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Analysis of Potentially Inappropriate Prescriptions (PIP) Based on STOPP/START Criteria in Geriatric Patients with Cardiovascular Disorders at Hasan Sadikin Hospital, Bandung, West Java, Indonesia

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Abstract

The geriatric population in Indonesia is increasing rapidly every year. The large number of drugs consumed by geriatric patients results in potentially inappropriate prescriptions (PIP) in the form of mis-prescribing drugs (potentially inappropriate medicines or PIM) and under-prescribing drugs (potentially prescription omission or PPO). In Indonesia, especially in Bandung, there is limited research on PIP in geriatric patients with cardiovascular disorders (CVDs), while other studies only conducted PIM in generally geriatric patients. This study aims to identify PIP and factors that influence PIM and PPO based on STOPP/START criteria and the relationship between the incidence of PIM and kidney function in geriatric inpatients with CVDs at Hasan Sadikin Hospital, Bandung, West Java, Indonesia. The present retrospective study was cross-sectionally conducted from January to December 2022. The Chi-square tests were carried out to determine factors that were significantly related to PIM and PPO. Of the 192 patients, 33.4% patients experienced PIM with the most being NSAIDs with eGFR <30 mL/min/1.73 m2 (36%). As many as 35% of patients experienced PPO with the most frequent PPO not being given angiotensin-converting enzyme inhibitor (ACEi) in patients with systolic heart failure (41.8%). Factors that were significantly associated with PIM were comorbid kidney dysfunctions (OR 5; 95% CI: 2.367-10.342), and no factors were found that were significantly associated with PPO. Taking everything into consideration, it was found that PIM and PPO were common in hospitalized geriatric patients with CVDs. Kidney dysfunctions are a risk factor for PIM. These findings suggest that it is important to evaluate prescribing for geriatric patients during hospitalization using STOPP/START criteria to reduce the prevalence of PIP. Optimizing prescribing to reduce PIP may provide improvement health outcomes and decrease adverse drug reaction (ADR) risk.

Keywords*:* angiotensin-converting enzyme inhibitor; cardiovascular disorders; potentially inappropriate medicines; potentially inappropriate prescriptions; potentially prescription omission

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Introduction

The global geriatric population is predicted to elevate from 9.3% in 2020 to approximately 16.0% in 2050 due to the tendency of a longer life expectancy.[1] Similarly in Indonesia, the geriatric population is expected to rapidly arise. It was reported that in 2020 the geriatric population in Indonesia reached an alarming rate of 9.92%, whereas in 2021 the population aged 65 years or more attained 10% in West Java.[2,3]

People with longer life expectancy often suffer from multimorbidity due to progressive homeostasis disorders related to the decrease of physiological function, pharmacokinetics, and pharmacodynamics.[4] Multimorbidity is linked with an increased risk of death, ailment, dysfunction of the organ, low quality of life (QoL), and adverse drug events (ADEs), which eventually implicates polypharmacy (the simultaneous use of five or more medicines by a patient to alleviate his numerous diseases.[5]

Polypharmacy in elderly patients often causes the escalation of PIP and unsafe prescribing. On that account, amending drug prescribing for elderly patients is crucial to ensure medication safety.[6] A useful strategy to identify PIP and to impede prescribing errors in multimorbid geriatric patients is by routinely applying STOPP/START (screening tool for older people's prescriptions/screening tool to alert doctors to the right treatment) criteria.[7] STOPP/START is an accurate, decent, and comprehensive screening tool that authorizes the physician to evaluate the prescription drugs of an elderly patient on his coexistent diagnoses.[8] STOPP criteria are designed to detect and identify PIM, whereas START criteria are focused on PPO.[7]

The occurrence of at least 1 PIM was found in 51% of 101 patients, while that of at least 1 PPO was found in 74% of 147 patients. The most common PIM was the treatment of aspirin in patients with no history of coronary, cerebral, or peripheral arterial disease. The most common PPO was not prescribing HMG-CoA inhibitors to patients with coronary, cerebral, or peripheral vascular disease.[9] Additionally, it was reported that an incidence of at least 1 PIM occurred at a range of 36.9 to 51.0%, whereas at least 1 PPO varied between 36.9 and 44.6% in a total of 249 older patients. The most common PIM was the use of proton pump inhibitors while the most common PPO was the omission of vitamin D supplements, thus a considerable observation is required by actively de-prescribing medicines that are not beneficial and starting advantageous medications.[10] PIPs and PIMs were persistent in elderly patients at hospital discharge and were linked with worsened re-hospitalizations and dependence on the activity of daily living 3 months after discharge.[11]

Several studies of PIM prescription were reported in Indonesia. A study conducted at Dr. H. Abdul Moeloek Hospital Lampung, Indonesia in 2018, described that the most PIM (25.81%) was the use of statins in older patients with coronary heart disease and cerebral vascular disease. There was a notable correlation between the occurrence of PIM and comorbidities.[12] Recently, the Indonesian version of STOPP (STOPP_INA) was developed using modified transcultural adaptation guidelines from the American Academy of Orthopedic Surgeons. The expert panel had agreed on a list of 81 criteria for adaptation of STOPP version 2 which was currently being evaluated clinically on hospitalized geriatric patients.[13]

Another study evaluated the STOPP/START to improve the Adapted Medication Appropriateness Index (MAI), the risk of ADRs, and the length of stay (LOS) in the Geriatric Inpatient Ward, Sanglah General

Hospital, Bali, Indonesia, concluded that the use of STOPP/START had improved medication appropriateness and reduced ADR risk and LOS.[14] However, these studies only identify PIM use which is not comprehensive in assessing both PIM and PPO and their associated factors.

