact that there was no correlation between premature rupture of the membrane and sepsis. Some factors may contribute to this finding, such as the patient's history and the fact that the patient didn't remember when the membrane ruptured. This condition also indicates that the post-delivery antibiotic always given in the PROM neonate as a standard procedure can decrease the risk of neonatal sepsis.[1]

Our study found that the mother's white blood cell count elevation (>15,000/µl) had a significant relationship with a 3.4 times higher incidence of EONS (OR=3.448, 95% CI=1.560 to 7.622, p=0.002). Meanwhile, Fitriana et al.'s[12] study at Mohamad Hossein Hospital Palembang had no significant relationship to EONS (OR=1.74, 95% CI=0.53 to 5.73, p=0.357).8 The cause of early-onset sepsis in this study was *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*. According to Juniatiningsih et al.'s[8] study at Dr. Cipto Mangunkusumo National Central General Hospital Jakarta and Sianturi et al.'s[15] study at Adam Malik Hospital Medan, the cause of EONS were generally Gram-negative bacteria, 80.5%, and 54,5%, respectively, such as *Acinetobacter calcoaceticus*, *Enterobacter aerogenes*, *Pseudomonas* sp., *Escherichia coli*.[8] and *Staphylococcus epidermidis*, *Pseudomonas* sp.[15] Meanwhile Hafidz et al.'s[24] study at Hasan Sadikin General Hospital Bandung, blood cultures were obtained *Staphylococcus hemolytic*, *Staphylococcus aureus*, *Staphylococcus hominis*, and *Klebsiella pneumoniae*.

Conclusions

There was a significant bivariate relationship between LBW, PROM, and the mother's white blood cell count elevation. Simultaneously, there was a significant relationship between the risk factors for the incidence of EONS, with an effect of 38.4%.

Conflict of Interest

All authors stated that this study had no conflict of interest.

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RESEARCH ARTICLE

Self-medication for Cough: a Study of Smokers and Non-smokers in Surabaya Colleges

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Abstract

The number of smokers among students is increasing. Smoking can cause coughing, the body's defense mechanism for clearing the airways. Cough can be treated with self-medication, which can cause drug-related problems. The level of knowledge and perception can influence the choice of cough medicine used. The purpose of this study was to determine the knowledge and perceptions of cough medicine self-medication in smokers and non-smokers. This research method was a case-control study using a questionnaire of knowledge (definition, method of use, and indications) and perceptions (definition, side effects, and experience) regarding using self-medicated cough medicine. The research sample was adult students at a private university in Surabaya from January 2023 to April 2023, and it was collected using a purposive sampling method. The sample size was 124 respondents, 62 smoking and 62 non-smoking students. The level of knowledge in both groups was high, namely 51.62% in the smoker group and 58.84% in the non-smoker group. Meanwhile, the perception level in the smokers group was mostly bad (56.45%), in contrast to the non-smokers who had a good level of perception (64.52%). There was a significant difference in the level of knowledge (0.00) and perception (0.00) between smokers and non-smokers regarding cough medicine self-medication. Therefore, smokers have the same high level of expertise but lower levels of perception than non-smokers. Health promotion programs to increase knowledge are essential considerations in optimizing self-medication.

Keywords: Cough, knowledge, perception, self-medication

Introduction

Smoking causes social, economic, and health problems. However, the percentage of smokers is still high in Indonesia. According to data from 2013, Indonesia has the third highest prevalence of smoking among the nine countries in North and Southeast Asia. Smoking is also high among Indonesian adolescents.[1] The Statistics Indonesia (*Badan Pusat Statistik*) noted that the percentage of the Indonesian population aged 15 years and over who smoke is 28.62% in 2023. This percentage increased by 0.36% from last year, which was 28.26%.[2] At the higher education level, students' knowledge of the dangers of smoking is much better compared to high school level youth, but there are still many students who smoke. These factors lead to a relationship between knowledge and smoking behavior.[3,4] Previous research by Alraeesi et al.,[3] on 500 patients attending primary healthcare clinics in Dubai found that around 53.4% of the current smokers had poor knowledge, while most of them who never smoked and ex-smokers had a good knowledge level (47.9%, 70.0%), respectively (p-value for both <0.05). The majority of non-smokers and ex-smokers had good knowledge levels ($p<0.05$) and positive attitudes toward anti-smoking statements; however, poor knowledge levels and negative attitudes were found more among current smokers ($p<0.05$). Another study by Haq et al.[4] of 7,998 people living in Jurong, China, showed that higher smoking-related knowledge, attitude, and practices (s-KAP) scores indicated more knowledge regarding the harmful consequences of smoking outcomes, a positive attitude, less smoking practices, and having a good plan to quit smoking ($p<0.05$).

Smoking behavior can lead to decreased lung function. Smokers will experience a decrease

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in forced expiratory volume in 1 second (FEV_1) of more than 31–62 ml/year. In people with impaired lung function, the amount of air that enters the lung function will be less than normal. The main pulmonary ventilation function disorder is restrictive (restriction syndrome) and impaired lung expansion.[5,6] In addition to decreasing lung function, smoking behavior is also a major risk factor for cough.[7–9]

The solution to dealing with coughs in smokers is to buy cough medicines without a doctor's prescription or over-the-counter (OTC). People prefer self-medication rather than going to the doctor. This experience reinforces that in the context of self-medication behavior, individual experience is the main factor.[10] Another reason for self-medication is because of the perception that the illness is mild and that the cost is cheaper, it is faster, and more practical, which is also a significant factor in choosing self-medication.[11,12]

Many types of cough medicines are used to treat coughs, depending on the kind of cough and its cause. Mucolytics are the most frequently recommended cough medicines because they are cough medicines that have the most significant effect on cough symptoms. Because mucolytics can suppress excessive mucus.[13–15] Apart from mucolytics, other cough medicines that can treat cough medicines are antitussive and expectorant groups.[16] Antitussive cough medicines have a suppression mechanism unsuitable for coughing up phlegm. Cough therapy with antitussives causes the frequency of coughing to decrease, and the risk of infection occurring will increase because mucus cannot be removed from the respiratory tract. The use of cough medicine must be correct, the dosage must be proper, and the method of use must also be correct.[8]

The problem that often occurs in the community when using cough medicines is the need for more knowledge about the proper and rational use of cough medicines and over-the-counter medications. Previous research by Lorensia et al.[8] showed that many adult smokers choose and use cough medicine incorrectly because active smokers have insufficient knowledge of cough.

There is some minimum knowledge that the community should understand because it is essential in self-medication. The knowledge includes recognizing disease symptoms, choosing products according to disease indications, following instructions on the drug brochure, and monitoring therapeutic results and possible side effects.[17,18] Knowledge in the form of stored representations of past visual experiences can influence perception in a variety of ways: enabling recognition and interpretation, this allows for perceptual discrimination among similar categories of members; this can have a perceptual enrichment effect; it provides internal solutions that can then be accessed in case of resolution of the perception problem; it provides rules or laws regarding geometric optics which are the basis for achieving phenomena such as constancy of perception and the like; this can lead to a recalibration of tactile or visual sensations.[19] Sufficient knowledge will influence a person's perception or do something because someone finds out the information around him. Knowledge is one of the predisposing factors that can influence the formation of one's behavior. Knowledge is the result of remembering something, including recalling events that have been experienced either intentionally or unintentionally, and this occurs after people make contact or observe a certain object.[12,20]

In previous research by Akande-Sholabi et al.,[21] of 866 healthcare students in a Nigerian University, showed that most respondents have good knowledge of self-medication practices and perception of self-medication practices (55.3%). Previous research in Indonesia that was conducted was an evaluation of knowledge and perceptions of choosing cough medicine among smokers by Lorensia et al.,[8] in 100 smokers in Surabaya city showed that there were still many smokers who make mistakes in choosing and using cough medicine because the knowledge that active smokers have regarding coughs is still inadequate. The novelty in this research is that students are considered to have reasonably good knowledge. This study compares smokers and non-smokers because experience also influences knowledge and perceptions.[22,23] The purpose of this study was to determine knowledge and perceptions about cough medicine self-medication in smoking and non-smoker students.

Methods

This study's design was cross-sectional, and the participants were divided into two groups: smokers and non-smokers. The research was conducted from January 2023 to April 2023 at a university in Surabaya, East Java, Indonesia. The

research variables were self-medication for cough medicine and knowledge perceptions about the use of self-medication for cough medicine. The ethical test number is 161/KE/I/2023 from the Universitas Surabaya.

The research variables were cough medicine self-medication (independent variable) and knowledge-perception of using self-medicated cough medicine (dependent variable). Self-medication means that the sufferer himself chooses the drug without a prescription to treat his cough. Types of self-medication include over-the-counter medicines and limited over-the-counter drugs.

The population was strata-1 students with active status at a university in Surabaya. The research sample was part of the population male (because the majority of smokers are men,[24] and gender can influence knowledge and perceptions in self-medication[24,25]), did not have chronic pulmonary respiratory disorders, had experience using self-medicated cough medicine, and was willing to be involved in research, using purposive and snowball sampling method. Respondents were selected randomly from active students who met the sample criteria at the Universitas Surabaya; then, the smoking group respondents were also added using the snowball sampling method. The sample size calculation in this study used the formula for unpaired category analytic research, namely:

$$n_1=n_2=\left[\frac{Z_\alpha\sqrt{2PQ}+Z_\beta\sqrt{P_1Q_1+P_2Q_2}}{P_1-P_2}\right]^2$$

description: n=sample size; Z_α=1.96;Z_β=0.84; P_2=62.9%~0.629; Q_2=1–P_2=0.371; P_1=37.1%; Q1=1–P1; P=total proportion=(P_1+P_2)/2; Q=1–P. So, this study's minimum sample size (n) per group was 62 adults.

Each respondent was interviewed using the knowledge and perception of self-medication cough questionnaire developed from previous research.[8,9,26] The normality test was performed using the SPSS version 25 application, and the validity test was performed using the corrected item-total correlation (CITC) technique.

Questionnaires with knowledge aspects were divided into several elements related to cough, cough symptoms, the use of cough medicine, and self-medication services. The tested questions were all valid because the $_{count}$ value was greater than the $_{table}$ value; each question in this research questionnaire was declared reliable because it had a Cronbach's alpha value of 0.645. The perception reliability test for each question on the questionnaire was reliable if Cronbach's alpha value was >0.610 and declared valid if the $_{count}$ value was greater than 0.312 (r-$_{table}$ value). The questions had a CITC value exceeding 0.312 (r-$_{table}$ value), while the reliability test was stated to be reliable because the value of Cronbach's alpha exceeded 0.610 (Table 1).

The data analysis is descriptive, using the frequency of knowledge and perceptions about cough medicine self-medication in smokers and non-smoker students, followed by the chi-square test using the SPSS version 25 application to compare knowledge and perceptions about cough medicine self-medication in smoking and non-smoker students. The significance level was set at $p<0.05$.

Results

This study involved 124 people divided into two groups, namely smokers and non-smokers, with 62 people. The Brinkman index is a determination of smoking degree based on the multiplication of the number of cigarettes smoked in 1 day by the duration of smoking in years. The Brinkman index is divided into three categories: light smokers (0–199), moderate smokers (200–600), and heavy smokers (>600). One of the various types of cigarettes respondents consume is filtered cigarettes, with multiple brands of cigarettes sold in Indonesia. All respondents in this study were categorized as light smokers (100%) and used many types of cigarettes, namely filter cigarettes with various brands.[27,28]

This study involved male students aged between 18–25 years (Table 2). The highest number of students was in the smoking group aged between 22–23 years (35.48%) as well as in the non-smokers group aged between 22–23 years (40.33%).

The results of all respondents will then be grouped into three categories: high, medium, and low. Respondents included in the high category were those with values <14.67, while those in the medium category had a range of values between 14.67 and 18.33. Respondents with a high category have a value range of >18.33 (Table 3).

The perceptions explained by the respondents will be described according to the questions in the questionnaire based on the causes of coughing,

Table 1 Reliability and Validity Tests of the Questionnaire

Variables	Item	CITC	Cronbach's Alpha
Knowledge of self-medication cough	1	0.492	0.645
	2	0.442	
	3	0.570	
	4	0.548	
	5	0.442	
	6	0.501	
	7	0.653	
	8	0.435	
Perception of self-medication cough	1	0.464	0.615
	2	0.589	
	3	0.504	
	4	0.483	
	5	0.636	

Note: CITC: corrected item-total correlation

how to treat coughs, use of cough medicines, and self-medication services. Table 4 describes the distribution of the perception profile of cough medicine self-medication.

The results of interviews regarding perceptions of self-medication cough show that both groups agreed that coughing is a disorder that can interfere with daily activities (91.94% and 91.94%). Both groups also agreed that coughs are treated with medicine (75.81% and 58.06%) to reduce or eliminate cough symptoms (75.81% and 69.35%). Both groups also said that the cough smokers experienced would disappear without needing medicine or seeing a doctor (70.7% and 66.13%) (Table 4).

Most respondents in the smoker and non-smoker groups had a high level of knowledge (51.62% and 54.84%). The test results showed a significant difference in the level of expertise regarding cough self-medication between the two groups (p=0.000). Most respondents in the smoker group had a low level of perception (56.45%), while most respondents in the non-smoker group had a high level of perception (64.52%). The test results showed a significant difference in the level of perception regarding cough self-medication between the two groups (p=0.000) (Table 5).

Discussion

Most of the respondents agreed with the statement that coughing is a disturbance in the body that can interfere with daily activities. Coughing experienced by smokers is generally a normal thing to happen because coughing in smokers is caused by chemicals from cigarettes that irritate the respiratory tract.[29,30] Apart from nicotine, cigarettes contain tar that changes into a solid and builds up colored plaque when entering the mouth.[31] Smoking can cause periodontal disease and lesions on the oral mucosa. Nicotine stomatitis is inflammation caused by heat in the hard and soft palate.[32] Smoking can also cause

Table 2 Frequency Distribution of Respondent Characteristics

Characteristics	Smoker Group		Non-smoker Group	
	n=62	%	n=62	%
Age (years)				
18–19	8	12.90	12	19.35
20–21	17	27.42	20	32.25
22–23	22	35.48	26	41.95
24–25	15	24.20	4	6.45

Table 3 Knowledge Profile of Cough Medicine Self-medication

No.	Questionnaire Knowledge	Respondents Who Answered Correct			
		Smoker Group		Non-smoker Group	
		n=62	%	n=62	%
1	Cough was not a disease but a symptom of a disease.	49	79.03	45	72.58
2	Self-medicated cough medicines were free-class cough medicines marked with a green circle and limited free groups marked with a blue circle.	47	75.81	43	69.35
3	Cough medicine has two main functions, namely as a symptomatic drug (works to relieve symptoms) and quasi-medicine (works to cure disease).	51	82.26	45	72.58
4	If there was a statement regarding cough medicine: "2×1 tablet a day after eating." So, the statement means cough medicine is taken twice daily in the morning and afternoon.	37	59.68	37	59.68
5	Self-medication was the activity of selecting and using drugs without using a doctor's prescription or initiative to treat a diseased condition in the body.	43	69.35	49	79.03
8	Drugs that can be purchased for self-medication treatment are only drugs with free and limited over-the-counter classes.	51	82.26	50	80.65

Table 4 Profile Perception about Self-medication Cough

No.	Questionnaire Perception	Respondents Who Answered Agree			
		Smoker Group		Non-smoker Group	
		n=62	%	n=62	%
1	In your opinion, is coughing a disturbance in the body that can interfere with daily activities?	57	91.94	57	91.94
2	How do you treat a cough by taking medicine?	47	75.81	36	58.06
3	In your opinion, can taking cough medicines reduce or eliminate coughs?	47	75.81	43	69.35
4	In your opinion, will the cough experienced by a smoker go away on its own without having to take medication or see a doctor?	44	70.97	41	66.13
5	Have you followed the directions on the packaging label when taking cough medicine on a self-medicated basis?	48	77.42	48	77.42

Table 5 Level of Knowledge and Perception about Self-medication Cough

Variables	Smoker Group		Non-smoker Group		p
	n=62	%	n=62	%	
Knowledge					
High	32	51.62	34	54.84	0.000
Moderate	15	24.19	13	20.97	
Low	15	24.19	15	24.19	
Perception					
High	27	43.55	40	64.52	0.000
Moderate	0	0	0	0	
Low	35	56.45	22	35.48	

Note: chi-square test, significant p<0.05

premature aging of both the skin and the skin's supporting systems, such as bones and tissue.[33] This substance is considered a foreign body by the body, causing a spontaneous reflex from the body to expel the foreign substance by coughing. Coughing is a physiological reflex mechanism that protects the respiratory tract from harmful substances, which helps clear the airways from phlegm/mucus. Coughing itself is also an early sign of symptoms of a respiratory tract disease.[29,30]

Self-medication is the leading choice for the community in dealing with health complaints, so the role of self-medication cannot be ignored.[11] Self-medication, according to the World Health Organization, is the selection and use of modern, herbal, and traditional medicines by individuals to treat diseases or symptoms. The meaning of self-medication is that the patient himself chooses the drug without a prescription to treat his illness. Drugs that can be used in self-medication are mandatory pharmacy drugs (*obat wajib apotek*, OWA) or hard drugs that pharmacists can hand over to patients at pharmacies without a doctor's prescription, over-the-counter drugs, and limited over-the-counter drugs.[34,35] Self-medication can be a source of errors in medication (medication error). This condition occurs due to the patient's lack of knowledge about the drug and the disease.[36] Likewise, perceptual knowledge can also shape decision-making patterns about drugs and diseases patients suffer.

The results of this study are similar to previous studies by Lorensia et al.,[9] in 100 smokers, the type of cough experienced by smokers is a cough with phlegm and cough without phlegm, depending on the smoker's category. The use of self-medication cough medicines is one way that many active smokers do to reduce the incidence of coughs they experience. The knowledge of active smokers about cough still needs to be improved so that many smokers are still wrong in choosing and using cough medicine.

In the distribution profile of knowledge about cough medicine self-medication, the results obtained on the question cough is a disease, but a symptom of the disease were obtained from respondents who answered correctly,[9] in the smoking group as many as 49 people (79.03%). Meanwhile, 45 (72.58%) responded correctly in the non-smokers group. Previous research on 163 pedicab drivers showed that most respondents had a low knowledge of self-medication of cough medicine (97 of 163).9 The results of the perception of self-medication of cough medicine indicated that most respondents had a negative level (78 of 163).

In the distribution profile of knowledge about cough medicine self-medication, the results obtained on the question cough is a disease, but a symptom of disease was obtained from respondents who answered correctly in the smoking group as many as 49 people (79.03%). Meanwhile, 45 (72.58%) responded correctly in the non-smokers group. Cough is a natural process that protects the airway. Cough can occur spontaneously or voluntarily. Reviews of adult chronic coughs report that at least 40% of adults with chronic coughs have no medical explanation.[37]

On the question that cough medicine has two main functions, namely as a symptomatic drug (works to relieve symptoms) and quasi-active medicine (works to cure disease),[38] the results showed that the number of respondents who

answered correctly in the smoker group was 51 people (82.86%) and the non-smoker group the results were 45 respondents who answered correctly (72.58%).