Taking everything into consideration, our work aims to analyze PIP based on STOPP/START criteria in geriatric patients with CVD at Hasan Sadikin Hospital, Bandung, West Java, Indonesia.

Methods

The protocol of the study was approved by the Research Ethics Committee of Universitas Padjadjaran Bandung, Indonesia, with the approval document number 830/UN6.KEP/EC/2022. The study has been granted permission by Hasan Sadikin Hospital Bandung with the document number LB.02.01/X.2.2.1/18741/2022. The data of inpatients were taken from the medical records from January to December 2022.

The design of the study was an observational cross-sectional retrospective. Data were collected at the Geriatric Ward, Hasan Sadikin Hospital Bandung, West Java, Indonesia. The inclusion criteria were the medical record number, name of the patient, age, gender, date of hospital admission and discharge, patients who were diagnosed with CVD according to the ICD 10, having comorbidities, name of multiple medications and duration of therapy, and laboratory data.

The exclusion criteria were patients with incomplete medical records, patients who underwent hemodialysis, and patients with >5 comorbidities. The screening tools to detect and identify potentially PIM and PPO were the STOPP/START version 2. This tool was published in 2015 with comprises 65 STOPP criteria and 22 START criteria. The criteria are a consensus of 19 geriatrics pharmacotherapy experts based on published studies and have been validated using the Delphi method. The STOPP and START criteria are arranged according to the body for ease of use and rapid application by clinicians which are used to assess treatment in the group over 65 years by looking at the risks and benefits.[8]

Data were collected on a Microsoft Excel in percentage (%). Variables were age, gender, comorbidities, LOS, and number of medications. Chi-square was applied to identify PIM and PPO in three age groups (65- 74, 75-84, and ≥ 85 years old), gender, comorbidities, number of medications (< 5 and ≥ 5 drugs), and LOS (< 5 days and ≥ 5 days). Variables with a P value ≤ 0.25 were further analyzed using the Multivariable Binary Logistic Regression and data were presented as odds ratios (ORs) and CI 95% with a P value of < 0.05 as significantly different. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) 25 for Windows.

Results and Discussion

The medical records of 261 geriatric inpatients (age > 65 years old) were initially collected in this study, however, only 192 data fulfilled the inclusion criteria (tabulated in Table 1). The retrospective data from the medical records of the 192 included geriatric inpatients revealed the occurrence of PIP at 134 (69.9%). Overall, there were 180 incidences of PIP, of which 89 (49.4%) were PIM and 91 (50.6%) were PPO. According to the STOPP criteria, 64 (33.4%) patients experienced at least 1 PIM, while following START criteria, 51 (26.6%) patients experienced at least 1 PPO. The details are presented in Table 2. The occurrence of PIP in geriatric inpatients based on the STOPP/START criteria is presented in Table 3.

The main findings of the present study in geriatric inpatients at Hasan Sadikin Hospital Bandung are (1) the incidence of PIP in geriatric inpatients was high (69.9%), of which 49.4% were PIM and 50.6% were PPO; (2) the most prescribed PIMs were NSAIDs to patients with an eGFR <50 ml/minute/1.73 m2 (36.0%), followed by the combination of NSAIDs with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis (25.8%); (3) factors affecting PIM were hypertension (P = 0.209), diabetes mellitus (P = 0.022), kidney dysfunction (P = 0.000), infectious disease (P = 0.196), osteoarthritis (P = 0.217), cancer (P = 0.078), liver dysfunction (P = 0.217), LOS (P = 0.152), and the number of medications (P = 0.206); (4) factors affecting PPO were hyperlipidemia (P = 0.074), respiratory disorders (P = 0.137), and infectious disease (P = 0.086), presented in Table 4. Variables with a P value ≤ 0.25 were further analyzed using the Multivariable Binary Logistic Regression and data were presented as odds ratios (ORs) and CI 95% with a P value of < 0.05 as significantly different in Table 5; and (5) a significant correlation between comorbidity and the incidence of PIM, in particular, kidney dysfunction was the main factor affecting PIM.

Studies of PIP in Indonesia are very limited. In fact, we found less than ten studies on PIM in Indonesia. To the best our knowledge, this is the first study conducted in Indonesia among geriatric patients with cardiovascular disorders at RSUP dr. Hasan Sadikin Bandung that identify comprehensively both PIM and PPO using the STOPP/START criteria version 2. Most patients found in this study were in the 65-74 year age group (79.2%). This research only included patients with cardiovascular disorders. More than a quarter of STOPP criteria are related to the cardiovascular system, possibly increasing the probability of identifying a greater number of cases satisfying the STOPP criteria. A total of 89 instances of PIM were identified and the three most frequent PIM were NSAIDs to patients with an eGFR <50 ml/minute/1.73 m^2 (36.0%), other NSAIDs were combined with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis (25,8%), and aspirin plus clopidogrel were prescribed to prevent the occurrence of secondary stroke (6,9%). These PIMs are related the renal system, the cardiovascular system, and antiplatelet/ anticoagulant drugs, respectively.