Self-medication is the activity of selecting and using drugs without using a doctor's prescription or initiative to treat a disease condition in the body.[39] The results showed that the number of respondents who answered correctly in the smoker group was 43, with a percentage of 69.35%. In the non-smoker group, the results of respondents who answered correctly in the non-smoker group were 49 respondents with a percentage of 79.03%.

On the question of the pharmacist is someone who is fully responsible for all activities in the pharmacy, starting from receiving prescriptions, supplying and dispensing drugs and counseling, as well as procurement management and management of the pharmacy.[40] The results showed that the number of respondents answered correctly in the smoker group was 55 people (88.71%). In the non-smokers group, the results of respondents who answered correctly were 59 people (95.16%).

In the question In self-medication service activities, the information needed includes how to use it, side effects of the drug that can be caused, how to store it, how long to use the drug, the dosage of the drug, and matters that need special attention such as unwanted drug reactions (allergic reactions).[11] The results obtained were that the number of respondents answered correctly in the smoker group was 61 respondents with a percentage of 98.39%. In the non-smoker group, the results of respondents who answered correctly in the non-smoker group were 60 respondents with a percentage of 96.78%.

Conclusions

Based on the research results, there were significant differences in the level of knowledge and perceptions regarding self-medication of cough medicine between smokers and non-smokers. Suggestions for further research included developing health promotion regarding self-medication treatment of cough medicines, including the relationship between smoking and cough symptoms.

Conflict of Interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Cardiac Histopathology Alterations Induced by Subchronic Mangosteen Rind Extract in Wistar Rats

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Abstract

Mangosteen (*Garcinia mangostana* L.) is renowned for its potent antioxidant characteristics, including free radical scavenging, and its antibacterial, antifungal, anti-inflammatory, and antidiabetic properties. This study aims to assess the subchronic toxicity effects of ethanol extract from mangosteen rind on the cardiac histopathology of male and female Wistar rats. This research was a posttest-only control group design. Forty biological specimens from 40 Wistar rats were divided into four groups, a control group, and three treatment groups, which were given ethanol extract of mangosteen rind with doses of 250 mg/kg, 500 mg/kg, and 1,000 mg/kg for 28 days. Cardiac specimens were prepared and examined using hematoxylin-eosin (HE) staining at the Anatomical Pathology Laboratory of Universitas Jenderal Achmad Yani in December 2021. The findings indicated that prolonged ingestion of large amounts of ethanol extract from mangosteen rind can cause toxic effects characterized by an inflammatory response in cardiac tissue. No fibrosis or hypertrophy was detected; however, inflammatory changes such as the presence of inflammatory cells, vacuolar changes, and neovascularization were observed. The inflammation observed might be due to excessive antioxidant administration leading to oxidative stress. Inflammatory cells may trigger fibrotic remodeling in the heart. The difference in the quantity of inflammatory cells between male and female rats suggests that gender influences the inflammatory response. Overall, administration of ethanol extract from mangosteen rind at doses of 250 mg/kg, 500 mg/kg, and 1,000 mg/kg cause subchronic toxicity effects on the heart histopathology of Wistar rats, marked by inflammation.

Keywords: Cardiac histopathology, ethanol extract, mangosteen, subchronic toxicity, Wistar rats

Introduction

Herbal medicines are pharmaceuticals derived from plants that have undergone extraction to be transformed into liquids, powders, or pills without including chemical compounds.[1] The advantages of using plants as medicinal components are that they are preferred over synthetic substances because the general public believes that herbal medicines have fewer side effects than synthetic medicinal ingredients.[2–3] Indonesia is a lucrative market with significant potential for herbal medicines and phytopharmaceuticals.4 Indonesia has utilized different varieties of plants as medicinal components, including the mangosteen fruit (*Garcinia mangostana* L.).[4–5]

Alpha mangostin and xanthone 5, 10, 20 mg/BW showed antidiabetic effects on fasting blood glucose level, insulin plasma, and Langerhans islet.[9] Alpha mangostin 5, 10, 20 mg/BW, xanthone 10, and 20 mg/BW showed potential effects on preventing tolerance and increasing peroxisome proliferator-activated receptor γ (PPARγ) expression on adipocytes.[10] GLUT-4 expressions also increased in adipocytes treated with 3.125 mM, 6.25 mM, and 25 mM α–mangostin, equivalent to pioglitazone. GLUT-4 expressions in mice cardiac-muscle cells that were treated with α-mangosteen, xanthone, glibenclamide, and metformin significantly increased when compared to the positive control group, except in the group treated with xanthone 5 mg/kgBW.[11]

To ensure the safety of utilizing natural ingredients as medicinal substances, it is imperative to undergo multiple phases of testing, including the assessment of toxicity.[12] A toxicity test is used to identify a harmful impact on a

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substance within a living system and gather data on the typical relationship between dosage and response.[13] The LD50 values were determined at 625 mg/kg, 1,250 mg/kg, 2,500 mg/kg, and 5,000 mg/kg. The results were classified as a non-toxic, practical category.[14]

The oral subchronic toxicity test is used to identify any toxic effects that may occur after repeated administration of the test preparation.[14] Other studies discovered that administering ethanol extract of mangosteen rind at doses of 250 mg/kgBW, 500 mg/kg BW and 1,000 mg/kgBW did not result in any subchronic toxicity effects on liver damage. This conclusion was reached by evaluating the serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) levels in rats. The administration of the mangosteen rind ethanol extract at a dose of 250 mg/kg BW resulted in elevated SGPT levels in male rats. Similarly, female rats also experienced an increase in SGOT levels after receiving the same extract dose. However, these increases did not reach toxic levels.[15]

The cardiac system serves as a pump that circulates blood throughout the body. The cardiac organ is composed of cylindrical cardiac muscle fibers located within the walls and septum of the heart.[16] Any harm inflicted upon this organ will disturb the functioning system within the human body. The cardiac organ is a vulnerable organ that different types of chemicals can harm. These toxic substances can affect the myocardium via neural or vascular pathways and circulate throughout the body.[17] Possible pathologies that may arise include cellular hypertrophy and fibrosis, which can be attributed to tissue damage.[18,19] Oxidative stress can lead to tissue damage. The most frequently observed histopathological findings in the cardiac are cardiomyocyte abnormalities, including hypertrophy and disorganized myocytes, as well as interstitial fibrosis. Hypertrophic cardiopathy is one of the diseases associated with these abnormalities.[18]

This study aims to investigate the harmful impacts of 28 days of orally administering ethanol extract from mangosteen rind at doses of 250 mg/kgBW, 500 mg/kgBW, and 1,000 mg/kgBW on the cardiac histopathology of Wistar rats that may cause histopathological changes like hypertrophy, inflammation, and fibrosis, while other parameters of subchronic toxicity test will not be reported in this study.

Methods

This study utilized male and female Wistar rats that met the following criteria: age range of 6–8 weeks, weight range of 150–200 g, and acclimatization period of seven days before treatment. AcclimatizationAcclimatization was conducted under standard room temperature conditions, with a light-dark cycle of 12 hours each. The animals were provided with ad libitum access to water and food and then randomly assigned to either the control or experimental groups.

The dosage used is determined following the guidelines provided by the National Agency of Drug and Food Control and the Organization for Economic Co-operation and Development (OECD). The experimental animals are divided into four groups, each comprising ten rats, with five rats of female sex and five rats of male sex. The control group received only water and feed. In contrast, the treatment group was administered water, feed, and a dose of mangosteen rind ethanol extract orally in varying amounts of 250 mg/kgBW (low dose), 500 mg/kgBW (medium dose), and 1,000 mg/kgBW (high dose), respectively. On the 29th day, animals were euthanized using the cervical luxation procedure after being anesthetized with ketamine. Cardiac specimens were prepared and examined at the Anatomical Pathology Laboratory of Universitas Jenderal Achmad Yani.

The experimental protocols adhered to the guidelines outlined in the Guide for the Care and Use of Laboratory Animals and were approved by the Health Research Ethics Committee of the Faculty of Medicine Universitas Padjajaran Bandung, under ethical approval number 686/UN6.KEP/EC/2021.

The organs were immersed in a 10% neutral buffered formalin (NBF) solution for fixation. Subsequently, the tissue undergoes a trimming procedure, precisely cut and placed into a cassette. The cassette is then subjected to dehydration, during which it is impregnated with paraffin and cleared using graded alcohol. The subsequent step involves the embedding of samples for printing and the slicing of tissues.[20,21]

In this study, the dye hematoxylin-eosin (HE) was utilized to enhance visibility under a

microscope and facilitate differentiation of the examined tissue components. Hematoxylin is a dye that stains explicitly the cell nucleus, while eosin acts as a contrasting dye. The preparations were submerged in a container filled with 100% xylol for 12 minutes to remove the paraffin. Perform dehydration using absolute ethanol I and II for 5 minutes, followed by the addition of 70%, 80%, and 96% alcohol for another 5 minutes. The slides underwent a 12-minute washing process with running water, followed by a 1-minute immersion in Mayer's hematoxylin. They were rewashed with running water and stained with eosin for 5 minutes. The preparations were rinsed twice with a solution of 75% alcohol. The preparations underwent a process of dehydration by being immersed in 70% alcohol eight times. Subsequently, they were exposed to 80% alcohol, 96% alcohol, and absolute ethanol I and II for 10 minutes each. The preparations were immersed in xylol for 12 minutes. Moreover, the slide is affixed by placing a cover glass over it.[20–22]

The ultimate phase of the procedure involves examining the tissue that has undergone the attachment process using an Olympus CX-23 microscope. The microscope employed was an optical microscope with a magnification of 400×, observing five fields of view for each microscopic sample. The preparatory reading method employs visual examination by the researcher to observe the damage to cardiac cells. This method involves straightforward and uncomplicated observations, which an anatomical pathology specialist subsequently validates.

The study examined the histopathological changes in each preparation, which were categorized according to the dosage of each treatment. The histopathological variables, including normal hypertrophy, inflammation, and fibrosis, will be summarized descriptively. Normal is characterized by the presence of cardiomyocytes and connective tissue of topical size and shape. Hypertrophy is characterized by abnormalities in the cardiomyocytes, such as hypertrophy (enlargement) and irregularly shaped cells. The presence of scar tissue characterizes fibrosis.[17,18,20–23]

Results

Figure 1 shows the histopathology images of each study group, male and female Wistar rat. The cardiac muscle cells in the negative control group exhibited no cellular abnormalities in the images. There are no structural alterations, such as an increase in muscle mass and enlargement of myocytes.

The image indicates that the majority of the myocytes exhibit a normal size. Subsequent to necrosis, fibrosis, characterized by a noticeable augmentation in collagen fibers, was not developed. No structural changes in hypertrophy were observed in the cardiac structure of male subjects in test group 1. The microscopic image continues to display myocytes of typical size and shape. No fibrosis is present in the image. However, inflammatory cells are present, suggesting an inflammatory process occurring in the cardiac muscle cells. No structural changes related to hypertrophy or fibrosis were observed in the cardiac structure of males in test group 2. The histopathological examination reveals myocytes of normal size. No fibrosis was detected in the image. However, the presence of inflammatory cells is evident.

No structural changes indicative of hypertrophy or fibrosis were observed in the cardiac structure of the male subjects in test group 3. The microscopic image depicts myocytes of typical dimensions. No fibrosis is present in this image. However, there is evidence of vacuolar degeneration in the cells. Microscopic examination of test group 3 reveals the presence of neovascularization. It demonstrates the presence of discernible histopathological distinctions among test groups 1, 2, and 3 compared to the control group, manifested as indications of inflammation.

Microscopic readings of the female cardiac organs test group 1 of the female subjects continued to exhibit myocytes that were both normal in size and regular in shape (Figure 2). No evidence of fibrosis is present in the image. No structural changes, such as hypertrophy or fibrosis, were observed in the cardiac structure of females in test group 2. The histopathological examination reveals myocytes of normal size. No fibrosis was detected in the image. However, there is evidence of an inflammatory process characterized by vacuolar and inflammatory cells. The examination of the three females did not uncover microscopic alterations in the form of hypertrophy or fibrosis. The microscopic image displays myocytes of regular dimensions.

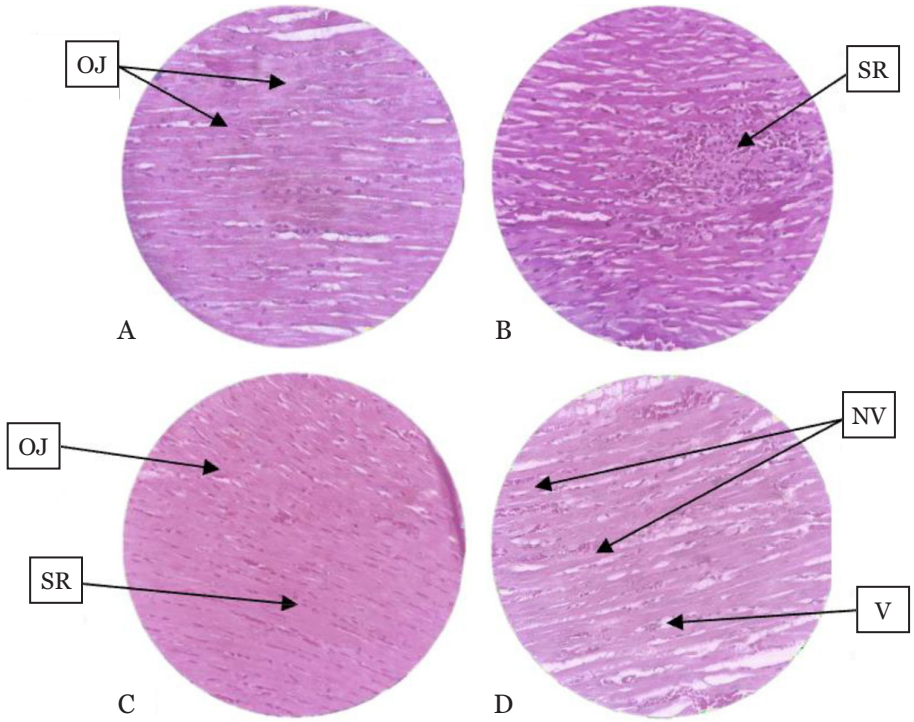

Figure 1 Histopathological Picture of 4 Male Test Groups with HE Staining (400×)

Note: (A) control group; (B) test group 1 ethanol extract of mangosteen rind 250 mg/kgBW; (C) ethanol extract of mangosteen rind 500 mg/kgBW; (D) test group 3 ethanol extract of mangosteen rind 1,000 mg/kgBW; OJ: cardiac muscle cell; SR: inflammatory cells; V: vacuolar; NV: neovascularization

No fibrosis is present in this image; however, neovascularization indicates an inflammatory process in the cardiac muscle cells. There are discernible histopathological disparities in inflammatory indicators among test groups 1, 2, and 3 compared to the control group.

Discussion

Following histopathological examination, no evidence of fibrosis or hypertrophy was observed. However, an inflammatory process was detected. It pertains to administering doses of mangosteen rind ethanol extract, categorized into three levels: 250 mg/kgBW, 500 mg/kgBW, and 1,000 mg/kgBW. Mangosteen contains various antioxidants, such as neutralizing free radicals, fighting against bacteria and fungi, reducing inflammation, and acting as an antihistamine.[8,24] Overconsumption of antioxidants can induce oxidative stress, harming organ cells.[19]

Cardiac hypertrophy can develop when the heart adjusts to a higher workload, producing additional sarcomeres and enlargement of the myocytes.[14] The study did not observe any signs of hypertrophy, indicating that the dose of mangosteen rind ethanol extract had no impact on hypertrophy in the cardiac organs of Wistar rats. The inflammatory process is a stage that is associated with fibrosis. The cell types that contribute to fibrotic remodeling of the heart include macrophages, mast cells, lymphocytes, cardiomyocytes, and vascular cells. These cells either directly produce matrix proteins, leading to fibrosis, or indirectly secrete fibrogenic mediators.[25]

This study did not observe any fibrosis, but it found an inflammatory process characterized by inflammatory cells, vacuolar changes, and increased vascularity. These findings suggest that the dose of ethanol from mangosteen rind can induce the release of inflammatory cell mediators in the cardiac organs of Wistar strain rats, potentially leading to fibrosis. Myocarditis is an inflammatory condition that affects the heart muscle cells, potentially leading to tissue

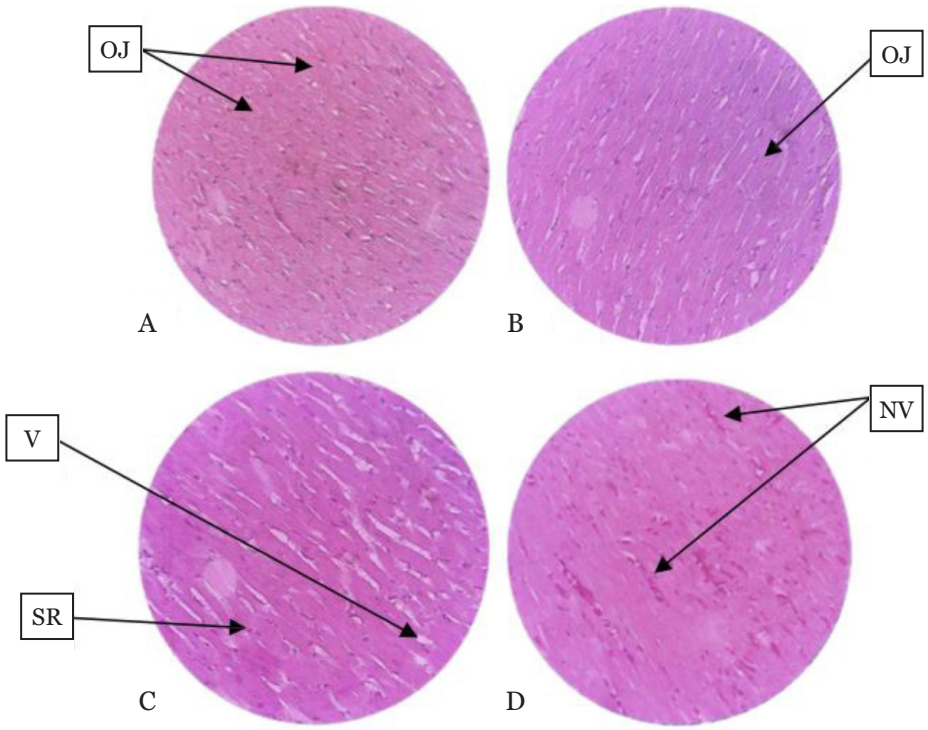

Figure 2 Histopathological Features of 4 Test Groups of HE-stained Females (400×)

Note: (A) control group; (B) test group 1 ethanol extract of mangosteen rind 250 mg/kgBW; (C) ethanol extract of mangosteen rind 500 mg/kgBW; (D) test group 3 ethanol extract of mangosteen rind 1,000 mg/kgBW; OJ: cardiac muscle cell; SR: inflammatory cells; V: vacuolar; NV: neovascularization

degeneration or necrosis.[26] The research findings reveal a disparity in the number of inflammatory cells between females and males, with males exhibiting a higher count. This discrepancy may be attributed to factors that induce inflammation, including gender.

Environmental factors, nutritional status, species, age, and gender can all influence the inflammatory response, causing it to vary between individuals. There may be variations between males and females in their immune system's reactions to foreign substances and their substances and disparities in their natural and acquired immune responses. Genes located on sex chromosomes and sex hormones, such as estrogen, progesterone, and androgen, play a role in the distinct control of immune responses between males and females. Males and females in mammals generally exhibit variations in the number and activity of cells involved in innate and adaptive immune responses, resulting in lower immune responses in males.[27]

Males exhibit a greater abundance of natural killer cells, while females demonstrate higher activity levels in neutrophil and macrophage phagocytes. Male mice exhibit a larger thymus, a higher quantity of thymocytes, and a distinct distribution of thymocyte subsets compared to female mice. The thymus is crucial in forming the immune system by generating a reservoir of peripheral T lymphocyte cells.[28,29] Research limitation in this study was inflammation was not included as a research variable by the researchers.

Conclusions

The administration of ethanol extract of mangosteen rind had a subchronic toxicity effect on the histopathological features of the cardiac tissue in Wistar rats, resulting in inflammatory features. The impact on male and female animal groups reveals a disparity in the number of inflammatory cells, with male rats exhibiting a higher quantity of inflammatory cells compared to female rats.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

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RESEARCH ARTICLE

Impact of Propolis Administration on Osteocrin Expression and Osteoblast-to-osteoclast Ratio in the Femurs of Rats Fed a High-fat Diet

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Abstract

A high-fat diet (HFD) is associated with bone inflammatory processes that can affect bone remodeling balance. Osteocrin produced by periosteal osteoblasts correlates with osteoblast activity, is expressed on osteoblast-derived cells, and is localized in osteoblasts and young osteocytes. Propolis is an antioxidant and anti-inflammatory in bone remodeling by inhibiting proinflammatory factors NF-κB and COX-2, reducing inflammatory suppression of cytokines responsible for osteoclast differentiation and osteoblast apoptosis. The flavonoid content increases the production of nitric oxide and osteoprotegerin, which enhances osteoblastogenesis. This study determined the effect of propolis administration on bone formation and resorption in bone previously damaged by an HFD. This research was conducted in the Animal Laboratory of Postgraduate Building Dipati Ukur and Genetics and Molecular Laboratory Eycman Building, Faculty of Medicine, Universitas Padjadjaran. The research time was from January 2023–May 2024. Male Wistar rats were divided into four groups: normal chow diet (NCD), NCD with propolis administration, HFD, and HFD with propolis administration. The 12-week-old rats were given an HFD for 12 weeks and then treated with propolis at a 300 mg/kgBW dose for nine weeks. The administration of propolis increased the ratio of osteoblasts-osteoclast cells in the femur of the HFD rats but did not affect periosteal osteocrin expression.

Keywords: Bone, HFD, osteoblast, osteoclast, osteocrin

Introduction

The public's consumption of high-fat foods and beverages increases as they taste good.[1] A high-fat diet (HFD) is defined as consisting of at least 35% of the total calories consumed from unsaturated and saturated fat. High-fat diets influence the development of osteoporosis by affecting bone formation and resorption.[2] A high-fat environment can inhibit osteoblast proliferation and differentiation of other osteogenic cells, increase skeletal sclerostin expression, cause osteocyte lacunocanalicular damage, and increase local glucocorticoid signaling in bone, thereby affecting glucocorticoid signaling in osteoblasts and osteocytes. Bone marrow adipose tissue also showed decreased mRNA levels of inflammatory genes, such as TNF-α, IL-1β, and lipocalin 2.[2,3] Rats fed a high-fat diet had lower bone mineral content, and decreased structural parameters on histomorphometric examination by peripheral quantitative computed tomography analysis.[4]

Osteocrin is a humoral factor produced by periosteal osteoblasts that regulate growth plate growth by increasing the proliferation of C-type natriuretic peptide (CNP) to regulate bone formation and chondrocyte maturation.[5] In-vivo studies by Bord et al.[6] showed that osteocrin is a bone-active molecule expressed on osteoblast-derived cells, localized on osteoblasts and young osteocytes, and correlated with osteoblast activity.

Propolis is collected by honeybees and used for many purposes due to its antioxidant, anti-inflammatory, antimicrobial, anticancer, analgesic, antidepressant, and anxiolytic properties.[7] It contains more than 108 active compounds, including antioxidant flavonoids, which are recognized for their diverse health effects.[8,9] Flavonoids stimulate osteoblastogenesis by increasing nitric oxide and osteoprotegerin production and inhibiting

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proinflammatory factors such as NF-κB and COX-2 that activate osteoclasts and thus stimulate osteoclastogenesis.[10,11] Propolis has been shown to enhance the bone remodeling process by reducing inflammatory suppression of cytokines responsible for osteoclast differentiation and osteoblast apoptosis.[12] A previous in-vivo study by Darmadi and Mustamsir[13] showed that propolis increased the number of osteoblasts and chondrocyte protein and decreased the number of osteoclasts in the femur of Wistar rats. Studies by Juwita et al.[14] showed an increase in the average ratio of osteoblasts to osteoclasts in the osteoporosis Wistar rats that were ovariectomized and given propolis orally. It indicates an increase in bone formation compared to the resorption due to a rise in osteoblasts and a decrease in osteoclasts. However, femoral metaphysis revealed that propolis does not affect cortical bone thickness. Therefore, this study was designed to determine the effect of propolis administration on bone formation and resorption in bone previously damaged by a high-fat diet.

Methods

The high-fat diet rat model derived from male 12-week-old Wistar rats was divided into four groups: normal chow diet (NCD), NCD with propolis administration, HFD, and HFD with propolis administration. The rats were fed an HFD (34.9% fat, 26.25% protein, and 26.3% carbohydrates) for 12 weeks, then treated with propolis at 300 mg/kgBW daily for nine weeks. Right and left femur bone samples were collected when the rats were 33–34 weeks old and kept in stored biological material.[15] This research was conducted in the Animal Laboratory of Postgraduate Building Dipati Ukur and Genetics and Molecular Laboratory Eycman Building, Faculty of Medicine, Universitas Padjadjaran. The research time was in January 2023–May 2024.

Osteocrin expression analysis using total RNA was extracted from stored left femur bone tissue using the Quick-RNA™ Miniprep-Kit and reverse transcribed using the SensiFAST cDNA synthesis kit according to manufacturer instructions. Osteocrin mRNA expression was quantified by real-time qPCR using the SensiFAST™ SYBR® No-ROX Kit.

Histological analysis of osteoblasts and osteoclast cells using right femur bone tissue that had previously been stored in 10% formalin was performed using right femur bone tissue that had previously been stored in 10% formalin. The tissue was decalcified in 8% HCl for ten weeks before being embedded in paraffin blocks and cut into four μm sections. The specimens were deparaffinized with xylene and rehydrated with graded alcohol before HE staining. The slides were examined using a Zeiss Image Z2 microscope at a magnification of 100× in three selected fields of view, and photomicrographs were taken of representative areas.

Data analysis is expressed as the mean±SD of triplicate measurements. The normality of the data was assessed using the Shapiro-Wilk test, with normally distributed data analyzed by one-way ANOVA and the Kruskall-Wallis test performed on data that is not normally distributed. The post hoc test was performed if the p-value was <0.05. Differences between groups were assessed using the independent t-test for normally distributed data and the Mann-Whitney test for data that were not normally distributed.

Ethical approval for this research was approved by the Research Ethics Committee of Universitas Padjadjaran (number 1456/UN6. KEP/EC/2023).

Results

There was no significant difference in osteocrin expression in the rat femur between the treatment groups (Table 1). Still, in general, HFD groups with or without propolis had lower median osteocrin expression than the NCD groups with or

Table 1 Osteocrin mRNA Expression in the Femur of Male Wistar Rats

Variables	NCD	NCD+propolis	HFD	HFD+propolis	p
Mean±SD	0.33±0.28	0.30±0.20	0.11±0.05	0.16±0.14	0.152[a*]
Median (min–max)	0.28 (0.06–0.74)	0.22 (0.14–0.73)	0.11 (0.04–0.19)	0.09 (0.04–0.41)	
Normality test[b]	0.263[+]	0.025[++]	0.243[+]	0.146[+]	

Note: n=3, [a]Kruskall-Wallis test, [b]Shapiro-Wilk test, [*]not significant, [+]normal data distribution, [++]abnormal data distribution

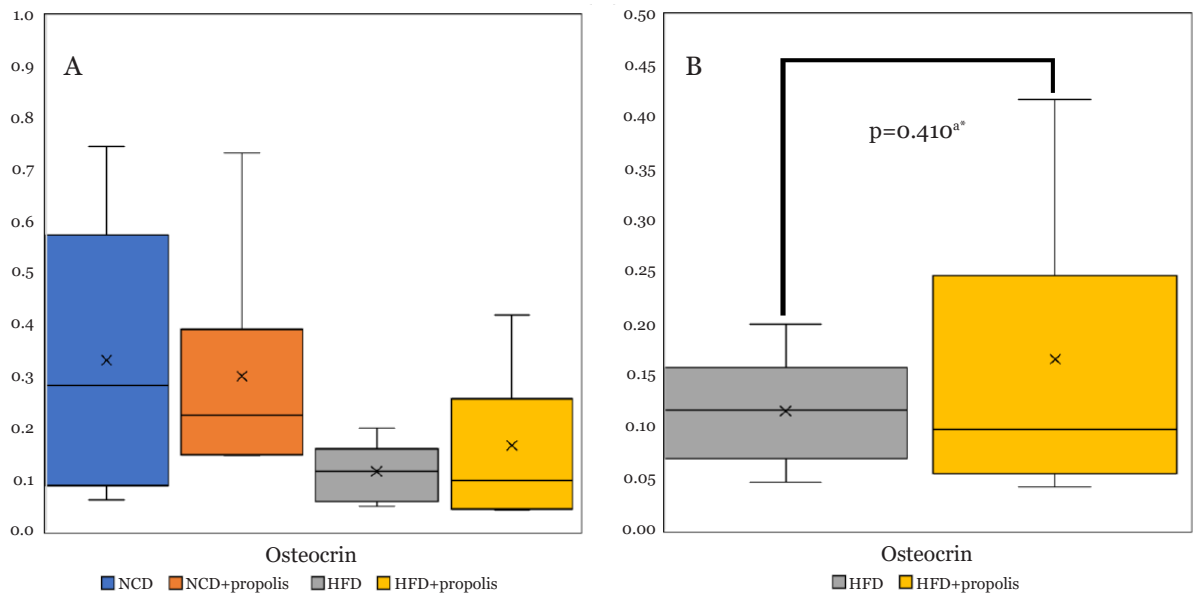

Figure 1 Comparison of Osteocrin mRNA Expression
Note: (A) four rat groups, (B) HFD groups, aindependent t-test, *not significant

without propolis (Figure 1A). Furthermore, there was a trend for increased osteocrin expression in the propolis-treated HFD rats compared to the HFD group, although this did not reach statistical significance (Figure 1B).

The osteoblast-osteoclast ratio in the femur of the four rat groups was significantly different with a p-value of 0.001 (Table 2), with the lowest ratio observed in the HFD groups (Figure 2A). An independent t-test of the HFD groups revealed that propolis significantly increased the test ratio (Figure 2B).

Discussion

A high-fat diet can lead to changes in bone structure due to a decreased number of osteoblasts and pre-osteoblasts, thus affecting bone remodeling. Progenitor cells undergoing adipogenesis can decrease progenitor cells, recruitment to osteoblastic cells, and bone formation. In addition, there is an increase in osteoporosis and increased osteoclast activity.[2,16]

Polyphenolic compounds in propolis act as antioxidants by inhibiting lipid peroxidation to protect bone and prevent excessive bone resorption, which can reduce bone density and strength through the clearance of reactive oxygen species. Flavonoids stimulate osteoblastogenesis by increasing nitric oxide and osteoprotegerin production and inhibiting proinflammatory factors such as NF-κB and COX-2 that activate osteoclasts and thus stimulate osteoclastogenesis.[10,11]

In this study, the lowest osteoblast-osteoclast ratios were observed in the femurs of the rats fed an HFD, with the highest ratio in the propolis-treated normal diet group. Although there was no significant difference in osteocrin expression between groups, the HFD groups tended to have the lowest osteocrin mRNA expression. It is hypothesized that the bone resorption caused by 12 weeks of HFD feeding and bone remodeling caused by four weeks of propolis treatment had no

Table 2 Osteoblast-osteoclast Ratio in the Femur of the Four Rat Groups

Variables	NCD	NCD+propolis	HFD	HFD+propolis	p
Mean±SD	7.96±2.33	12.37±7.24	3.11±0.98	4.84±1.67	0.001[a*]
Median (min–max)	6.92 (6.02–11.67)	11.30 (0–23.24)	2.83 (2.01–4.76)	4.51 (2.50–8.00)	
Normality test[b]	0.12[+]	0.46[+]	0.35[+]	0.49[+]	

Note: [a]One-way ANOVA test, [b]Shapiro-Wilk test, [*]significant, [+]normal data distribution

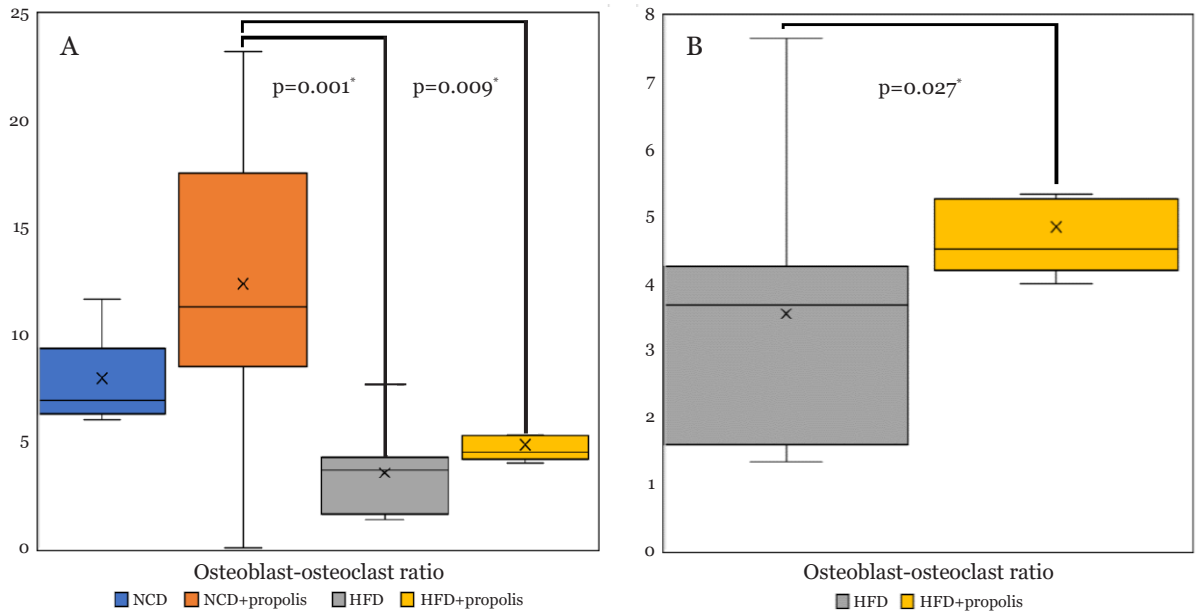

Figure 2 Comparison of the Osteoblast-osteoclast Ratio
Note: (A) four rat groups, (B) HFD groups, independent t-test, Mann-Whitney test, *significant p<0.05

observable effect on the periosteum because these processes begin in the bone endosteum, whereas osteocrin is in the periosteum. The periosteum is the outermost fibrous layer that maintains the bone structure, and the cambium layer contains osteoprogenitor cells. The endosteum layer consists of connective tissue, osteoblasts, pre-osteoblasts, and osteoclasts and is involved in bone repair and remodeling.[17] Osteocrin produced by periosteal osteoblasts is a mechanotransducer that regulates growth plate growth by increasing chondrocyte proliferation and maturation for bone elongation. CNP stimulates the osteogenic differentiation of periosteal osteoprogenitors to induce bone formation.[18]

In this study, the rats were terminated at 31–33 weeks of age, which reflects 24–25 years in humans. It is suspected that at this age, the process of bone elongation has decreased along with the closure of the epiphyseal plate. Rat regrowth peaks at 4–6 months of age.[19,20] Osteocrin for bone lengthening correlates with increasing CNP. Osteocrin expression is localized in osteoblasts and young osteocytes during bone formation and development and will decrease with age.[18]

Conclusion

The administration of propolis increases the ratio of osteoblasts to osteoclasts in the femur of rats fed a high-fat diet.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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RESEARCH ARTICLE

Cytotoxicity Effect of Aqueous Propolis Extract of *Geniotrigona thoracica* Sumatrans on Colo-201 Colon Cancer Cell Line and Senescence Colo-201 Colon Cancer Cell Line Induced by Low-dose Doxorubicin

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Abstract

Propolis, a resinous compound honeybees produce, demonstrates an extensive spectrum of powerful biological properties. However, the anti-cancer activity of propolis derived from *Geniotrigona thoracica* Sumatrans has yet to be reported. Thus, we sought to investigate the cytotoxicity of aqueous propolis extracts from *Geniotrigona thoracica* Sumatrans against Colo-201 colon cancer cell line and senescence Colo-201 colon cancer cell line induced by low-dose doxorubicin. This study was conducted at the Parasitology Laboratory of Human, Safety, and Environment, Universitas Padjadjaran Bandung from January to May 2024. This study assessed cell viability using the WST-1 test. Non-induced Colo-201 cells were treated with an aqueous extract of propolis (AEP) 100 ppm, or 5-fluorouracil (5-FU) 5 mg/ml as the positive control or water as a vehicle on untreated control. Colo-201 senescence was induced by doxorubicin 0.1 µM for three days. Doxorubicin-induced Colo-201 senescence was then treated with AEP 100 ppm, with 5-FU 5 mg/ml as the positive control, or with the combination of AEP 100 ppm and 5-FU 5 mg/ml, or water as a vehicle on untreated control. The data were analyzed using SPSS version 25.0, a one-way ANOVA, and Tukey's post hoc test. The results showed that AEP has cancer-killing effects on Colo-201 cells and Colo-201 senescent cells induced by low-dose doxorubicin. AEP-treated Colo-201 cells and Colo-201 senescent cells induced by low-dose doxorubicin viability were significantly reduced to 37.15% and 13.72%, respectively, although slightly higher than those of the 5-FU-treated one at this concentration. There was also a decrease in the cancer-killing effect of 5-FU from 88.55% in non-induced Colo-201 cells to 41.5% in the doxorubicin-induced Colo-201 senescence model. In conclusion, aqueous extract of propolis from *Geniotrigona thoracica* Sumatrans showed cancer-killing-effects both on the Colo-201 colon cancer cell line and senescence Colo-201 colon cancer cell line induced by low-dose doxorubicin.