The three most common PPO were related to the cardiovascular system: ACEi in patients with chronic heart failure (38; 41,8%), beta-blockers for ischemic heart disease (22; 24,1%), and statin for coronary/cerebral/ peripheral vascular diseases (13; 14,3%). In comparison to our results, the study conducted at the hospital in Lampung, Indonesia, described that the PIM (25.81%) was in the use of statins in older patients with coronary heart disease and cerebral vascular disease. The authors also confirmed that there was a notable correlation between the occurrence of PIM and comorbidities.[12]

The retrospective observational study conducted at primary healthcare facilities in Karawang, Indonesia, reported a high prevalence of PIM (52.2%) in older patients, with the most prescribed PIM were chlorpheniramine, mefenamic acid, ibuprofen, and nifedipine.[15] The other study conducted on 91 older outpatients at a hospital in Jakarta, described the PIM as 1.9% of a total of 560 drugs which were benzodiazepines, anticholinergics, antipsychotics, and glimepiride.[16] The prevalence of PIM at a regional public hospital in Banjarmasin was 63.1%.[17]

Table 1. Characteristic of the geriatric inpatients at Hasan Sadikin Hospital Bandung

Characteristics	Number (n)	(%)
Age (years old)		
65-74	152	79.2
75-84	37	19.3
≥ 85	3	1.6
Gender		
Male	136	70.8
Female	56	29.2
Comorbidities		
Hypertension	117	61.0
Kidney dysfunction	63	33.0
Diabetes mellitus	52	27.0
Respiratory disorders	36	19.0
Hyperlipidemia	28	15.0
Electrolyte imbalance	28	15.0
Infectious disease	16	8.3
Gastrointestinal disorders	15	8.0
Nervous system disorders	9	5.0
Hematology disorders	7	4.0
Cancer	6	3.0
Osteoarthritis	3	1.6
Liver dysfunction	3	1.6
Number of medications		
≥ 5 medications	180	93.8
< 5 medications	12	6.3
Length of stay		
≥ 5 days	103	53.6
< 5 days	89	46.4

Table 2. Geriatric inpatients at Hasan Sadikin Hospital Bandung that were categorized by STOPP/START

Number of criteria per patient	STOPP		START	
	Number (n)	%	Number (n)	%
1	47	24.5	51	26.6
2	9	4.7	17	8.9
3	8	4.2	2	1.0
Total	64	33.4	70	36.5

STOPP (screening tool for older people's prescriptions); START (screening tool to alert doctors to the right treatment)

A cross-sectional study using the medical records of geriatric patients at the tertiary hospitals in Chengdu, China, from 2016-2018 reported an increase in the incidence of PIM from 71.17% in 2016 to 73.39% in 2018. The common prescribed PIMs in inpatients were diuretics, benzodiazepines, NSAIDs, antipsychotics, and selective serotonin reuptake inhibitors.[18] Another high incidence of PIP was also reported in Korea. According to the STOPP criteria, most potential inappropriate prescribing was of cardiovascular medications (37,9%) and based on START criteria, the CVDs drugs also comprised most of the PPO (37%).[19] Similarly with our study, the most prescribed PIM and PPO were NSAID and cardiovascular medication. A cross-sectional study conducted at the university hospital in Sao Paulo, Brazil, announced that PIMs were received by 32 (13,9%) of 230 patients and PPOs were received by 90 (39,1%) patients. The most common PPOs were the absence of ACEi in patients with chronic heart failure (13%).[20]

Another study in Ethiopian geriatrics patients hospitalized with cardiovascular disorders also reported underuse of ACEi among hospitalized chronic heart failure (14,5%).[21] These study similar with our study showed a higher prevalence of this PPO (41,8%) because the physicians, depending on the patient's prognosis, did not consider the prescription of ACEi to be appropriate.

In the present study, almost all patients (91,6%) had comorbidities. Hypertension (61%), kidney dysfunction (33%), and diabetes mellitus (27%) were the three most frequent disease identified. In this study, kidney dysfunction diagnose was independently associated with PIM and those patients diagnosed with that comorbidity had a 4,95-fold increased risk of taking PIM than their counterparts. Most of patients received more than 5 medications in this study but failed to achieve statistical significance. In fact, concurrent use of 5 or more medicines is reported as a risk factor for a significant increase in PIM prescription.[22] Age, gender, and length of stay were not correlated with both PIM and PPO even in the binary regression analysis in our study. This could be attributed to the small sample size employed in the present study.

Our study demonstrated that the most prescribed PIMs were NSAIDs to patients with an eGFR <50 ml/minute/1.73 m^2 (36.0%). NSAIDs work by reversibly blocking the activity of both isoforms of cyclooxygenases, thus altering the production of prostaglandins in numerous tissues. NSAIDs were reported for their adverse effects on the kidney, gastrointestinal tract, and cardiovascular system. Numerous studies confirmed that NSAIDs have been linked with an elevated risk of acute kidney injury.[23]

Table 3. The occurrence of PIP in geriatric inpatients at Hasan Sadikin Hospital Bandung based on the STOPP/START criteria

PIP incidence	Number (n)	%
PIM	**89**	**49.4**
Digoxin was prescribed to a patient suffering heart failure with a normal function of the systolic ventricle	1	1.1
Loop diuretic was used to treat swollen ankles without clinical/biochemical/radiological evidence of heart failure, liver failure, kidney failure, or nephrotic syndrome	1	1.1
Loop diuretic was prescribed as the first-line medication for hypertensive patients	5	5.6
Thiazide diuretics were prescribed to a patient with hypokalemia (serum $K^+ < 3.0$ mmol/l), hyponatremia (serum $Na^+ < 130$ mmol/l), hypercalcemia (corrected serum $Ca^{2+} > 2.65$ mmol/l)	1	1.1
Aldosterone antagonists (such as spironolactone and eplerenone) were combined with ACEi, ARB, amiloride, or triamterene, without monitoring the levels of serum potassium	1	1.1
ACEi or ARB were prescribed to patients with hyperkalemia.	3	3.4
Beta-blockers were prescribed to patients with bradycardia (< 50 beats/minute), heart block type II, or complete heart block	3	3.4
Aspirin was prescribed in combination with vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors in patients with chronic atrium fibrillation	4	4.5
Aspirin plus clopidogrel were prescribed to prevent the occurrence of secondary stroke	15	6.9
Other NSAIDs were combined with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis	23	25.8
NSAIDs were prescribed to patients with an eGFR <50 ml/minute/1.73 m^2	32	36.0
PPO	**91**	**50.6**
Vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors were prescribed to patients with chronic atrium fibrillation	2	2.2
Antiplatelets (aspirin or clopidogrel or prasugrel or ticagrelor) were prescribed to patients with coronary/cerebral/peripheral vascular diseases	6	6.6
Antihypertensive medications were prescribed to patients with persistent SBP >160 mmHg and/or DBP >90 mmHg; or to diabetic patients with SBP >140 mmHg and/or DBP > 90 mmHg	4	4.4
Statins were prescribed to patients with coronary/cerebral/peripheral vascular diseases except for patients > 85 years old	13	14.3
ACEi was prescribed to patients with systolic heart failure and/or coronary arterial disorders	38	41.8
Beta-blockers for ischemic heart disease	22	24.1
Beta-blockers for persistent systolic heart failure	4	4.4
L-DOPA or dopamine agonists for patients with idiopathic Parkinson's disease	2	2.2
Total PIP	**180**	**100**

ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; DBP: diastolic blood pressure; L-DOPA: L-dihydroxyphenylalanine or levodopa; NSAIDs: non-steroid anti-inflammatory drugs; PIM: potentially inappropriate medicines; PIP: potentially inappropriate prescription; PPO: potentially prescription omission; SBP: systolic blood pressure;

Table 4. Statistical Analysis of the Variables Affecting PIM and PPO Occurrence in Geriatric Inpatients with Cardiovascular Disorders

Variable	PIM (N = 64)	Not PIM (N = 128)	P-Value	PPO (N = 70)	Not PPO (N = 122)	P-Value
Age (years old)						
65-74	49	103	0.811	58	94	0.338
75-84	14	23		12	25	
≥ 85	1	2		0	3	
Gender						
Male	17	39	0.575	21	35	0.847
Female	47	89		49	87	
Comorbidities						
Hypertension	43	74	0.209*	40	77	0.414
Diabetes mellitus	24	28	0.022*	22	30	0.305
Hyperlipidemia	7	21	0.311	6	22	0.074*
Respiratory disorders	11	25	0.695	17	19	0.137*
Kidney dysfunction	36	27	0.000*	26	37	0.333
Gastrointestinal disorders	4	11	0.568	5	10	0.793
Infectious disease	3	13	0.196*	9	7	0.086*
Hematology disorders	2	5	0.785	3	4	0.720
Osteoarthritis	2	1	0.217*	1	2	0.910
Cancer	0	6	0.078*	1	5	0.306
Nervous system disorders	3	6	1.000	2	7	0.363
Electrolyte imbalance	11	17	0.470	11	17	0.737
Liver dysfunction	0	3	0.217*	1	2	0.910
Length of stay						
≥ 5 days	39	64	0.152	66	114	0.300
< 5 days	25	64		4	8	
Number of medications						
≥ 5 medications	62	118	0.206*	41	62	0.816
< 5 medications	2	10		29	60	

* indicates the variable may affect PIM or PPO (P < 0.25); PIM: potentially inappropriate medicines; PPO: potentially prescription omission

Table 5. The Multivariable Binary Logistic Regression of Factors Affecting PIM Occurrence in Geriatric Inpatients with Cardiovascular Disorders