Keywords: Aqueous extract of propolis, Colo-201 cells, colon cancer cell line, fluorouracil, *Geniotrigona thoracica* Sumatrans, senescence, WST-1 assay

Introduction

Cancer is a broad term for many diseases affecting any body region. Other terminology used include malignant tumors and neoplasms. One distinguishing aspect of cancer is the rapid formation of aberrant cells that grow past their normal borders and eventually infiltrate neighboring sections of the body and spread to other organs; this process is known as metastasis. The leading cause of cancer-related death is widespread metastases. Cancer is the most common cause of death worldwide, accounting for approximately ten million deaths by 2022. In 2022, the most prevalent new cancer cases were lung cancer (2.48 million new cases), breast cancer (2.3 million new cases), colorectum (1.92 million new cases), prostate cancer (1.46 million new cases), and stomach cancer (968 thousand new cases). In Indonesia, based on Global

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Conservatory Cancer 2022, the number of new cases of cancer was 408,661, with a death toll of 242,988.[1] Based on the Indonesia Basic Health Survey (*Riskesdas*) in 2018, the prevalence of cancer in Indonesia is 1.8 per 1000 population.[2] It is the second most prevalent new cancer case among men (29 thousand new cases) and the fourth among men and women (35 thousand new cases).[3]

In 2022, Hanahan[4] edited and expanded the list of cancer hallmarks as the understanding of cancer mechanisms deepened. In the updated list of cancer hallmarks, senescent cells have been added to the list of new cancer hallmarks. Cell senescence is characterized by irreversible cell cycle arrest by causing telomere shortening.[5] Many chemotherapeutic drugs, such as doxorubicin (Dox), affect the cellular states of cancer cells, including senescence induction.[6] Dox is frequently used for the treatment of breast, esophageal, liver, and other cancers because it triggers cell growth arrest with senescent markers.[7] Dox causes senescence through a p53-dependent mechanism and telomere disruption in various malignancies.[8] Nevertheless, cellular senescence suppresses proliferation activity; these cells will continue to be metabolically active and contribute significantly to developing drug resistance and tumor recurrence.[9] 5-fluorouracil (5-FU) is the primary chemotherapeutic drug used in the treatment of colorectal cancer. Cardiotoxicity is a relatively infrequent but concerning side effect of 5-FU therapy. This condition is especially troublesome in the context of colorectal cancer since 5-FU is one of the essential components of first-line treatments.[10]

Propolis is a natural substance produced by honey bees from numerous botanical resources. It has become recognized for its pharmacological benefits, including antibacterial, antiviral, anti-inflammatory, and anti-cancer properties.[11] For example, propolis from *Tetragonula sapiens* shows the prospect of decreasing diabetes and hypertension.[12] In recent years, substantial in vitro and in vivo research has revealed that propolis has anti-cancer potential. Propolis inhibits cancer cell proliferation, induces apoptosis by regulating different signaling pathways and halting the tumor cell cycle, induces autophagy and epigenetic modulations, and inhibits tumor invasion and metastasis. Propolis targets cancer-related signaling pathways, including p53, β-catenin, ERK1/2, mitogen-activated protein kinase (MAPK), and NF-κB.[13]

Propolis is a resinous mixed form that includes beeswax and partially digested exudates from plant leaves and buds. Its chemical composition changes substantially according to the bee species, geographic area, plant type, and meteorological conditions. Propolis is well known for its antioxidative, antibacterial, anti-inflammatory, and anti-cancer effects.[14] Studies have shown that the presence of caffeic acid phenethyl ester, artepillin C, and chrysin is responsible for propolis' anti-cancer properties. The majority of earlier research revealed that propolis and its active chemicals prevent cancer progression by targeting numerous signaling pathways, including phosphoinositide 3-kinases (PI3K)/AKT and MAPK signaling molecules, and causing cell cycle arrest. Propolis' anti-cancer actions are broad since it targets various cancer metabolic targets. Critical pathways for cancer treatment include preventing metastatic spread, inhibiting NF-κB nuclear localization, regulating gene expression, inactivating matrix metalloproteinases, activating tumor suppressors, and altering TNF-related apoptosis-inducing ligand resistance.[15]

In Indonesia, there are several types of honey-producing bees. A recent study revealed that Indonesian stingless bee propolis collected from South Sulawesi, Bintan, and Lampung may include a wide range of phytochemical substances and antioxidant compounds.[16] Another honey-producing bee is the bees from genus *Trigona*. *Trigona* sp. is a species of bee distributed on the islands of Sumatra, Kalimantan, Java, and Maluku. Propolis from *Trigona incisa* and *Trigona fusco-balteata*, native to East Kalimantan, Indonesia, has in vitro cytotoxic activity against human cancer cell lines.[17] *Trigona incisa* propolis had the highest in vitro cytotoxicity against the SW620 colon cancer cell line, with 6% cell survival at 20 μg/ml concentration. The following study on propolis of *Trigona incisa* revealed that it has moderate in vitro anti-cancer effect on human cancer cell lines, and cardol or 5-pentadactyl resorcinol was shown to be the main active component, causing apoptosis in SW620 cells within 6 hours and cell cycle arrest at the G1 subphase.[18] However, no research has been conducted on propolis produced from *Geniotrigona thoracica*

Sumatrans. Therefore, its anti-cancer activity is unknown. Thus, we sought to investigate the cytotoxicity of the aqueous extract of propolis of *Geniotrigona thoracica* Sumatrans on Colo-201 colon cancer cell line and senescence Colo-201 colon cancer cell line induced by low-dose doxorubicin.

Methods

Raw propolis used for this study was purchased from beekeepers in Sumatera, Indonesia. This propolis was used in this study because it had previously been checked in a certified laboratory using gas chromatography-mass spectrometry tools. Raw propolis purchased from beekeepers and processed by PT Liberta was extracted using the maceration method with water as the solvent. The resulting solution was thickened using a rotary evaporator to form a paste, which was then dried in a sterile environment to obtain an aqueous extract of propolis (AEP). The dried extract was dissolved in sterile distilled water, sonicated for 4×30 minutes, and filtered through a 0.22-micron membrane to ensure sterility. The final concentration of the AEP solution used in this research was 100 ppm.[19]

This study was conducted at the Parasitology Laboratory of Human, Safety, and Environment (HSE), Universitas Padjadjaran from January to May 2024. The Parasitology Laboratory of HSE at Universitas Padjadjaran provided the Colo-201 colon cancer cell line [ATCC CCL-224], which Ehime University Japan had given. Cells were cultured in RPMI 1640 [Corning 10-040-CV], 10% Panexin basic [PAN Biotech P04-96900], 100 U ml-1 penicillin, and 100 μgml^{-1} streptomycin [PAN Biotech P06-017100], and then incubated at 37°C in a humidified atmosphere with 5% CO^2 until 80–90% confluence. The medium for growth was discarded, and cells were treated with trypsin-EDTA (Servicebio G4001). Tripsynization was put off by adding an equal volume of growth medium. Cells were suspended and placed in a tube, then centrifuged at 500 ×g for 5 minutes. The supernatant was discarded, and the pellets were resuspended in a 4–5 ml growth medium. The cell suspension was transferred into a T-flask containing a growth medium with a cell density of 10,000/cm^2. Medium was renewed every two days. Cells were incubated at 37°C with 5% CO^2.[20]

For senescence induction, 0.1 μM Dox was used to induce senescence on the Colo-201 colon cancer cell line because previous studies have shown that 0.1 μM Dox-induced senescence in the cancer cell line.[21] Cells were seeded at a density of 10 or/cm^2 for 24 hours and then treated with 0.1 μM Dox for three consecutive days to induce senescence of Colo-201 cells. The Colo-201 senescent cells were treated with AEP, 5-FU, or both AEP and 5-FU.

This experimental research employed a post-test-only control randomized group design with n=3 and a group size of 5 for both Colo-201 cells and Colo-201 senescent cells. The treatment in the Colo-201 group included untreated cells (Colo-201 cells), treatment control (Colo-201 cells with 5-FU 5 mg/ml), colo-201 cells with Dox 0.1 μM, treated cells (Colo-201 cells with AEP 100 ppm), and colo-201 cells with a combination of Dox 0.1 μM, AEP 100 ppm, and 5-FU 5 mg/ml. The treatment on Colo-201 senescent cell group included untreated cells (Colo-201 cells), doxorubicin-induced colo-201 senescent cells, doxorubicin-induced Colo-201 senescent cells with AEP 100 ppm, doxorubicin-induced Colo-201 senescent cells with 5-FU 5 mg/ml, and doxorubicin-induced Colo-201 senescent cells with combination of AEP 100 ppm and 5-FU 5 mg/ml.

Cell viability was assessed with ten μl WST-1 (4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate) in RPMI medium and incubated at 37°C for 4 hours. First, 100 μl cells were plated (20×103 cells per well) and incubated for 24 hours at 37°C in a humidified atmosphere with 5% CO^2. After 24 hours, the medium was removed and replaced with 90 μl of fresh medium, ten μl of AEP (100 ppm) in RPMI, and 10 μl of 5-FU (5 mg/ml) in different plates and in triplicate, followed by 48 hours of incubation—the cells with no treatment served as the control. Ten μl of WST-1 was applied to each well. The plate was incubated for 4 hours in an incubator with 5% CO^2 at 37°C. The absorbance was measured at 450 nm using a microplate reader [MultiskanSky Go]. Statistical analyses were done with SPSS version 25.0 using one-way ANOVA (Tukey's multiple comparison test). Figures were made with GraphPad Prism 5 (San Diego, CA, USA), and data were presented as a mean±SD. A value of $p<0.05$ was considered statistically significant.[22]

Results

As shown in Figure 1, AEP showed cancer-killing effects on Colo-201 cells compared to the control. AEP 100 ppm could lower the viability of Colo-201 cells, which is 37.15%, slightly higher than those treated with 5-FU, which is 11.45% at this concentration. The Tukey's post hoc test showed significant differences from the control ($p<0.05$). Figure 1 also showed that 0.1 µM Dox did not affect the viability of the cell. Therefore, 0.1 µM Dox could be used as a senescence induction dose.

As shown in Figure 2, AEP showed cancer-killing effects on Dox-induced Colo-201 cells compared to Dox-induced Colo-201 cells without treatment. Interestingly, the senescence-induction protocol by 0.1 µM Dox for three days could result in decreased viability of Colo-201 cells to 20.75%. Tukey's post hoc test showed significant differences compared to the control ($p<0.05$) but did not show statistically significant differences among treatments.

There was also a decrease in the cancer-killing effect of 5-FU from 88.55% in non-induced Colo-201 cells to 41.5% in the Dox-induced Colo-201 senescence model, meaning that the doxorubicin-induced Colo-201 senescence model were more resistant to 5-FU (Table). AEP 100 ppm could lower the viability of Dox-induced Colo-201 cells to 13.72%, slightly higher than those treated with 5-FU with 8.63% at this concentration.

Discussion

This research found that administration of AEP in Colo-201 cells and Colo-201 senescent cells induced by low-dose doxorubicin resulted in reduced viability of Colo-201 cells (37.15%) and Colo-201 senescent cells induced by low-dose doxorubicin (13.72%). This research also showed a decrease in the cancer-killing-effect of 5-FU from 88.55% in non-induced Colo-201 cells to 41.5% in the doxorubicin-induced Colo-201 senescence model; this phenomenon was caused by the Colo-201 senescent cells model having a phenotype that was more resistant to 5-FU. Interestingly, the doxorubicin-induced Colo-201 cells also showed decreased cell viability (20.75%). This research employed an aqueous extract of propolis and WST-1 to assess cytotoxicity in the Colo-201 colon cancer cell line and senescence Colo-201 colon cancer cell line induced by low-dose doxorubicin which is a novel approach in experimental research. This study's

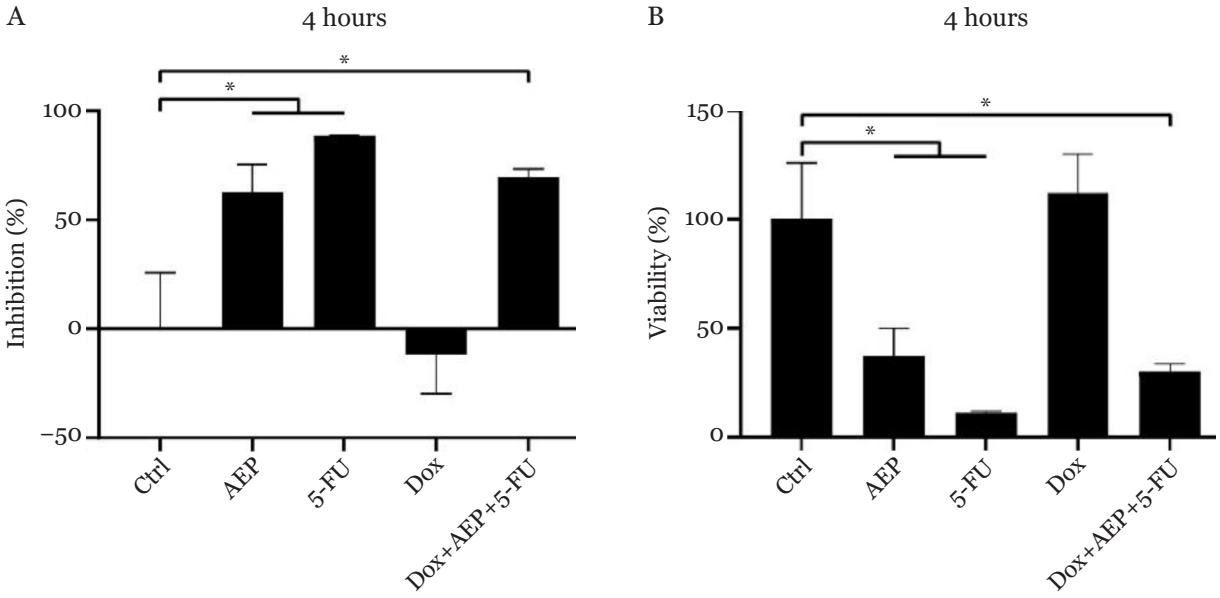

Figure 1 Colo-201 Cells Treated with Aqueous Extract of Propolis of *Geniotrigona thoracica* Sumatrans

Note: (A) percentage of cell growth inhibition; (B) percentage of viable cells; Ctrl: control; AEP: aqueous extract of propolis 100 ppm; 5-FU: 5-fluorouracil 5 mg/ml; Dox: doxorubicin 0.1 µM; *shows significant differences compared to the control based on the Tukey's post hoc test with $p<0.01$; the data is shown as means±SD with n=3

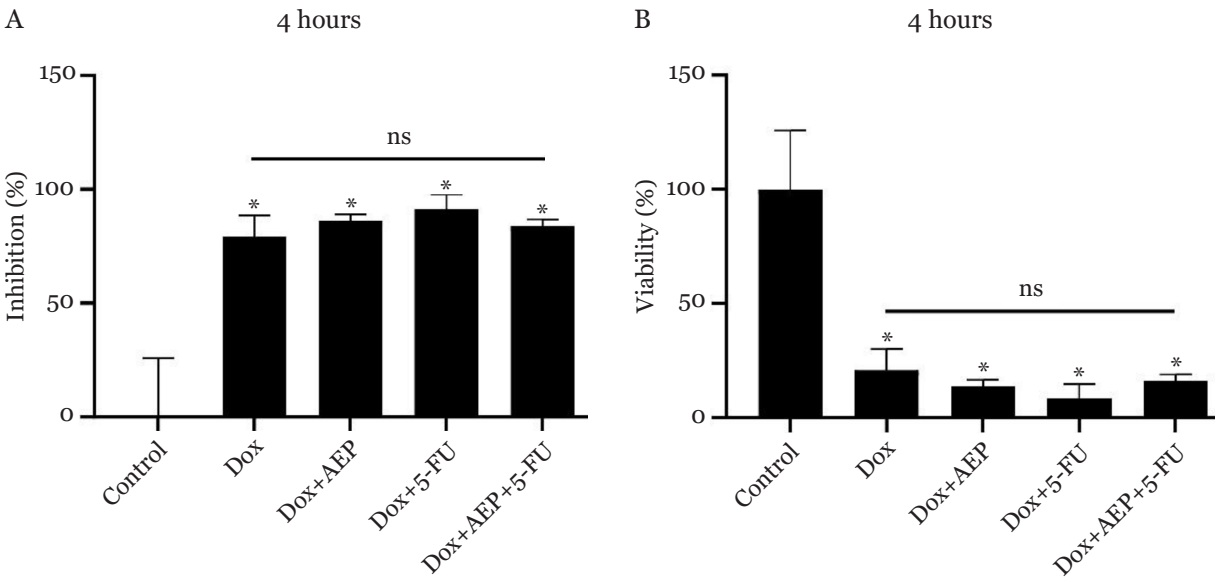

Figure 2 Doxorubicin-induced-senescence Colo-201 Cells Treated with Aqueous Extract of Propolis of *Geniotrigona thoracica* Sumatrans

Note: (A) percentage of cell growth inhibition; (B) percentage of viable cells; Control: Colo-201 cells; Dox: Colo-201 cells induced by 0.1 μM doxorubicin for 3 days; AEP: aqueous extract of propolis 100 ppm; 5-FU: 5-fluorouracil 5 mg/ml; *shows significant differences compared to the control based on the Tukey's post hoc test with $p<0.05$; ns: shows no statistically significant differences among treatments; the data is shown as means±SD with n=3

limitations are the necessity to characterize the half maximal inhibitory concentration, the effect of aqueous extract of propolis on non-cancerous cells, and the characterization of the compounds of aqueous extract propolis from *Geniotrigona thoracica* Sumatrans stingless bee.