Variable	P value	OR	CI 95%
Comorbidities			
Hypertension	0.266	1.50	0.735-3.062
Diabetes mellitus	0.118	1.81	0.861-3.797
Kidney dysfunction	0.000*	4.95	2.367-10.342*
Infectious disease	0.128	0.34	0.083-1.368
Osteoarthritis	0.211	5.18	0.394-67.993
Cancer	0.999	N/A	N/A
Number of medications	0.166	3.26	0.613-17.298

International consensus guidelines recommend circumventing NSAIDs in patients with an eGFR value of less than 30 ml/minute/1.73 m^2.[24] A cohort study on 187 patients in Sweden, of whom 105 were using NSAIDs and 82 bought NSAIDs over the counter, described that 42% of those purchasing NSAIDs over the counter revealed an eGFR < 60 ml/minute/1.73 m^2. The study suggested that geriatrics were oblivious to the risks associated with NSAIDs, which include the risk of kidney injury.[25]

A cross-sectional study on adult patients with chronic kidney damage at the Main Alexandria University Hospital in Egypt concluded that drugs, e.g., diuretics or renin-angiotensin-aldosterone system inhibitors, that may demonstrate drug-drug interaction with NSAIDs, was reported in 36%. NSAIDs were suggested to be used with caution among chronic kidney damage patients.[26]

Another observed PIM was a combination of NSAIDs with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis, which was recorded at 25.8%. A combination of aspirin with clopidogrel (6.9%) was found in prescription to prevent the occurrence of secondary stroke.

The combination of NSAIDs with an antithrombotic given to elderly patients could escalate the risk for adverse events, such as concurrent bleeding. As reported in a retrospective cross-sectional, single-center study on 156 geriatric hospitalized patients at the Gondar University Hospital, Ethiopia, an inappropriate prescribing of antithrombotic therapy was observed.[27] It was clearly understood that there are numerous physiological changes and a continuous decline of organ function in elderly patients, e.g., a decrease in muscle mass and total water, in accordance with an increase in fat ratio, which may lead to the pharmacokinetics of drugs. A diminishing of the liver and kidney function may cause a slower metabolism and excretion process of drugs, thus, elevating the occurrence of toxicity.[28-30]

Conclusion

Our observational cross-sectional retrospective study conducted at the Geriatric Ward, Hasan Sadikin Hospital in Bandung, West Java, Indonesia, by employing STOPP/START criteria, confirmed that the incidence of potentially PIP in geriatric inpatients was high. The most prescribed PIMs were non-steroid anti-inflammatory drugs (NSAIDs) to patients with an eGFR <50 ml/minute/1.73 m^2, followed by the combination of NSAIDs with antiplatelets, vitamin K antagonists, direct thrombin inhibitors, or Xa factor inhibitors without PPI prophylaxis. There is a significant correlation between comorbidity and the incidence of PIM.

These findings suggest the importance of evaluating the prescriptions for geriatric patients during hospitalization to reduce the incidence of potentially inappropriate prescriptions. This research require future studies whether STOPP/START criteria application improved health outcomes and decrased cost.

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Conflict of Interest
None declare

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Cost-Effectiveness Analysis of Favipiravir and Remdesivir as COVID-19 Treatment in South Tangerang, Banten Province - Indonesia

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Abstract

COVID-19 is a contagious ailment primarily attributed to the severe acute respiratory syndrome coronavirus. Indonesia persists in confronting the COVID-19 pandemic, and South Tangerang City has emerged as one of the municipalities in Indonesia that has been significantly affected. There are two categories of medications employed for COVID-19 treatment according to government policies, namely favipiravir and remdesivir. This study aims to assess the cost-effectiveness of favipiravir and remdesivir medications at the South Tangerang General Hospital, Indonesia. The present study employs a retrospective research design characterized by a quantitative approach, utilizing cross-sectional methodologies. The analysis mostly consists of descriptive techniques. The sample consisted of 479 individuals, with 246 individuals receiving outpatient treatment and 233 undergoing inpatient treatment. The inclusion criteria for this study consisted of individuals diagnosed with COVID-19 who had tested positive for the antiviral medications favipiravir and remdesivir. The findings indicated that the Average Cost-Effectivenss Ratio (ACER) for inpatients treated with favipiravir was IDR 2,354,319,859, but for those treated with remdesivir, it amounted to IDR 3,501,513,488. Regarding the outpatient population utilizing favipiravir, the total expenditure amounts to IDR 420,083,118. Similarly, patients utilizing remdesivir incur a total expenditure of IDR 797,282,432. It is worth noting that the Cost-Effectivenss Ratio (CER) for patients using favipiravir is IDR 1,545,621, whereas patients using remdesivir have a CER of IDR 2,309,705. This study makes a valuable contribution to the existing body of research by demonstrating the cost-effectiveness of favipiravir. Consequently, future studies investigating the overall effectiveness of favipiravir in COVID-19 patients must employ more comprehensive criteria.