Research on senescent cancer cell lines is still scarce. Senescent cancer cell lines can be obtained using senescence induction protocol using low-dose doxorubicin.[21] Administration of a combination of *Garcinia mycorrhiza* fruit extract and doxorubicin without a senescence-induction protocol has been shown not to affect cell viability.[23] Research into the effects of propolis on cancer cell lines and senescent cancer cell lines has never been carried out. Recent research revealed that curcumin, caffeine, and thymoquinone potentially induced apoptosis of both proliferative and senescent colon cancer HCT116 and breast cancer MCF7 cell lines.[24]

Table Differences in the Percentage of Viability Cells and Cancer-killing-effects of Colo-201 Cells and Doxorubicin-induced Colo-201 Senescence with Various Treatments

	Colo-201 Cells		Dox-induced Colo-201 Cells	
	Cell Viability	**Cancer-killing-effects Compared to Untreated Colo-201 Cells**	**Cell Viability**	**Cancer-killing-effects Compared to Untreated Dox-induced Colo-201 Cells**
Untreated Dox-induced Colo-201 cells			20.75%	
With AEP	37.15%	62.85%	13.72%	66.12%
With 5-FU	11.45%	88.55%	8.63%	41.5%
Untreated Colo-201 cells	100%		100%	

Note: AEP: aqueous extract of propolis 100 ppm; 5-FU: 5-fluorouracil 5 mg/ml; Dox-induced Colo-201 cells: Colo-201 cells induced by 0.1 μM doxorubicin for 3 days; cell viability: percentage of viable cells

Based on another study, the cytotoxicity of propolis extracts from *Trigona sirindhornae* against two head and neck squamous cell carcinoma (HNSCC) cell lines, a dichloromethane extract of propolis (DMEP) was prepared to generate three fractions: DMEP-A, DMEP-B, and DMEP-C. This study shows that *Trigona sirindhornae*-produced propolis displays cytotoxic effects against HNSCC cells. Moreover, DMEP-B and DMEP-C differentially inhibited the proliferation of a metastatic HNSCC cell line.[25]

Propolis from stingless bees has a variety of mechanisms with anti-cancer potential. These mechanisms include apoptotic events; modulation of BAX, BAD, BCL2-L1 (BCL-2 like 1), and BCL-2; mitochondrial membrane depolarization; increased caspase-3 activity; poly (ADP-ribose) polymerase (PARP) cleavage; and necroptosis-induced cell death via receptor-interacting protein kinase 1 (RIPK1) activation. Furthermore, a link between substances with antioxidant and anti-inflammatory properties is revealed, which aids in preventing cancer growth.[26]

In another study conducted on stingless bee propolis from Indonesia, propolis isolated from *Trigona incisa* induced apoptosis in the SW620 human colorectal cancer cell line. Cardol, a critical bioactive ingredient in *Trigona incisa* propolis from Indonesia, has high in vitro antiproliferative action against the SW620 colorectal cancer cell line (IC50 of 4.51±0.76 µg/ml). Cardol causes G0/G1 cell cycle arrest and apoptotic cell death. Cardol-induced cellular death in SW620 cells was induced by increased oxidative stress and the mitochondrial apoptotic pathway, which could be a potential molecular explanation for Cardol's antiproliferative action.[27] Recently, a study found that products derived from the stingless bee *Trigona* spp. from Luwu Utara (South Sulawesi, Indonesia), particularly a water-soluble extract of propolis and bee pollen, inhibited the proliferation of the human breast cancer MCF-7 cell line. The results of the DPPH (2,2-diphenyl-1-picrylhydrazyl) antioxidant experiment demonstrated that water-soluble propolis and bee pollen had high antioxidant activity, with half-maximal effective doses against DPPH radicals of 1.3 and 0.4 mg/ml, respectively. Water-soluble propolis and bee pollen had substantial antiproliferative activity in MCF-7 cells, with IC50 values of 10.8±0.06 and 18.6±0.03 mg/ml, respectively ($p<0.05$). The current findings suggested that water-soluble propolis and bee pollen could be progressively researched as breast anti-cancer therapies.[28]

At last, propolis and its components have been shown to suppress cancer signaling pathways, including PI3K/AKT/mTOR, NFκB, JAK-STAT, TLR4, VEGF, TGFβ, and apoptosis and autophagy. Propolis and its polyphenolic/flavonoid components may have anti-cancer effects through the following cellular and molecular mechanisms: (i) suppression of cancer/precancerous cell proliferation via direct cytotoxic effect or immunomodulatory effect; (ii) reduction in cancer stem cell populations; (iii) inhibition of specific oncogene signaling pathways; (iv) antiangiogenic effects; (v) modulation of the tumor microenvironment; (vi) inhibition of cellular glucose uptake and metabolism in the cancer cell; and finally, (vii) as a supplementary or complementary approach to conventional anti-cancer.[29]

Conclusions

The aqueous extract of *Geniotrigona thoracica* Sumatrans's propolis showed cancer-killing effects on the Colo-201 colon cancer cell line and senescence Colo-201 colon cancer cell line induced by low-dose doxorubicin. This finding suggested that the aqueous extract of *Geniotrigona thoracica* Sumatrans's propolis could be used as a complementary treatment for colon cancer.

Conflict of Interest

The authors stated that they have no conflicts of interest.

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RESEARCH ARTICLE

Correlation of Subject Characteristics, Work Stress Levels, and Smoking Patterns among Educational Personnel at X University, Indonesia

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Abstract

Human resources are among the crucial aspects of an organization, including in higher-education organizations. Educational personnel, a key component of the education system, are prone to work stress, which may trigger smoking behavior. Personal characteristics may also influence smoking behavior. This cross-sectional observational analytic study aimed to analyze the relationship between characteristics, work stress level, and smoking behavior of educational personnel of X University, Indonesia. On 30 April–Mei 2021, subjects were recruited through total sampling based on inclusion and exclusion criteria (n=100, all males). A questionnaire that had been tested for validity and reliability was used to collect data on subject characteristics and behaviors, while DASS-42 was used to measure work stress. Age, education level, length of work, and work stress were the independent variables, while smoking was the dependent variable. Data collected were analyzed univariately and bivariately using the chi-square test, with $p<0.05$ considered significant. Age, education, and length of work were found to be significantly correlated with smoking ($p=0.007$, 0.016, and 0.009, respectively). However, stress levels did not correlate with smoking ($p=0.786$). This suggests that age, education, and length of work significantly influence smoking behavior. It's crucial to interpret these findings with caution, especially considering that all subjects are males, who have been proven less prone to stress than females. This caution is necessary to ensure a comprehensive understanding of the factors influencing smoking behavior among educational personnel.

Keywords: Behavior, characteristics, cigarettes, smoking, stress

Introduction

Human resources, like assets and capital, play a pivotal role within an organization or company. It is essential to address and manage variables such as work motivation, job satisfaction, work performance, discipline, and stress to enhance employee productivity.[1] Work stress can be interpreted as the strain experienced by employees when confronted with the expectations of efficiency and effectiveness in playing their roles. It emerges when employees need help to meet their job demands amidst time constraints to finish the job, unclear responsibilities, lack of necessary supporting facilities, and conflicting tasks. These will collectively contribute to work-related stress.[1]

Work stress is not new but has become the most critical management issue globally. Approximately two of three workers experience work-related stress. Recent estimates indicate that this contributes to employers incurring an annual expenditure of around $200 billion due to absenteeism, delays, burnout, reduced productivity, high turnover rates, workers' compensation, and increased health insurance costs. It is believed that around 80% of diseases and morbidities are triggered and exacerbated by stress.[2]

Work stress is a prevalent issue in United States workplaces, as highlighted by the National Institute of Occupational Health and Safety (NIOSH). According to NIOSH, a survey conducted by Northwestern National Life revealed that roughly 40% of workers face intense work-related stress. Additionally, a Families and Work Institute study found that approximately 26% of individuals experience stress frequently or very frequently. A third survey, conducted by Yale University and reported by NIOSH,

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indicated that 29% of workers feel pretty or very stressed during work hours.[2]

In Indonesia, work-related stress poses a significant concern, leading to a mental and emotional disorder rate of 9.8%. Furthermore, a staggering 35% of work-related stress cases have fatal consequences.[3,4] Work stress does not only occur in the business world. It is also observed in the education sector. It affects members of the educational units, including education personnel.[5] Education staff working in a higher education institution are required to provide good services to students to ensure that they feel comfortable and supported during their college experience, ultimately facilitating the achievement of their educational goals. On the other hand, education personnel are also tasked with assisting the faculties in their teaching activities. Those resulted in a cumulative workload, as both tasks are time-sensitive and require immediate completion. This situation eventually triggers work-related stress among the education personnel.[6]

Work stress is characterized by three types of complaints: physiological, psychological, and behavioral complaints. Physiological complaints encompass a spectrum of bodily symptoms, ranging from headaches or dizziness to digestive disorders, back pain, sexual disorders, asthma or shortness of breath, nervousness, appetite loss, malaise, and lethargy. Within the psychological domain, individuals may experience irritability, anger, feelings of pressure, anxiety, restlessness, and a propensity for becoming easily discouraged. The behavioral complaints observed are lack of concentration, forgetfulness, procrastination, enthusiasm, smoking habits, and alcohol consumption.[7]

Smoking behavior, the act of burning cigarettes or other tobacco products, inhaling the smoke, and exhaling it, is a significant global health concern. It not only harms the smoker's health but also poses substantial risks for passive smokers. Smoking remains a major health concern globally, contributing to fatal conditions that claim the lives of approximately 6 million people annually. The risk for smoking-related mortality is higher among active smokers compared to passive smokers.[8]

Indonesia is one of the developing countries with the highest cigarette consumption. It ranks third as the country with the highest number of smokers globally after China and India. The increased cigarette consumption significantly contributes to the substantial smoking-related disease burden and mortality rate. In this country, more than 230,000 deaths annually are attributed to cigarette consumption as smoking continues to dominate societal habits. The average cigarette consumption in Indonesia has also been higher among workers compared to non-working individuals, with 11.1% cigarette consumption among workers as opposed to 7.9% among non-working individuals.[8] This study examined the relationship between subject characteristics, work stress level, and smoking behavior among educational staff at X University.

Methods

This research constitutes an observational analytical study conducted using a cross-sectional approach. The population selected was male educational personnel working at X University on 30 April–Mei 2021. Sampling was performed using the total sampling technique, which included all male education personnel working at X University. Male participants were selected based on the finding of the Indonesia Basic Health Research 2018 that the majority of smokers aged >15 years are males (62.9%) and that the global prevalence of male smokers is still higher than their female counterparts.9 The inclusion criterion for this study was male education personnel still actively working at X University. Those who were on leave or sick during data collection were excluded. Based on the inclusion above and exclusion criteria, the final sample size was 100. Data were collected using a validated and reliable questionnaire for subject characteristics and smoking behaviors, while the Depression Anxiety Stress Scale (DASS)-42 was used to measure work stress. Considerations of ethical issues are included with number: 002/KEPK-Unisba/III/2021.

The independent variable in this study was subject characteristics of age, education level, work tenure, and work stress. Meanwhile, smoking behavior was assigned as the dependent variable. The primary data obtained were then processed and analyzed univariately and bivariately. The univariate analyses applied were frequency distribution, percentage, mean value, minimum and maximum range, and

standard deviation, which was then followed by a bivariate analysis using the chi-square test ($\chi 2$) to determine the relationship between the subject characteristics—age, education, and work tenure—and smoking behavior. In addition, the relationship between stress levels and smoking behavior was also analyzed. A confidence interval of 95% and a 5% margin of error were applied, with a p-value of less than 0.05 deemed to demonstrate statistical significance. All analyses used the Statistical Product and Service Solution (SPSS) program version 25.0.

Results

Table 1 describes the characteristics of the study subjects. Of 100 male respondents, the majority were 31–40 years old (48%), graduated from diploma IV or had a bachelor's degree (45%), and had worked at X University for more than 15 years (38%).

Table 2 lists the stress levels experienced by the subjects and their smoking behavior. Work stress is categorized into five levels: normal, mild, moderate, severe, and very severe. Most subjects experienced an average stress level (n=53, 53%) and were non-smokers (n=62, 62%). Only 38 subjects were active smokers (38%).

The results of the analysis to determine the relationship between subject characteristics and smoking behavior are displayed in Table 3. Two variables are said to have a significant relationship if the probability or the p-value is smaller than 0.05. In the context of this study, age, education level, and work tenure showed substantial relationships with smoking behavior, as their p-values were below 0.05 ($p<0.05$).

Based on Table 4, the work stress level was examined for its significant relationship with smoking behavior by looking at the probability value (p-value). The results of the analysis using the chi-square test ($\chi 2$) revealed a p-value of 0.786, which was more significant than 0.05 ($p>0.05$). Consequently, work stress levels do not exhibit a substantial relationship with smoking behavior.

Table 1 Subject Characteristics

Characteristics	n=100 (%)
Age (years)	
≤30	11 (11)
31–40	48 (48)
41–50	20 (20)
>50	21 (21)
Education	
Elementary to junior high school/equivalent	1 (1)
Senior high school/equivalent	35 (35)
Diploma I/II	3 (3)
Diploma III	9 (9)
Diploma IV/bachelor	45 (45)
Postgraduate	7 (7)
Work tenure (years)	
≤5	37 (37)
6–10	22 (22)
11–15	2 (2)
>15	39 (39)

Table 2 Work Stress Levels and Smoking Behavior

Variables	n=100 (%)
Work stress level	
Normal	53 (53)
Mild	12 (12)
Moderate	15 (15)
Severe	10 (10)
Very severe	10 (10)
Smoking behavior	
Active smoker	38 (38)
Non-smoker	62 (62)

Discussion

This study showed that of a sample of 100 male subjects, the majority (48%) fell within the age range of 31–40 years, and almost half of the subjects (45%) held a diploma IV or bachelor's degree. Additionally, 39 subjects (39%) reported that they had been working in the university for more than 15 years.

According to the previous study, men have a higher tendency to smoke than females. He believed that this is due to the norms of society that associate smoking with masculinity for men while stigmatizing female smokers. These assumptions create a conducive environment for initiating smoking among men. It contributes to the ease of men to adopt smoking habits.[9]

Meanwhile, another previous study on factors causing work stress among employees

Table 3 Relationship between Subject Characteristics and Smoking Behavior

Variables	Smoking Behavior			p*
	Active Smoker n=38 (%)	Non-smoker n=62 (%)	Total n=100 (%)	
Age (years)				
≤30	2 (18)	9 (82)	11 (100)	0.007
31–40	13 (27)	35 (73)	48 (100)	
41–50	9 (45)	11 (55)	20 (100)	
>50	14 (67)	7 (33)	21 (100)	
Education				
Elementary to junior high school/ equivalent	1 (100)	0 (0)	1 (100)	0.016
Senior high school/equivalent	20 (57)	15 (43)	35 (100)	
Diploma I/II	2 (67)	1 (33)	3 (100)	
Diploma III	2 (22)	7 (78)	9 (100)	
Diploma IV/bachelor	10 (22)	35 (78)	45 (100)	
Postgraduate	3 (43)	4 (57)	7 (100)	
Work tenure (years)				
≤5	7 (19)	30 (81)	37 (100)	0.009
6–10	8 (36)	14 (64)	22 (100)	
11–15	1 (50)	1 (50)	2 (100)	
>15	22 (56)	17 (44)	39 (100)	

Note: *chi-square test (χ2), 95% confidence interval

demonstrated that individuals in the older age category, over 40 years old, are more prone to severe anxiety. This vulnerability is attributed to declining physical conditions and challenges in effectively balancing workloads with age-related factors.[10] A previous study examining factors related to work stress in workers working with chemical hazards in a confined space at PT Z also found that age was linked to work stress. In contrast, a previous study found no effects of age on work stress when studying workers in factory workers in Makassar, Indonesia.[11]

Nevertheless, age indeed significantly influences smoking behavior, often demonstrated through a sharp increase in smoking during productive years due to misconceptions of

Table 4 Relationship between Stress Level and Smoking Behavior

Stress Level		Smoking Status			p*
		Active Smoker n=38	Non-smoker n=62	Total n=100	
Normal	n	18	35	53	
	%	34%	66%	100%	0.786
Mild	n	4	8	12	
	%	33%	66%	100%	
Moderate	n	6	9	15	
	%	40%	60%	100%	
Severe	n	5	5	10	
	%	50%	50%	100%	
Very severe	n	5	5	10	
	%	50%	50%	100%	

Note: *chi-square test (χ2), 95% confidence interval

the effect of tobacco on working ability, which usually takes root during adolescence. In older age, smoking habits markedly decline as health conditions start to deteriorate, making smoking cessation necessary.[9]

The educational level also influences smoking behavior as individuals with higher educational backgrounds are more aware of the impact of smoking behavior, which may motivate them to reduce their smoking habit gradually.[9]

In terms of work stress levels, which are divided into 5 (five) categories: standard, mild, moderate, severe, and very severe, this study found that most subjects (53%) had an average stress level. The fact that all subjects of this study were males should be considered in the interpretation of this study, as females are more likely to experience stress than their male counterparts.[12] This can be seen in a previous study on education personnel at the Faculty of Nursing, Universitas Padjadjaran Indonesia, where 72% of the subjects were females. Their study demonstrated that 25 subjects (41.7%) experienced low-stress levels, while the remaining 24 (40%) and 11 (18.3%) subjects experienced severe and moderate stress levels, respectively.[12]

Among this study population 38%were active smokers, as depicted in Table 2. It seems to be a common situation as Lianzi and Pitaloka,[9] in their study in 2014 on the relationship between knowledge about cigarettes and smoking behavior in the administrative staff of Universitas Esa Unggul, also stated that 51.2% of the administrative staff of the said university is active smokers, which is dominated by those in the age group of 31–40 years. Likewise, a previous study in 2014 on knowledge, attitudes, and psychological factors related to smoking behavior in employees of the Jakarta III Ministry of Health Polytechnics revealed that 45.5% of the employees smoked because they believed that smoking could relieve stress and provide psychological comfort.[13]

With the notion that two variables are considered to have a significant relationship if the p-value is less than 0.05, it is apparent that this study found that age, education, and work tenure have a substantial relationship with smoking behavior. It is supported by a previous study by Fernando et al.[14] examining the relationship between education, occupation, age, and smoking behavior in Pontianak city that there is a relationship between age and smoking behavior. Their finding stated that smoking behavior has started since childhood (10–13 years), and the age group (22–40 years) is the group with the highest prevalence of smoking, which is in line with the finding in this study that the prevalence of smoking at the age of <15 years is lower than the age ≥15 years.

However, this finding is not supported by the conclusions of a study by Nurfadhilah et al.[15] on the determinants of smoking behavior in workers of public facilities and infrastructure management in Kampung Rambutan, Jakarta, Indonesia, where respondents aged <30 years are more likely to smoke. However, her study presented insignificant relationships. 'Inayati[16] proposes an interesting idea based on her research that despite the lack of relationship between age and cigarette consumption, each additional year of a person's age tends to decrease cigarette consumption because smoking-related harm is heightened as an individual grows older.

In this study, education has a relationship with smoking behavior, which is supported by the findings of Nurfadhilah et al.[15] stating that there is a significant relationship between education level and smoking behavior among employees of public facilities and infrastructure management in Kampung Rambutan. Employees with lower have a 5.333 higher chance of adopting smoking habits than their more educated colleagues. A study by Fernando et al.[14] on the relationship between education level, occupation, age, and smoking behavior in Pontianak even suggested education as the most influential factor of smoking in Pontianak. The inclination to smoke tends to diminish with higher levels of education. These findings align closely with Lawrence Green's theory, which posits that education is a pivotal characteristic influencing individual behavior. Education significantly impacts the depth and quality of one's knowledge. Knowledge, in turn, acts as a predisposition for behavior. Well-informed individuals are less likely to adopt smoking habits.[14]

In this study, work tenure was identified as linked to smoking. It supports the finding of Lianzi and Pitaloka,[9] stating that the longer people work in a company, the more stressed they are and the higher the likelihood of developing smoking habits. Work tenure is defined as the period that an employee has been working in a firm, which can include work during the day and night, while

the working period is when the employee works in a specific place. As an individual spends more time at work, their exposure to work-related hazards, including behaviors like smoking, tends to increase.[9]

Stress is closely related to an individual health condition and can be influenced by changes or deviations in behavior, including the adoption of smoking habits. In this study, of 53 with an average stress level, 18 (34%) were active smokers, while of 12 with a mild stress level, four (33%) were active smokers. Furthermore, of 15 subjects with moderate stress levels and 10 subjects with a severe stress level, 6 (40%) and five people (50%) were active smokers, respectively. When data on this aspect was analyzed using the chi-square test ($\chi 2$), it was observed that the stress level does not correlate with smoking behavior ($p=0.786$, $p>0.05$).

This result is contradictory to the finding of Aisyah et al.[17] on factors that influence smoking behavior among Indonesian army soldiers in Jakarta, stating a relationship between respondents' stress levels and smoking behavior. It coincides with the findings of a study performed by Oktriansyah et al.[18] in 2023 on the relationship between stress, social environment, and smoking behaviors among health care workers of RYZ hospital in X city that demonstrated significant correlations between the three variables, with stress and social environment have a 52% of effective contribution to smoking behavior. The remaining 48% might be attributed to other variables not studied in their study.

The link between work stress and smoking behavior is also stated by Siagian et al.[8] in a study on factors influencing smoking behavior among electricity company workers in South Sorong regency. The impact of work stress on smoking behavior is evident. As work stress levels increase, so does the prevalence of smoking behavior. Excessive stress can significantly hinder an individual's capacity to cope with their environment and work demands. The findings from a 2017 study conducted by Stubbs et al.,[19] which investigated the correlation between stress and smoking behavior across 41 countries in Europe, Africa, Asia, and America continents, have also revealed a significant association between stress and smoking behavior.

In 2021, a study in Denmark discovered that the relationship between smoking and stress is very complex and that stress in childhood or adolescence is a risk factor for someone to start smoking. Furthermore, the desire to smoke will increase after exposure to stress. Perceived stress is also a barrier for people to quit smoking. People who experience a high level of stress will have a lower chance of quitting smoking.[20]

The relationship between work stress and smoking behavior can be explained as follows. According to a prior study by Asih et al.,[21] work stress refers to tension arising from human interaction with their job. This condition can lead to physical and psychological imbalances, impacting an employee's emotions, cognitive processes, and overall well-being. Stress is not always bad, even though it is often discussed in a negative context, because stress can also positively influence it. Stress becomes positive; for example, it offers potential outcomes when it becomes an opportunity. For example, many professionals view pressure as a heavy workload and tight deadlines as positive challenges that improve the quality of their work.[21] According to researchers, challenge stress—arising from work-related challenges—is distinct from obstacle stress, which impedes goal achievement. Occasionally, companies intentionally introduce challenges to enhance employee motivation and prompt swift task completion by imposing tight deadlines.[21]

The symptoms of stress are categorized into physical, psychological, and behavioral symptoms. The physical manifestations of stress encompass alterations in metabolism, heightened heart rate and respiration, elevated blood pressure, headaches, and the potential risk of heart attacks. Psychologically, stress gives rise to job dissatisfaction, feelings of pressure, anxiety, irritability, boredom, and a tendency toward procrastination. Meanwhile, the behavioral symptoms encompass shifts in productivity, absenteeism, alterations in dietary patterns, heightened alcohol or cigarette consumption, rapid speech, restlessness, and disruptions in sleep.[21]

As previously mentioned, work stress is associated with smoking behavior. Stress not only influences individuals to initiate cigarette consumption but also impacts those who are already smokers, as they tend to smoke more during stress.[22] This notion is also proposed by Nurfadhilah et al.,[15] stating that respondents with

severe stress smoked more.

Contrary to the previous studies, this study indicates that stress does not exhibit a significant association with smoking behavior. Notably, the majority of respondents (53%) reported normal stress levels, implying that other unexplored factors contribute to smoking behavior within this study cohort. Various factors may affect smoking behaviors, including social, psychological, lifestyle, and family-related factors.[23] Other research shows that a person's knowledge and experience in terms of smoking can affect smoking habits.[24]

Conclusions

The findings from this study stated that age, education level, and work tenure exhibited a significant relationship with smoking behavior. However, work stress levels do not show a significant relationship with smoking behavior.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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RESEARCH ARTICLE

Effectiveness of Red Ginger (*Zingiber officinale* var. Rubrum) Foot Hydrotherapy in Lowering Blood Pressure among Pregnant Women with Hypertension

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Abstract

Pregnancy hypertension is one of the complications of pregnancy. One nonpharmacological treatment to reduce hypertension is the foot hydrotherapy method with red ginger (*Zingiber officinale* var. rubrum). The essential oil content of red ginger provides a warm effect and spicy aroma so that blood vessels widen and blood flow becomes smooth. The research aims to determine the effectiveness of red ginger foot hydrotherapy in lowering blood pressure among pregnant women with hypertension. This one-group pretest-posttest pre-experimental study design was conducted at the Talaga Community Health Centre, West Java, from May 2023 to July 2023. The sample was 32 pregnant women with hypertension. Bivariate analysis test using paired t-test. The average systolic blood pressure measurement results for pregnant women before the intervention were 154.09 mmHg, and after the intervention was given 140.22 mmHg, there was a decrease of 13.87 mmHg. The average diastole for pregnant women before the intervention was 100.22; after the intervention, it was 91.62, resulting in a reduction of around 8.6 mmHg. The paired t-test with a p-value <0.001 shows the effectiveness of foot hydrotherapy with red ginger in reducing blood pressure in pregnant women with hypertension. Red ginger using the foot hydrotherapy method has been proven effective in lowering blood pressure in pregnant women. To reduce the risk factors for pregnancy with hypertension, pharmacological and nonpharmacological therapy is a solution that needs to be considered. This research can become a reference for evidence-based midwifery practice in providing midwifery care.

Keywords: Foot hydrotherapy method, hypertension, pregnant women, red ginger

Introduction

The prevalence of hypertension in women of reproductive age is estimated to be 7.7%. Hypertensive disorders of pregnancy are one of the complications that occur during pregnancy, with the classification of chronic hypertension, hypertension in pregnancy, as well as preeclampsia and eclampsia; it is a significant cause of maternal and perinatal morbidity and mortality.[1,2]

Maternal mortality rates are increasing every year. In 2021, there were 7,389 maternal deaths in Indonesia, compared to 4,627 in 2020. Of the 2021 deaths, 2,982 were related to COVID-19, 1,330 to bleeding, and 1,077 to hypertension in pregnancy.[3,4]

Management of hypertension in pregnancy can be done by pharmacological and nonpharmacological therapy.[5] Pharmacological methods used by standard services are antihypertensive drugs and standard antenatal care (routine blood pressure monitoring). Pharmacological therapy in hypertension has good effectiveness, but its application can cause side effects at the beginning of use, and antihypertensive drugs that are consumed regularly will cause unwanted long-term effects and can cause headaches and shortness of breath.[6] Nonpharmacological efforts that can be made to reduce hypertension are by providing hyperthermia technology. One is foot hydrotherapy (soaking feet using warm water), which relies on the body's response to water and its low-tech approach.[7] Scientifically, soaking the foot, especially with warm water, has many benefits for the body, especially in improving blood circulation. Soaking the feet in warm water

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with a temperature of 37–39°C is vital because cold heat alternation can occur, which stabilizes the work of the heart and blood flow.[8] One of the herbal ingredients that can be combined with foot baths is red ginger (*Zingiber officinale* var. rubrum). The essential oil content in red ginger will provide a warm effect and a spicy odor so that blood vessels become wide and blood flow becomes smooth.[9,10]

Previous studies have explained that the provision of foot soak therapy with red ginger decoction affects lowering blood pressure in pregnant women with preeclampsia.[11,12] In Inayah and Anonim[13] in the intervention group, there was a decrease in systolic 29.35 mmHg and diastolic 16.00 mmHg, research by Malibel et al.[14] experimental method in rats given with nanoemulsion RGE (360 mg/200 g b/b) experienced a significant decrease in systolic blood pressure ($p<0.05$) from 142±1 mmHg to 107±6 mmHg and diastolic blood pressure from 106±1 mmHg to 84±4 mmHg.

This study aimed to determine the effectiveness of red ginger (*Zingiber officinale* var. rubrum) foot hydrotherapy in lowering blood pressure among pregnant women with hypertension.

Methods

This quantitative research employs a pre-experimental, one-group pretest-posttest design. Observations were made before and after the intervention.

Pretest → Treatment → Posttest
O1 → X → O2

Description: O1: blood pressure monitoring in pregnant women with hypertension before foot hydrotherapy with red ginger; X: foot hydrotherapy with red ginger; and O2: blood pressure monitoring in pregnant women with hypertension after foot hydrotherapy with red ginger.[15]

This study included all 256 pregnant women who visited the Talaga Community Health Centre, West Java, from May 2023 to July 2023. The total sample found was 32 pregnant women with hypertension.

The stages in this research began with identifying the research sample; a sample of 32 pregnant women with hypertension was obtained, and after giving informed consent, the experimental intervention was carried out. The media used for foot hydrotherapy with red ginger was a water thermometer and a watch to help measure the water temperature—and warm water with a temperature of 37°C. The researchers visited every house of participants for seven days, ranging from 15 to 30 minutes in the morning. Data analysis was done univariately and bivariately using normally distributed data with a paired t-test.[16] Research ethics follow the rules determined by the Institute of Health Sciences Kuningan number 41/EP/Stikku/2023.

Results

The results of the univariate analysis in this study describe the characteristics of respondents, including age, parity, gestational age, and body mass index. The results of the analysis of the characteristics of respondents can be seen in Table 1.

Table 1 Characteristics of Respondents

Characteristics	n=32
Age (years)	
<20	3
20–35	13
>35	16
Parity	
Primigravida	7
Multigravida	17
Grande multipara	8
Gestational age (week)	
13–24 (trimester II)	11
25–36 (trimester III)	21
Body mass index	
Underweight	0
Normal weight	14
Obese	18

Table 2 Overview of Systole and Diastole Blood Pressure Measurement Results of Pregnant Women with Hypertension

Blood Pressure	Min	Med	Max
Pretest sistole	140	152.50	180
Pretest diastole	90	98.50	113
Posttest sistole	123	138.50	162
Posttest diastole	84	91.00	101

Table 3 Overview of Average Blood Pressure Pretest and Posttest of Foot Hydrotherapy with Red Ginger

Blood Pressure	Mean	SD	Min	Max
Pretest sistole	154.09	9.596	140	180
Pretest diastole	100.22	5.999	90	113
Posttest sistole	140.22	9.339	123	162
Posttest diastole	91.62	4.654	84	101

Table 1 shows that pregnant women with hypertension are primarily found in pregnant women aged >35 years, totaling 16 of 32 respondents. Multigravida became the most parity of pregnant women, totaling 17 of 32 respondents. Most of the third trimester gestational age was 21 of 32 respondents. The highest body mass index is obesity, totaling 18 of 32 respondents.

Table 2 describes the result of blood pressure measurements in pregnant women with hypertension in the Talaga Health Centre work area in 2023; the lowest systole before the intervention was 140 mmHg, and the highest was 180 mmHg. For diastole before treatment, the lowest was 90 mmHg, and the highest was 113 mmHg. In blood pressure measurements after treatment, the lowest systole was 123 mmHg, and the highest was 162 mmHg, while for diastole, the lowest was 84 mmHg, and the highest was 101 mmHg.

Table 3 shows that the average systole blood pressure in pregnant women before treatment was 154.09 mmHg, and after treatment, it was 140.22 mmHg, so there was a decrease of about 13.87 mmHg. The average diastole in pregnant women before treatment was 100.22; after treatment, it was 91.62, so there was a decrease of about 8.6 mmHg.

The results of bivariate analysis in this study were used to determine the effectiveness of foot hydrotherapy with red ginger on lowering blood pressure in pregnant women with hypertension in the working area of Talaga Health Center in 2023.

Based on the paired t-test analysis results, blood pressure measurements before and after treatment were obtained at a p-value of <0.001.

Discussion

Every pregnant woman in the age group not at risk or risk <20 and >35 years must carry out intensive pregnancy monitoring to minimize risk factors for hypertension in pregnancy through adequate and regular antenatal care visits.[17] Parity in pregnant women can determine the risk factors for hypertension in pregnancy, especially in primigravida. There is an immunologic disorder (blocking antibodies) where the production of inhibitory antibodies is reduced and can inhibit the maternal spiral artery's invasion rate by trophoblasts to a certain extent to interfere with the function of the placenta. Meanwhile, when looking at gestational age in trimesters I, II, and III, it can be known with the theory of placental implantation ischemia, which reads that the older the gestational age causes high blood pressure to increase. When hypertension occurs in the second trimester of pregnancy (20 weeks), pregnant women tend to experience Preeclampsia characterized by laboratory results of positive urine protein.[18] Calculation of body mass index, especially in pregnant women with obesity, hurts the mother and the fetus she is carrying, both during pregnancy, childbirth, and postpartum. One of the impacts of the mother is at risk of chronic hypertension because excessive body mass index can make the heart too heavy and pressure on blood vessels increases due to thick fat.

Research results by Arinda and Khayati[9] show that increasing blood pressure in pregnant women is a form of adaptation during pregnancy. Increased left ventricular work, left ventricular

Table 4 Analysis of the Effectiveness of Foot Hydrotherapy with Red Ginger on Reducing Blood Pressure in Pregnant Women with Hypertension

Blood Pressure	n=32	Mean	p
Systole blood pressure before treatment–systole blood pressure after treatment	32	15.719	0.001
Diastole blood pressure before treatment–diastole blood pressure after treatment	32	8.594	0.001

mass, and end-diastolic phase volume in pregnant women increase cardiac output. During early pregnancy, cytotrophoblast cells enter the uterine spiral arteries and replace the endothelial layer by damaging the medial elastic tissue, muscles, and nerves sequentially.[19] The increase in blood pressure due to the body's adaptation process during pregnancy is an increase in cardiac output due to increased left ventricular work, left ventricular mass, and volume at the end of the diastolic phase in pregnant women. Hypertension in pregnancy mainly occurs in the second to third trimester of pregnancy.[9,20] Increased blood pressure in pregnant women is a form of adaptation during pregnancy. There is an increase in left ventricular work, left ventricular mass, and end of diastolic phase volume in pregnant women, increasing cardiac output. During early pregnancy, cytotrophoblast cells enter the uterine spiral artery and replace the endothelial layer by damaging the medial elastic tissue, muscles, and nerves in sequence.[19] The increase in blood pressure due to the body's adaptation process during pregnancy is an increase in cardiac output due to increased left ventricular work, left ventricular mass, and end-of-diastolic phase volume in pregnant women. Hypertension in pregnancy mainly occurs from the second to third trimester of pregnancy.[20]

The average systole blood pressure in pregnant women after treatment was 140.22 mmHg, so there was a decrease of about 13.87 mmHg. While the average diastole was given a treatment of 91.62, so there was a decrease of about 8.6 mmHg. This study is in line with research conducted by Hafidz et al.,[11] which shows that pregnant women respondents experienced a decrease in blood pressure after being given a foot soak with warm water by as many as 16 people (100%). Foot soak therapy with a red ginger decoction is one technique to reduce blood pressure by soaking the feet in warm water containing red ginger decoction.[21]

The warm feeling of ginger can widen blood vessels to facilitate blood circulation and ease the work of the heart.[22] The widening of blood vessel diameter will be followed by a decrease in blood pressure. The mechanism of lowering blood pressure comes from the heat effect of warm water and the essential oil content in ginger, which also has a hot sensation that will hit the skin on the soles of the feet to the ankles; there is a conduction process between warm red ginger boiled water and the skin of the feet so that vasodilation (dilation) of blood vessels occurs. The dilation of blood vessels will stimulate baroreceptors located in several parts of the body, one of which is in the carotid sinus and aortic arch. Furthermore, it will send impulses to the medulla oblongata and activate the parasympathetic nerves. In this study, foot hydrotherapy with red ginger was performed because the essential oil content in red ginger was the highest compared to other gingers.

To reduce the risk factors for pregnancy with hypertension, pharmacological and nonpharmacological therapy is a solution that needs to be considered. This research can become a reference for evidence-based midwifery practice in providing midwifery care.

Conclusion

Red ginger using the foot hydrotherapy method has been proven effective in lowering blood pressure in pregnant women.

Conflict of Interest

None declared.

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RESEARCH ARTICLE

Effectiveness of Kegel Exercises on Perineal Wound Healing among Postpartum Women

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Abstract

Perineal wound refers to a laceration or wound that occurs along the birth canal (perineum) due to the delivery process. Wound healing is a method involved in replacing and repairing damaged tissue's capacity. This study aims to determine the effectiveness of Kegel exercises on perineal wound healing. It was a quasi-experimental study with one group pretest-posttest design conducted in March–May 2023. Forty-five women with perineal wounds at the Arosbaya Public Health Center, a reputable healthcare facility in Bangkalan, East Java province, Indonesia known for its comprehensive postpartum care, were selected as the study samples through a random sampling technique. The pre-test was done by observing the perineal wound before doing Kegel exercises. At the intervention stage, respondents did Kegel exercises daily for seven days. The post-test was carried out on day 7, and then observation of the perineum wound was carried out. Data were collected using an observation sheet. T-test was applied for the statistical tests. The study results show that after carrying out Kegel exercises, the majority of the 45 respondents experienced changes; namely, 25 people experienced good wound healing, and the remaining 20 experienced poor wound healing. The calculated t value was higher than the t table value (−16.523>−2.015) and had a significance value of <0.05 (0.000<0.05). This study's findings have practical implications for postpartum care, as they highlight the potential of Kegel exercises in promoting perineal wound healing, thereby enhancing the knowledge and practice of healthcare professionals and postpartum women.

Keywords: Kegel exercises, perineal wound, postpartum

Introduction

Childbirth often causes perineal tears or lacerations in both primigravidas and multigravidas with a stiff perineum. Perineal tears often occur during childbirth, which makes midwives try to find interventions with the slightest risk.[1] Perineal tear can occur spontaneously or due to an episiotomy to widen the birth canal.[2–6] Delayed healing of perineal wounds can increase the risk of infection.[2,3,5,6]

Barriers to the healing process of perineal episiotomy wounds include lack of nutrition that slows down the healing process, the bad habit of smoking at a young age, an increase in corticosteroids levels due to stress, as well as disturbances in oxygenation which interfere with collagen synthesis that further inhibits epithelialization and causes infection.[3,7] There are several impacts of incorrect treatment of perineal wounds. Lochia and damp conditions will support the growth of bacteria, which can cause perineal infection. In addition, such infection can spread to the bladder tract and even postpartum maternal death.[8] Slow and poor management of complications may lead to death.