Keywords*:* COVID-19, CEA, favipiravir, remdesivir

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Introduction

The COVID-19 virus has disseminated across many global regions, including Southeast Asia, which ranks fourth in terms of recorded cases. Specifically, Southeast Asia has reported a total of 61,191,036 confirmed COVID-19 cases, with 806,499 fatalities.[1] Indonesia continues to grapple with the ongoing COVID-19 pandemic. According to national data, the cumulative number of verified COVID-19 cases in the country stands at 6,811,780, with a corresponding total of 161,865 deaths. The Banten Province is ranked fifth in terms of the number of cases, with a total of 363,348 reported cases and 2,982 fatalities. South Tangerang City, located in Banten Province, has recorded the highest number of COVID-19 instances within the region, amounting to 120,513 cases and resulting in 786 fatalities.[2]

The South Tangerang General Hospital serves as a designated healthcare facility for treating and managing people diagnosed with COVID-19. The hospital has observed a notable rise in the number of COVID-19 patients. This is evident from the data indicating that in 2020, there were 236 patients, followed by 1,056 patients in 2021, and further escalating to 1,240 patients in 2022. The COVID-19 pandemic presents a significant problem for hospitals due to the relatively high financial burden associated with managing patients affected by the virus. Hospitals are mandated to establish isolation facilities for patients, as well as provide additional medical interventions such as antiviral medications, oxygen therapy, and intensive care.[3]

The escalation of COVID-19 cases in Indonesia has led to a heightened need for medications that exhibit promising potential and have been identified as crucial components in COVID-19 treatment protocols. As per an official document titled "Decree of the Minister of Health number HK. 01.07/MENKES/4826/2021" about the maximum retail price of medications during the COVID-19 pandemic, the government has identified a total of eleven distinct categories of pharmaceuticals. To date, there remains a lack of targeted therapeutic interventions or treatments for the management of COVID-19.[4]

According to a study conducted by Rahmandani et al., in 2021, the research findings indicate that the ACER of oseltamivir IDR 4,419,677 was lower than the CER of favipiravir IDR 4,615,014. Consequently, the utilization of the more economically advantageous drug is oseltamivir in comparison to favipiravir.[5]

Methods

The present study employs a retrospective research design, adopting a quantitative approach and utilizing a cross-sectional method. The analysis primarily focuses on descriptive statistics, and the data collection process involves retrieving retrospective information from secondary sources. The present study utilizes secondary data comprising medical record data and billing data obtained from the South Tangerang General Hospital, specifically about patients diagnosed with COVID-19.

The present investigation was carried out during the period spanning from July 2022 to August 2023. The participants in this study consisted of individuals who tested positive for COVID-19, underwent COVID-19 medication therapy, and fulfilled the specified inclusion and exclusion criteria at the South Tangerang General Hospital in 2022.

The aforementioned inclusion criteria pertain to patients who have received a positive confirmation for COVID-19 and were currently receiving treatment at South Tangerang City Hospital. Additionally, these

criteria encompass COVID-19 patients who were utilizing favipiravir and remdesivir medications, as well as those who have been deemed cured by medical professionals based on negative results from the Real-Time Polymerase Chain Reaction (RT-PCR) test.

The sampling technique employed in this study utilized a non-probability sampling approach, namely the purposive sampling method. The researchers employed the Lemeshow formula to ascertain the sample size utilized in this investigation. The findings indicate that the sample size for outpatients was 245.9, rounded to 246 samples. Similarly, the sample size for inpatients was 232.5, rounded up to 233 samples.

The present work has obtained ethical approval from the Ethics Committee for Medical and Health Research at Universitas Gadjah Mada. The document in question is an acceptance letter with the reference code KE/FK/1319/EC/2023.

Results and Discussions

Characteristics of Respondents

This study examined the demographic features of the respondents, including their age, gender, and medication usage. The data presented in Table 1 reveals that the age group exceeding 51 years has the highest prevalence of COVID-19 cases among both outpatients and inpatients in South Tangerang city, accounting for 35% and 37.8% respectively. Moreover, the prevalence of COVID-19 predominantly affects individuals of the female gender in both outpatient and inpatient settings, with respective proportions of 66.3% and 61.4%. Furthermore, in the context of pharmaceutical interventions for managing COVID-19 cases in South Tangerang city, a significant proportion of patients, specifically 78.5% of outpatients and 70.8% of inpatients, were administered favipiravir as the primary medication.

Ages

Based on the data collected in this study, it was observed that individuals who received inpatient and outpatient therapy with the medications favipiravir and remdesivir exhibited a higher proportion of respondents aged 51 years and above. Specifically, 35% of outpatients and 37.8% of inpatients fell into this age category.

Age is considered to be a significant risk factor in the transmission of the COVID-19 virus. This assertion is substantiated by a study undertaken by Dyana Sarvati in 2023, the study elucidates that the senior population represents a susceptible age group that is prone to a range of illnesses, including COVID-19.[6] The findings of this study are consistent with prior research conducted by Halimbar et al, 2023, at the Hajj Hospital in the East Java Province, which demonstrated that individuals between the ages of 51 and 60 exhibited the highest prevalence of COVID-19 infection.[7]

Sex

The demographic attributes of the respondents were collected in order to identify the individuals who participated in this study as COVID-19 patients. These attributes encompassed gender and age. According to the findings of this study, the gender distribution of COVID-19 patients receiving both inpatient and outpatient care was predominantly female. (66.3% of inpatients and 62.2% of outpatients). The findings of this study align with the statistics published on the official website of the government, which indicates a higher prevalence of COVID-19 cases among females compared to males in Indonesia. The findings of this study are further corroborated by Fathurrahman et al in 2023, which posits a higher prevalence of female patients relative to male patients.[8]