In Indonesia, 75% of women who give birth vaginally experience perineal wounds. In 2020, it was found that 57% of women had perineal sutures (28% due to episiotomy and 29% due to spontaneous lacerations). The prevalence of women in labor who experienced perineal wounds in Indonesia in the 25–30 year and 35–39 age groups were 24% and 62%, respectively.[9] Further studies in 2016 revealed that the incidence of perineal wound infections among postpartum women was 1.22%. Maternal mortality rate (MMR) data in East Java province in 2022 revealed 46 cases of maternal death due to bleeding, 41 cases due to hypertension, 1 case due to infection, 8 cases due to circulatory system disorders, and 0 cases due to metabolic

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disorders.[10]

Based on data obtained at Private Midwife of Yuni Sri Rahayu, there were 13 women with normal delivery from November–December 2012, wherein 10 of them experienced perineal rupture. Seven of the ten women who experienced perineal rupture were primiparous (70%), and three were multiparous (30%).[11]

Perineal tears occur in almost all vaginal births, whether the tears are intentional with an episiotomy or spontaneous tears as a result of childbirth.[3–6,12] Some perineal tears require suturing; some do not.[4,5,12] Data derived from the Arosbaya Public Health Center (PHC) showed that there were 425 postpartum women in 2022, and almost half of them experienced perineal lacerations. A previous study explained that perineal wound treatment is done by keeping the perineum dry and clean, washing perineal wounds with clean water and soap every time after urinating or defecating, avoiding using hot water for soaking, and preventing the administration of traditional medicine.[13–15] In such a study, 3 of 24 respondents had poor wound healing, and four had good wound healing. Meanwhile, overall, wound healing was good by 17 respondents.[16] A study by Patterson et al.[15] found that 56% of respondents carried out early mobilization, and 48.8% of respondents who were given antibiotics experienced rapid wound healing. Early mobilization can be performed through Kegel exercises to tighten the abdominal and pelvic floor muscles. Based on several Kegel exercise research results can increase blood circulation to the vaginal area. Pregnant blood oxygen and lots of nutrients are needed to regenerate vaginal cells and tissue that experienced episiotomy damage.[15,16]

The impact of perineal rupture includes infection in the suture wound, which can spread to the bladder canal or birth canal so that it can result in complications. Moreover, bleeding can also occur due to open blood vessels that do not heal completely.[17]

Wound healing is a process of replacement and repair of the function of damaged tissue, which involves the integration of physiological processes.[18] The healing properties of all wounds are the same, with variations depending on the location, severity, and extent of the injury. The healing time for the perineal wound is stated as fast if it lasts within 1–6 days, as normal if it stays within 7–14 days, and as long if it remains within ≥14 days.[19]

Pharmacological and non-pharmacological interventions can accelerate the healing process of perineal wounds. One example of non-pharmacological interventions is Kegel exercises.

Kegel exercises act as a therapy for stress and urge incontinence to strengthen the pelvic floor or the pubococcygeal muscles. Kegel exercises aim to strengthen the pelvic muscles.[20] Kegel exercises have the benefit of helping postpartum healing by alternately contracting and releasing the pelvic floor muscles, namely by making the stitches tighter, accelerating healing, relieving hemorrhoids, and improving urine control.[21] Frequent Kegel exercises can increase circulation in the perineum, thereby accelerating healing and reducing swelling. Patients can do Kegel exercises immediately after childbirth regularly every day so that it will help perineal suture healing.[22] A study by Sheng et al.[23] explained that a lack of time and motivation was a barrier to Kegel exercises in postpartum women. Such a study also found information regarding the importance of husband support towards physical activity. Postpartum women who received support from their husbands would have the motivation to do Kegel exercises.

A study conducted by Wojcik et al.[16] regarding the effectiveness of Kegel exercises and deep breathing relaxation on perineal pain among postpartum women showed a difference in perineal pain before and after Kegel exercises and deep breathing relaxation. In addition, Kegel exercises were more effective than breathing relaxation.

Based on preliminary data conducted at Arosbaya PHC, there were 45 of 125 postpartum women in the last three months experienced first-third degrees perineal lacerations and had never performed Kegel exercises.

This study aims to determine the effectiveness of Kegel exercises in healing perineal wounds among postpartum women with first-third-degree lacerations.

Methods

This was a quasi-experimental study with one group pretest-posttest design and pre-test by observing the perineal wound before doing Kegel exercises. At the intervention stage, respondents did Kegel exercises daily for seven days. The post-test was carried out on day 7, and then observation

of the perineum wound was carried out. The population in this study involves all postpartum women at Arosbaya PHC, Bangkalan regency, Madura, East Java province, Indonesia known for its comprehensive postpartum care, with as many as 51 people. Based on the result of sample calculation using the Slovin formula, 45 people were selected as the study samples through a random sampling technique. This study was conducted for three months, from March to May 2023. The independent and dependent variables were the Kegel exercise technique and perineal wound healing. The independent variable of the Kegel exercises technique was assessed using a checklist/standard operating procedures guided by the researcher while performing the intervention. Further, the researcher determined the intervention categories. The dependent variable of perineal wound healing was assessed through observation. Bivariate analysis was performed on both variables that were hypothesized to be related or correlated. A normality and homogeneity test was previously applied before the data analysis test. The Kolmogorov-Smirnov test was used for the normality test, while the one-way ANOVA test was applied for the homogeneity test. If the p-value was <0.05, it indicated that the data were not normally distributed, then the Wilcoxon test was used for the data analysis test. If the p-value was >0.05, it noted that the data were normally distributed, then the sample t-test would be applied for the data analysis test. The current study had an ethical test at the Health Research Ethics Commission of the Faculty of Science Health, Universitas PGRI Adi Buana Surabaya, and it was declared to have passed the ethical review with Certificate number 079-KEPK.

Results

The result shows that all 45 respondents are the same age, between 21 and 35. Table 1 shows that the majority of respondents' education data is from senior high school (25 of 45). Respondent parity data is mostly primipara (26 of 45), and all respondents are unemployed/domestic.

Table 2 revealed that before being given Kegel exercises, the majority of respondents experienced moderate wound healing by 23 of 45 respondents. Furthermore, a small number of respondents experienced poor wound healing by 22 of 45 respondents. After being given Kegel exercises, the respondents experienced good wound healing by 25 respondents and 20 respondents had moderate wound healing.

Table 1 Frequency Distribution of Respondent Characteristics

Characteristics	n=45
Education	
Elementary to junior high school	12
Senior high school	25
Diploma/graduate	8
Parity	
Primigravida	26
Multipara	19
Grande multipara	0
Work	
Work	0
Not/housewife	45

Table 2 Frequency Distribution of Perineal Wound Healing among Postpartum Women

Perineal Wound Healing	Before n=45	After n=45
Good	0	25
Moderate	23	20
Poor	22	0

Based on Table 3, it was revealed that the majority of respondents performed good Kegel exercises (24 of 45). Table 4 shows that the mean value of perineal wound healing before Kegel exercises was 6.51 (SD=0.991), which is lower than after the exercise (SD=0.988).

Based on Table 5, it was found that most of the respondents with moderate wound healing performed good Kegel exercises technique by 11 of 45 respondents, and nine respondents performed moderate wound healing. On the other hand, most of the respondents with good wound healing performed good Kegel exercise

Table 3 Frequency Distribution of Kegel Exercises Technique

Kegel Exercises	n=45
Poor	5
Moderate	16
Good	24

Table 4 Kegel Exercises Technique and Perineal Wound Healing among Postpartum Women

Information	n=45
Perineal wound healing before intervention	
Mean±SD	6.51±0.991
Median (min–max)	7.00 (5–8)
Kegel exercises	
Mean±SD	2.42±0.690
Median (min–max)	3.00 (1–3)
Perineal wound healing after intervention	
Mean±SD	8.58±0.988
Median (min–max)	9.00 (7–10)

techniques, with 13 of 45 respondents; seven respondents performed moderate Kegel exercise techniques, and the remaining five respondents performed poor Kegel exercise techniques. Research shows that the more people who use Kegel well, the better the healing will be, with a p-value<0.05.

Discussion

The study results showed that most respondents had moderate perineal wound healing before Kegel exercises, 23 of 45 respondents, and the remaining 22 respondents had poor wound healing. The categories of wound healing were determined according to redness, edema, ecchymosis, discharge, and apposition (REEDA) scale. Redness, swelling, bleeding spots, fluid discharge, and poor approximation of laceration in the perineum were found.

Kegel exercises should be a routine action carried out by postpartum women. In such a goal, the role of midwives is crucial. Midwives can teach Kegel exercises when a woman is having a pregnancy check-up so that she understands the importance of Kegel exercises during the postpartum period, especially in reducing pain and healing wounds.[16]

Based on the research results, it can be seen that after performing Kegel exercises, most respondents experienced changes, with 25 of 45 people experiencing good wound healing and the remaining 20 of 45 people experiencing poor wound healing.

This finding aligns with a previous study that applied quasi-experimental with a two-group, pretest-posttest design. This study gave treatment to one group through Kegel exercises. The population and samples in the study were postpartum mothers with grade I and II perineal lacerations. The results of the Mann-Whitney statistical test showed an effect of Kegel exercises on the healing time of perineal wounds among postpartum mothers at Private Midwife Yeni Nurhayani.[24]

Kegel exercises had a significant influence on wound healing because it was found that respondents who regularly performed Kegel exercises had a fast healing process for perineal wounds. Kegel is part of postpartum care, so poor knowledge will affect the length of wound healing.[25]

In the statistical analysis test, a paired samples test was applied based on the pre-test or before intervention results and the post-test or after intervention using Kegel exercises. It was found a significance value of (0.000<0.05). Thus, it can be concluded that H0 was rejected and H1 was accepted, indicating the effect of Kegel exercises on perineal wound healing among postpartum women at Arosbaya PHC, Bangkalan. Another previous study showed that Kegel exercises

Table 5 Cross Tabulation between Perineal Wound Healing and Kegel Exercises Technique among Postpartum Women

Perineal Wound Healing	Kegel Exercises Technique			Total n=45
	Poor n=5	Moderate n=16	Good n=45	
Poor	0	0	0	0
Moderate	0	9	11	44
Good	5	7	13	56
p				0.000

significantly accelerated the healing of perineal wounds among postpartum women.[23] Kegel exercises performed regularly and consistently can help strengthen and tighten the perineal muscles, encouraging a faster healing process.The pubococcygeus muscles influence oxygenation circulation and facilitate blood circulation, thereby allowing new tissue growth to heal the suture wound (accelerating the proliferative phase).[26]

Kegel exercises have been known as valuable exercises in strengthening women's pelvic muscles.[26] Kegel exercises can also provide essential benefits during the healing process of perineal wounds after delivery.[16] Such exercises involve contraction and relaxation of the pelvic muscles, including the pelvic floor muscles, which can accelerate the healing process of perineal wounds.

The study finding is in line with a previous study which explained that Kegel exercises were more effective than deep breathing relaxation for perineal wound healing among postpartum women.[23]

After normal delivery, Kegel exercises can improve the recovery of perineal wounds in postpartum women. In addition, Kegel exercises can help increase blood circulation to the perineal area, increase tissue elasticity, and strengthen the pelvic muscles, thereby accelerating wound healing and reducing discomfort.

Conclusions

Kegel exercises had an effect on perineal wound healing among postpartum women. There is a need to provide information to postpartum mothers about providing obstetric services to perineal wound patients using Kegel exercises.

Conflict of Interest

All authors declared no conflict of interest.

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RESEARCH ARTICLE

Anti-hyperuricemia Potential of Ethyl Acetate Fraction from Ethanolic Stem Extract of *Arcangelisia flava*

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Abstract

Arcangelisia flava, with its secondary metabolites in flavonoids, has shown promising potential as an alternative treatment for hyperuricemia. The study aimed to determine the effectiveness of the ethyl acetate fraction from the ethanolic stem extract of *Arcangelisia flava* in inhibiting xanthine oxidase. This research, conducted at the Medical Basic Chemistry Laboratory Universitas Sriwijaya in September–December 2022, used in vitro study methods. The stem of *Arcangelisia flava* was extracted by maceration using ethanol. The ethanolic stem extract of *Arcangelisia flava* was then fractionated using n-hexane and ethyl acetate. The ethyl acetate fraction and ethanolic extract of *Arcangelisia flava* were measured to inhibit the xanthine oxidase using UV-vis spectrophotometry with allopurinol as a comparison. The IC_{50} was calculated by linear regression. The ethanol extract and ethyl acetate fraction have flavonoids, alkaloids, terpenoids, and quinones. The IC_{50} value of the ethanol extract was 30.04 ppm, the ethyl acetate fraction was 23.99 ppm, and the allopurinol was 17.16 ppm. The ethyl acetate fraction inhibited xanthine oxidase better than the ethanol extract. The study's significant finding is that the ethyl acetate fraction of the ethanolic stem extract of *Arcangelisia flava* strongly inhibits xanthine oxidase, offering a potential new avenue for treating hyperuricemia.

Keywords: *Arcangelisia flava*, ethyl acetate fraction, xanthine oxidase inhibitory

Introduction

One of the common diseases in society is hyperuricemia, or what is commonly called gout arthritis. Hyperuricemia is generally when uric acid levels are >7 mg/dl in the blood. Uric acid levels >6.8 mg/dl significantly increase the risk of uric acid crystallization.[1] Crystallization of uric acid occurs in soft tissues and joints through monosodium urate crystals, which appear as needle-shaped crystals when viewed under a microscope. Uric acid deposition, such as uric acid stones, can also occur in the kidneys, usually mixed with calcium oxalate crystals.[2]

The first-line treatment of hyperuricemia is a xanthine oxidase inhibitor, namely allopurinol.[3] This drug blocks the transformation of uric acid precursors into uric acid.[4] The xanthine oxidase functions in the production of uric acid by destroying purine nucleotide.[5] Allopurinol could be a xanthine oxidase inhibitor broadly used to treat gout. Allopurinol is additionally an uncommon but well-known cause of possibly extremely intense liver damage that habitually presents with noticeable extreme touchiness highlights such as those seen with sedate response with eosinophilic and systemic side effects. This incorporates fever, broad hasty, eosinophilic, a typical lymphocytosis, lymphadenopathy, and other organ-inclusion with ordinary idleness of 2–6 weeks.[6]

Natural xanthine oxidase inhibitors using phytomedicines (herbal medicines) are increasing.[7] One of them is yellow wood (*Arcangelisia flava*).[1,8–11] *Arcangelisia flava* in Figure was found in Sumatra, Java, Kalimantan,

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Sulawesi, Nusa Tenggara, Halmahera, Papua, Thailand, Philippines, Indochina, and Malaya.[12,13] The part of *Arcangelisia flava* was generally used as a traditional medicine by Southeast Asians as an antibacterial, antidiarrhea, antiasthma, antimalarial, antifungal, and antitumor for its stem. However, other plant parts, such as the roots, are occasionally used.[1,8–11]

The secondary metabolite compounds of *Arcangelisia flava* were alkaloids, saponins, tannins, and flavonoids.[1,11] Quercetin, which is one of the flavonoids, has been clinically proven to be able to treat gout through inhibition of xanthine oxidoreductase, which is the last step in the production of intracellular uric acid, by administering tablets containing 500 mg of quercetin for four weeks, can significantly reduce plasma uric acid concentration by 26.5 μmol/l.[14] Methanol extract of *Arcangelisia flava* has a phenolic content of 6.274 mg GAE/g and a total flavonoid content of 1.66%.[8] The xanthine oxidase inhibitory of ethanol extract of *Arcangelisia flava* showed that the stem (IC_{50}=30.44 ppm) has the activity of lowering uric acid levels better than the leaves (IC_{50}=174.62 ppm).[15] Ethanol is a universal solvent, so ethanol extracts can provide large yields and high phytochemical results. Because it is not yet known which fraction is active from this ethanol extract against the inhibition reaction, it is necessary to fractionate using solvents with different polarity, especially semi-polar solvents such as ethyl acetate, where ethyl acetate solvents can dissolve certain flavonoid compounds. The study aimed to determine the effectiveness of the ethyl acetate fraction from the ethanolic stem extract of *Arcangelisia flava* in inhibiting xanthine oxidase.

Methods

All protocols were based on the certificate of ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya No. 104-2022. The stem of *Arcangelisia flava* was obtained from Musi Rawas district, South Sumatera, Indonesia, and determined in the Biosystematics Laboratory, Department of Biology, by the Faculty of Mathematics and Natural Sciences, Universitas Sriwijaya, Palembang, in September–December 2022 used in vitro study method.

The extraction method used in this study was a meticulous cold extraction with maceration. A 750 g stem of *Arcangelisia flava* simplicia was soaked in 96% ethanol for 3×24 hours and filtered. This process involves maceration three times with 96% ethanol, ensuring a comprehensive extraction. The extract filtrate was dried using a rotary evaporator. The ethyl acetate fraction was prepared from the ethanolic stem extract of *Arcangelisia flava* by putting 23 g of ethanol extract into a separatory funnel, adding 250 ml of n-hexane, shaking it for 30 minutes, and then letting it stand. Separate the filtrate and residue. This liquid-liquid extraction was repeated three times, ensuring the thoroughness of the process. The remaining extract obtained from the first extraction was again reacted with 250 ml of ethyl acetate, shaken for 30 minutes, and allowed to stand again to form the remaining extract and ethyl acetate filtrate. The ethyl acetate filtrate was evaporated to obtain the ethyl acetate fraction from the ethanolic stem extract of *Arcangelisia flava*. A comprehensive approach was used to identify second metabolites in simplicial

Figure Yellow Wood (*Arcangelisia flava*)

with qualitative analysis called phytochemical screening,[16,17] ensuring the accuracy and reliability of our results.

The solution was prepared by incorporating 1 mg of the sample into a beaker glass and adding a few drops of dimethyl sulfoxide (DMSO) until dissolved. Dissolve sample with sodium phosphate buffer pH 7.5 to 10 ml. The test stock solution with a concentration of 100 ppm was then diluted, and four kinds of concentrations were obtained: 50 ppm, 25 ppm, 12.5 ppm, and 6.25 ppm. Allopurinol solution was prepared by weighing 10.225 mg of allopurinol powder, adding four drops of 1 M NaOH, then putting it into a 5 ml measuring flask and adding CO_2-free aqua dest to the limit.

The xanthine substrate solution was prepared using the 99.5% xanthine substrate (Sigma-Aldrich, X0626), which has a mass weight of 152.11 g/mol. In this study, 100 ml of 0.15 mM xanthine substrate was used 0.15 mM xanthine substrate solution was prepared by incorporating 2.293 mg of xanthine substrate into a glass beaker, which was then dissolved with five drops of 1 M NaOH. This solution was added with sodium phosphate buffer pH 7.5 to reach a volume of 100 ml. The xanthine oxidase enzyme solution was prepared by adding 12.5 mg of xanthine oxidase from bovine milk lyophilized powder (Sigma-Aldrich, X4376) to a 5 ml measuring flask and dissolving it with phosphate buffer to a volume of 5 ml.