In addition, the COVID-19 pandemic has had a significant impact on the physical and psychological well-being of working moms, leading to increased workload and stress levels. These factors can have detrimental effects on the body's immune system, as highlighted by Safarina et al in 2021.This finding aligns with the research conducted by Khaerunnisa et al., in 2022, which suggests that women have a higher susceptibility to stress when confronted with novel situations.[8-10]

Pharmaceuticals

Remdesivir and Favipiravir are antiviral agents that have demonstrated efficacy in individuals with moderate to severe symptoms. These medications belong to the class of prodrug nucleotide analogues and are capable of inhibiting the RNA polymerase of the COVID-19 virus. In vitro studies have indicated their potential action against the SARS-CoV-2 virus.[11] The findings of this study indicate that the medications utilized by individuals diagnosed with COVID-19 throughout the 2022 timeframe, whether they were admitted to the hospital or received treatment as outpatients, predominantly consisted of Favipiravir. Specifically, 78.5% of outpatients and 70.8% of inpatients were discovered to have been prescribed this particular drug, as illustrated in Table 1.

The findings of the aforementioned study align with previous research conducted at the East Java Province Hajj Hospital, which indicates that the utilization of favipiravir is more prevalent among COVID-19 patients at the hospital as compared to remdesivir.[7] A previous study conducted by revealed that the utilization of the antiviral medication Favipiravir was more prevalent among COVID-19 patients in comparison to oseltamivir.[5]

The figure represents the total count of patients who have been prescribed and are currently utilising the pharmaceutical compounds known as favipiravir and remdisivir. Out of a total of 165 patients, 130 individuals, constituting 78.8% of the sample, utilised favipiravir. In contrast, a significant proportion of patients (79.4% or 54 out of 68) in the remdesivir group exhibited positive outcomes.

The efficacy of a medicine can be determined by the reduction in recovery time observed among patients. A recent study conducted at the East Java Province Hajj Hospital revealed that the average length of stay (LOS) for patients treated with favipiravir was 11.22 days, which was the shortest LOS seen. Conversely, patients treated with remdesivir had the greatest LOS, with an average of 13.13 days.[7] This phenomenon arises due to the utilisation of favipiravir, a purine nucleic acid analogue that has been authorised for the therapeutic management of influenza. The efficacy of this compound lies in its ability to effectively impede the RNA Polymerase (RdRp) of several viruses, including influenza, norovirus, and Ebola virus.[12]

Based on the preceding discourse, it is advisable that all healthcare personnel engaged in the provision of inpatient care consistently adhere to the Standard Operating Procedures governing the management of patients afflicted with COVID-19. It is imperative for all officers to possess knowledge regarding the specific classification of COVID-19 medication that aligns with the level of severity exhibited by the infection. The selection of appropriate complementary medication can potentially enhance the rate of recovery among COVID-19 patients receiving inpatient care.

Upon contrasting outpatients and inpatients in Table 3, it can be observed that favipiravir exhibits the best level of efficacy in treating patients with COVID-19. The efficacy rate of favipiravir for individuals receiving outpatient

Table 1. Characteristics Respondents

Characteristics of Respondents	Outpatients		Inpatients	
	n	%	n	%
Ages				
<25	40	16.3%	24	10.3%
26-30	31	12.6%	25	10.7%
31-35	24	9.8%	24	10.3%
36-40	25	10.2%	28	12.0%
41-45	18	7.3%	19	8.2%
46-50	22	8.9%	25	10.7%
>51	86	35.0%	88	37.8%
Sex				
Male	83	33.7%	90	38.6%
Female	163	66.3%	143	61.4%
Pharmaceuticals				
Favipiravir	193	78.5%	165	70.8%
Remdesivir	53	21.5%	68	29.2%

Table 2. COVID-19 Patients Length of Stay

Length Of Stay (LOS)	The specific pharmaceutical interventions for COVID-19 Patients			
	Favipiravir (n=165)		Remdesivir (n=68)	
	N	%	N	%
1-5 Days	29	17,6%	10	14,7%
6-10 Days	130	78,8%	54	79,4%
11-20 Days	6	3,6%	3	4,4%
>21 Days	0	0	1	1,5%
Total	165	100%	68	100%

The LOS for individuals diagnosed with COVID-19 is notably reduced to a range of 6 to 10 days when considering the administration of favipiravir and remdesivir medications

care is 78%, but for those receiving inpatient care, it is 71%. Based on the findings of the study, it can be inferred that the efficacy of favipiravir is attributed to its demonstrated effectiveness against positive-stranded RNA viruses, including noroviruses and flaviviruses. Hence, it exhibits antiviral properties against the SARS-CoV-2 virus. The findings indicate that the administration of favipiravir yields positive outcomes in enhancing the clinical condition of individuals afflicted with COVID-19.