The xanthine oxidase inhibition assay procedure was performed using a UV-vis spectrophotometer using the method shown in Table 1.[17] The inhibition activity was calculated using the formula:

$$\%\text{inhibition}=((A-B)-(C-D))/((A-B))\times 100\%$$

Based on the results obtained after using this formula, the sample concentration and percentage inhibition of the xanthine oxidase enzyme were plotted using the linear regression equation (x, y): y=a+bx; with x: sample concentration, and y: enzyme inhibition presentation.

The calculation is continued by assessing the inhibition concentration of 50% (IC_{50}). IC_{50} shows the sample concentration that can inhibit the activity of the xanthine oxidase enzyme by 50%. After obtaining a linear equation (x, y), IC_{50} can be calculated by entering a value of 50 in the variable y so that the equation is obtained: $IC_{50}=(50-a)/b$; with a: intercept and b: slope.

Results

A 750 mg of *Arcangelisia flava* stem simplicia was macerated with 96% ethanol solvent to obtain 23.54 grams of ethanol-concentrated extract. From 23 grams of ethanol-concentrated extract, liquid-liquid fractionation was obtained so that the ethyl acetate fraction was 1.52 grams. The results of this yield can be seen in Table 2.

The ethanol extract and ethyl acetate fraction obtained were tested for secondary metabolite content using phytochemical tests, showing flavonoids, alkaloids, terpenoids, and quinone in

Table 1 Inhibition Xanthine Oxidase Enzyme Procedure

Substances	Volume (µL)					
	Blanco		Sample		Allopurinol	
	A	B	C	D	C	D
Phosphate buffer pH 7.5	300	300	300	300	300	300
DMSO	100	100	-	-	-	-
Sample	-	-	100	100	-	-
Allopurinol	-	-	-	-	100	100
Xanthine oxidase enzyme	-	100	-	100	-	100
Aqua dest	100	100	100	100	100	100
Incubated for 5 minutes at 37°C						
Xanthine substrate	200	200	200	200	200	200
Incubated for 30 minutes at 37°C						
HCl 0.5 M	200	200	200	200	200	200
Measure the absorbance at a wavelength of 293 nm						

Note: A: absorbance of blanco (without sample), B: absorbance control of blank (without sample and enzyme), C: absorbance of sample/allopurinol, D: absorbance control of sample/allopurinol (without enzyme)

Table 2 ***Arcangelisia flava*** **Stem Extraction Results**

Sample	Weight	Yield	
Ethanol extract	750 g	23.54 g	3.14%
Ethyl acetate fraction	23 g	1.52 g	6.61%

ethanol extract and ethyl acetate fraction (Table 3).

The inhibition of the ethyl acetate fraction compared to the ethanol extract was higher, especially at doses of 25 ppm, with inhibition differences of 30.25%. On the contrary, the inhibition of ethyl acetate fraction compared to allopurinol was only higher at doses of 50 ppm, with a difference in inhibition of 4.53%, and a difference in IC_{50} value of 6.83 ppm (Table 4).

The result shows that the ethyl acetate fraction has an IC_{50} value lower than ethanol extract and a higher IC_{50} than allopurinol. If the IC_{50} value is <25 ppm, the inhibitory ability of the substance is classified as very strong, the IC_{50}=25–50 ppm is strong, IC_{50}=50–100 ppm is less strong, and IC_{50}>100 ppm is weak. Allopurinol and the ethyl acetate fraction were classified as very strong inhibitors of the xanthine oxidase enzyme.

Table 3 Results of Phytochemical Screening of ***Arcangelisia flava***

Chemical Groups	Results	
	Ethanol Extract	Ethyl Acetate Fraction
Flavonoids	+	+
Alkaloid: Dragendroff	+	+
Alkaloid: Mayer	+	+
Alkaloid: Wagner	+	+
Tannins	–	–
Terpenoids	+	+
Steroids	–	–
Saponins	–	–
Quinones	+	+

Note: +: presence, –: absence

Discussion

Oxygen can be reduced by xanthine oxidase to superoxide anion, which will turn into hydrogen peroxide, a reactive oxygen species (ROS) toxic to cells in the body. In the presence of xanthine oxidase enzyme, xanthine/hypo-xanthine will be converted into uric acid. Uric acid is a pro-oxidant and can induce the formation of other radicals that can oxidize lipid membranes. Excessive xanthine oxidase activity can damage cells due to these free radicals.[17–19] To counteract ROS, antioxidants are needed. A large number of natural and synthetic products have been discovered.[17–22]

Several studies have shown that some plant extracts have antioxidant activity, such as the gooseberry plant, which can inhibit the cyclooxygenase enzyme, thus inhibiting the formation of prostaglandins.[20] Dry fruit extract of *Phaleria macrocarpa* (Scheff.) Boerl has an antioxidant effect at a dose of 62.5 mg.[21] Some plants that have essential oils also have potent antioxidant activity, such as clove extract,

Table 4 Xanthine Oxidase Inhibition and IC_{50}

Sample	Concentration (ppm)	Inhibition Percent	Linear Regression Equation	IC_{50} (ppm)	Inhibition Effect
Ethanol extract	50	79.16	y=1.53x+4.12	30.04	Strong
	25	42.69			
	12.5	31.32			
	6.25	6.49			
Ethyl acetate fraction	50	83.29	y=1.65x+10.37	23.99	Very strong
	25	72.94			
	12.5	34.98			
	6.25	5.14			
Allopurinol	50	87.82	y=1.30x+27.63	17.16	Very strong
	25	70.43			
	12.5	48.24			
	6.25	26.25			

while the nanoemulsion form with a combined formulation of clove extract and grape seed oil, it was found that the less the concentration of clove extract, the smaller the antioxidant activity.[22]

Based on previous literature studies, some secondary metabolites that have been investigated can inhibit the enzyme xanthine oxidase, including flavonoids, alkaloids, saponins, tannins, and terpenoids.[1,11,15,18,19] In the results of the phytochemical test, the ethanol extract and ethyl acetate fraction of the ethanolic stem extract of *Arcangelisia flava* contains secondary metabolites such as flavonoids, alkaloids, and terpenoids, which are bioactive compounds in plants that can inhibit xanthine oxidase enzyme.

In another study, the ethyl acetate extract of the flesh of *Salacca edulis* Reinw. was more active in inhibiting xanthine oxidase with an IC_{50} value of 24.75 ppm. In contrast, ethanol extract has an IC_{50} value of 44.95 ppm.[23] Phytochemical testing of *Arcangelisia flava* (L.) Merr. contained tannins, triterpenoids, and alkaloids. From analyzing the chemical compounds are known as 9-octadecenoic acid (Z)-(CAS) oleic acid (40.42%); 3,6-octadecadienoic acid methyl ester (CAS) methyl 3,6-octadecadienoate (24.88%); hexadecanoic acid (CAS) palmitic acid (6.54%); 9-octadecenoic acid (Z)-, methyl ester (CAS) methyloleate (4.56%); and phenol, 2-methoxy-(CAS) guaiacol (3.19%).[24]

The roots of this plant contain glycosides and alkaloids, particularly the isoquinoline group, specifically berberine, jatrorizin, and palmatine. There are minor alkaloids such as columbamine, dehydrocoridalmin, homoaromolin, talifendin, and diterpene fibraleusin. From phytochemical study on the *Arcangelisia flava* have alkaloid group (berberine, thalifendine, jatrorrhizine, palmatine, columbamine, dehydrocorydalmine, dihydro berberine, 8-hydroxy-berberine, homoaromoline, limacine, pycnarrhine), terpenoids group (fibleucin, 6-hydroxyfibleucin, fibraurin, 6-hydroxyfibraurin, tinophyllol, 2-dehydroarcangelisinol, 6-hydroxyarcangelisin, 2a,3a-epoxy-2,3-dihydropenianthic acid methyl ester, 2a,3a-epoxy-2,3,7,8a-tetrahydropenianthic acid methyl ester, 2b, 3a-dihydroxy-2,3,7,8a-tetrahydropenianthic acid-2,17-lactone), others group (p-hydroxybenzaldehyde, vanillin, 20-hydroxyecdysone, pachybasin).[11]

Arcangelisia flava stem extract indicates the content of berberine compounds in large quantities. Berberine had a bright yellow color at TLC and appeared in the 420 nm area in the UV-vis spectrum.[25] Berberine has anti-inflammatory and antiangiogenic effects in a rheumatoid arthritis rat model by decreasing inflammatory factors and suppressing p-ERK, p-p38, and p-JNK activation. Moreover, it is detailed that doxanthine oxidaserubicin-induced vascular congestion and inflammatory cell penetration within the liver were vastly weakened by berberine pretreatment.[26]

Conclusion

The ethyl acetate fraction of the ethanolic stem extract of *Arcangelisia flava* has antihyperuricemia potential with better xanthine oxidase inhibition than the ethanol extract.

Conflict of Interest

All of the authors have declared that they have no conflicts of interest.

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RESEARCH ARTICLE

Exploring the Association between Diabetes Mellitus, Obesity, and Recurrent Stroke Events: a Cross-sectional Study

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Abstract

Stroke is the most significant cause of death and cause of disability in the world because it causes neurological deficits in sufferers, such as muscle paralysis, swallowing weakness, communication damage, and vision disorders to cause death. Stroke can be recurrent and have a severe impact compared to the initial attack. The purpose of this study was to explore the association between diabetes mellitus, obesity, and the incidence of recurrent strokes in post-stroke patients at a regional general hospital in Aceh province. It is a cross-sectional study carried out from 3–12 August 2022. The sampling technique used in this study was a purposive sampling of 154 patients. The instruments used were questionnaires of patient demographic characteristics, data analysis using chi-square assays, and logistic regression. The results showed that there was no association between diabetes mellitus ($p>0.05$) and obesity ($p>0.05$) with the incidence of recurrent strokes. One of the preventive measures for the occurrence of recurrent strokes is to provide education about the prevention of recurrent strokes related to diabetes mellitus and obesity, one of which is a healthy lifestyle. In conclusion, there is no relationship between diabetes mellitus, obesity, and the incidence of recurrent strokes in post-stroke patients at a regional general hospital in Aceh province.

Keywords: Diabetes mellitus, obesity, recurrent strokes

Introduction

Stroke is a condition of nervous disorder characterized by blockage or rupture of blood vessels, which causes a reduction or disruption in the blood supply to the brain, causing brain cells to die due to insufficient or inadequate oxygen and nutrition.[1–3] Stroke is the second major cause of death and disability worldwide.[4–6] In 2019, there were 12.2 million incident cases of stroke, 101 million prevalent cases of stroke, 143 million disability-adjusted life-years (DALYs) lost due to stroke, and 6.55 million deaths from stroke. The incidence of strokes increased by 70.0%, prevalent strokes increased by 85.0%, deaths from stroke increased by 43.0%, and DALYs due to stroke increased by 32.0%. The burden of stroke in people younger than 65 has increased worldwide, the incidence has increased by 25% among adults aged 20–64; and stroke burden towards younger age groups, particularly in low- and middle-income countries.[5,7–9] The number of deaths due to stroke reached 252,473 cases or 14.83% of the total deaths due to disease in Indonesia. Indonesia is ranked seventh in the world for death rate due to stroke.[10]

The incidence of recurrent strokes is a critical clinical endpoint, leading to death, re-hospitalization, and long-term disability. Neurological disorders caused by recurrence are more serious, more difficult to treat, and have a higher mortality rate. Therefore, the study emphasizes the essential need for secondary prevention after the first stroke to reduce recurrence. This is a key takeaway from the study that healthcare practitioners and researchers should consider in their practice and future research.[11,12]

One prevention that can be done is to minimize the risk factors for recurrent strokes from modifiable risk factors, especially obesity.[13–17] This is supported by several studies that state that physical activity, age, gender, hypertension, diabetes mellitus, obesity, and cholesterol

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are factors associated with the occurrence of recurrent strokes.[16,17]

Data on stroke patients who recovered at a regional general hospital in Aceh province is still high; stroke patients also often experience repeated hospitalizations. Based on the description, this study aims to understand the link between diabetes mellitus and obesity and the incidence of recurrent strokes. The objective of this study was to explore the association between diabetes mellitus, obesity, and the incidence of recurrent strokes in post-stroke patients at a regional general hospital in Aceh province.

Methods

Quantitative research with a cross-sectional study was conducted at a regional general hospital in Aceh province in Indonesia. A total of 154 post-stroke patients who went to the Neuroscience Polyclinic participated in this study. Sampling criteria include patients who had an ischemic stroke more than once, were ≤25 years old, compos mentis consciousness, did not have aphasia, Wernicke and Broca, and were willing to be involved in this study with sign informed consent.

The data collection was carried out from 3–12 August 2022. The instrument used is a socio-demographic questionnaire. Technique data collection using health checks and guided interviews. Data analysis using a chi-square test. To overcome the trust of researchers to set inclusion criteria, a detailed description of the research arrangements should be created using questionnaires that have been tested for content validity by experts. This instrument has also undergone a content validity test by 2 (two) expert personnel, namely a neurology specialist doctor and a nursing doctor. Ethical clearance was obtained from the Research Ethics Committee, Faculty of Nursing, Universitas Syiah Kuala, Banda Aceh with ethics number 112018140722.

The univariate and bivariate analyses were used to analyze the collected data. In this study, univariate analysis was carried out to obtain the frequency distribution of each independent variable (diabetes mellitus and obesity) and the frequency distribution of the dependent variable (recurrent stroke incidence). Bivariate analysis uses the chi-square test to see the association between independent and dependent variables.

Results

The socio-demographic characteristics of stroke patients in this study can be seen in Table 1. Most stroke patients at a general regional hospital in Aceh province were aged between 41–60 years (58.1%), and a higher proportion of females (57.8%) than males. Sixty-nine (44.8%) stroke patients were self-employed, 105 (68.2%) had primary school education, and 128 (83.1%) were married. Risk factors for recurrent stroke in subjects were 88 (57.1%) did not have diabetes mellitus and 102 (66.2%) were not obese.

Meanwhile, Table 2 shows that as many as 154 post-stroke patients who were treated at a regional general hospital in Aceh province experienced recurrent strokes, with 125 (81.2%) patients experiencing recurrent strokes ≤2 times.

Table 1 Socio-demographic Characteristics of Stroke Patients

Characteristics	n=154	%
Age (years)		
18–40	10	6.5
41–60	90	58.4
>61	54	35.1
Gender		
Man	65	42.2
Woman	89	57.8
Employment		
Unemployment	39	25.3
Retiree	4	2.6
Farmer	26	16.9
Civil servants	16	10.4
Self-employed	69	44.8
Education		
Primary school	105	68.2
Junior high school	13	8.4
Senior high school	36	23.4
Marital status		
Unmarried	2	1.3
Married	128	83.1
Divorced	24	15.6
Diabetes mellitus		
Not	88	57.1
Yes	66	42.9
Obesity		
Not	102	66.2
Yes	52	33.8

Table 2 Incidence of Recurrent Strokes

Recurrent Strokes	n=154	%
Age (years)	10	6.5
Obesity	102	66.2

Table 3 shows the association between diabetes mellitus, obesity, and the incidence of recurrent strokes in post-stroke patients at a general regional hospital in Aceh province. The results showed that most post-stroke patients who experienced recurrent stroke ≤2 times and >2 times did not have diabetes mellitus, 71 (80.7%) and 17 (19.3%), respectively. Meanwhile, most patients who were not obese and experienced recurrent stroke ≤2 times and >2 times were 85 (83.3%) and 17 (16.7%), respectively. There was no association between diabetes mellitus, obesity, and recurrent strokes, with p-values of 1.000 and 0.457, respectively (p>0.05).

Discussion

The results of the study found that 88 (57.1%) post-stroke patients did not suffer from diabetes mellitus, as many as 71 (80.7%) patients experienced recurrent strokes ≤2 times, and 66 (42.9%) post-stroke patients with diabetes mellitus, as many as 54 (81.8%) patients experienced repeated strokes >2 times, the results of the analysis showed a p-value of 1.000 which means that there is no relationship between diabetes mellitus and the incidence of recurrent strokes. This research is in line with previous research conducted by several researchers that there is no relationship between diabetes mellitus and the incidence of recurrent strokes.[18,19]

Different studies show diabetes mellitus is a risk factor for intracranial stenosis. Diabetes increases the accelerated formation of atherosclerotic stenosis through a decrease in fibrinolytic activity. Based on this study, the odds ratio associated with diabetes mellitus ranges from 4 to 5.9.[20] Patients with intracranial atherosclerosis had a higher prevalence of diabetes mellitus (67%) than those with osteosclerosis extracranial atherosclerosis (60% and 48%, respectively).[11]

The systematic review and meta-analysis carried out summarize the available data on the effects of diabetes on stroke recurrence among patients with ischemic stroke and its subtypes. The study found a significant risk of stroke recurrence in ischemic stroke patients with diabetes compared to those who were not diabetic.[21] Of all the risk factors, the available data strongly link diabetes to the occurrence of stroke. Diabetes does not depend on other conventional risk factors for stroke (especially ischemic stroke) and provides a risk of more than two times for various vascular diseases. Says that people with diabetes mellitus are at risk of developing other diseases, including heart disease, peripheral artery disease, and cerebrovascular disease (stroke).[22]

The study results found that out of 154 respondents, as many as 102 (66.2%) respondents did not have obesity, and as many as 52 (33.8%) respondents were obese. Furthermore, it was found that out of 154 respondents, as many as 102 respondents who were not obese but suffered recurrent strokes ≤2 times as many as 85 (83.3%) and who had repeated strokes >2 times as many as 17 (16.7%), of the 52 respondents who had obese strokes and had repeated strokes ≤2

Table 3 Association between Diabetes Mellitus, Obesity, and the Incidence of Recurrent Strokes

Risk Factors	Recurrent Strokes				Total		α	p
	≤2 Times		>2 Times					
	n=154	%	n=154	%	n=154	%		
Diabetes mellitus								
None	71	80.7	17	19.3	88	100	0.05	1.000
Not none	54	81.8	12	18.2	66	100		
Obesity								
Not	74	84.1	14	15.9	88	100	66.2	0.457
Yes	85	83.3	17	16.7	102	100	33.8	

times as many as 40 (76.9%) and those who had repeated strokes >2 times as many as 12 (23.1%). The analysis results showed a value of p=0.457, which means there is no relationship between obesity and the incidence of recurrent strokes. Overweight and obesity are the accumulation of abnormal or excessive fat that poses a health risk. A person with a BMI of 30 kg or more is considered obese, and a BMI equal to or more than 25 kg is considered overweight.[23] Being overweight or obese is a significant risk factor for several chronic diseases, including diabetes, heart disease, and cancer.[24]

The results of this study are in line with research that has been conducted, which found that obesity is not a causal factor in recurrent strokes in patients.[25] However, the result of a different study concluded that obesity is a significant risk factor for recurrent stroke.[26] A healthy lifestyle including a high diet quality, and a high level of physical activity was shown to significantly reduce the risk of the incidence of recurrent strokes in patients.[17]

Conclusion

This study concluded that there was no association between diabetes mellitus, obesity, and the incidence of recurrent strokes in post-stroke patients at a regional general hospital in Aceh province.

Conflict of Interest

There is no conflict of interest in this study.

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