Nowadays, favipiravir has been granted approval and is being employed as a therapeutic intervention for COVID-19 in several nations. According to the available published statistics and literature, the nations that have been reported to utilise favipiravir include China, Hungary, India, Korea, Poland, Portugal, Russia, Serbia, Thailand, and Turkey.[13,14]

Comparable findings were observed among individuals receiving inpatient care. The total cost of remdesivir for inpatients is IDR 9,005,714 or USD 586.04, which is considered to be relatively high. In the interim, it is noteworthy to mention that the price of Favipiravir is at IDR 7,232,512 or USD 470.65. The presumed rationale behind the substantial cost disparity between administering remdesivir to outpatients versus

Table 3. Comparative Analysis of the Efficacy of Drug Therapy between Outpatient and Inpatient COVID-19 Patients

Pharmaceutical interventions for COVID-19	Number of Outpatients	Effectiveness Parameters	Pharmaceutical Effectiveness (%)
Favipiravir	193	$= \frac{\text{Total patients who started recovery}}{\text{Total patients}} x\ 100\%$	78%
Remdesivir	53	$= \frac{\text{Total patients who started recovery}}{\text{Total patients}} x\ 100\%$	22%
Total		246	100%
Pharmaceutical interventions for COVID-19	Number of Inpatients	Effectiveness Parameters	Pharmaceutical Effectiveness (%)
Favipiravir	165	$= \frac{\text{Total patients who started recovery}}{\text{Total patients}} x\ 100\%$	71%
Remdesivir	68	$= \frac{\text{Total patients who started recovery}}{\text{Total patients}} x\ 100\%$	29%
Total		233	100%

inpatients is that hospitalisation allows for greater oversight and control of the patient, whereas home-based treatment affords patients more autonomy and independence from direct medical supervision. The expenses associated with remdesivir treatment for outpatients are higher.

The mean expenditure for COVID-19 treatment per individual amounts to IDR 43,595,339.94. The component with the greatest average cost is the accommodation room, which amounts to IDR 10,690,794.62, or 24.52% of the overall average cost. Conversely, the lowest average cost is attributed to professional services such as physiotherapy, dietitians, and other related expenses, amounting to IDR 3,042.64.14 The study findings indicate that the direct expenses incurred by patients for medical services, specifically laboratory and radiology, were found to be the most substantial for both inpatients and outpatients who were prescribed remdesivir.

In the case of inpatients, the costs amounted to IDR 1,391,037, whereas for outpatients, the expenses reached IDR 2,342,446. Similarly, patients utilising favipiravir incurred direct costs of IDR 1,580,758 for inpatients and IDR 2,151,522 for outpatients. Based on the findings of the study, it can be observed that laboratory support examinations impose the greatest financial burden in comparison to the overall costs of pharmaceuticals and medical gas for both inpatients and outpatients.[16]

The findings presented in Table 6 demonstrate the ACER calculations for both inpatient and outpatient COVID-19 cases. The ACER for inpatients treated with favipiravir is observed to be IDR 2,354,319,859, while for those treated with remdesivir, it amounts to IDR 3,501,513,488. Regarding the individuals receiving outpatient care, the expenditure on the medication Favipiravir totals IDR 420,083,118, while those utilising the drug remdesivir incur a cost of IDR 797,282,432.

The utilisation of alternative therapies that demonstrate greater cost-effectiveness is contingent upon the identification of alternative therapies that exhibit lower ACER is in comparison to conventional therapies.

Table 4. Average Direct Medical Costs of Outpatient COVID-19 Patients in South Tangerang City

Pharmaceutical interventions for COVID-19	Everage of Pharmaceutical Costs (IDR)	Average Outpatient Rate (IDR)	Average Outpatient Treatment Rate (IDR)	Average Laboratory Costs (IDR)	Average Radiology Costs (IDR)	Average Total Costs (IDR)
Favipiravir	20.445	75.000	4.263.225	1.908.522	243.000	6.510.191
Remdesivir	558.877	75.000	8.663.934	2.234.446	108.000	11.640.256

The highest cost for remdesivir is observed in outpatient COVID-19 patients, amounting to IDR 11,640,256 or USD 757.48. In contrast, the expenses borne by patients for favipiravir are significantly reduced, amounting to approximately 50% less at a total of IDR 6,510,191 or USD 423.65

Table 5. Average Direct Medical Costs of Inpatients COVID-19 Patients in South Tangerang City

Pharmaceutical interventions for COVID-19	Everage of Pharmaceutical Costs (IDR)	Average cost of medical support (IDR)	Average cost of inpatient room (IDR)	Average cost of Physician Treatment (IDR)	Average cost of paramedical measures (IDR)	Average inpatient cost (IDR)	Average Total Costs (IDR)
Favipiravir	20.410	1.219.085	1.580.758	1.178.636	2.601.739	631.883	7.232.512
Remdesivir	559.622	1.391.037	1.696.176	1.301.462	3.274.750	782.668	9.005.714

Table 6. Results of Calculation of ACER for Outpatients and Inpatients of COVID-19 patients

Pharmaceutical interventions for COVID-19	Total Healthcare Costs (IDR)	Effectiveness	ACER
Outpatients			
Favipiravir	327.664.832	78%	420.083.118
Remdesivir	175.402.135	22%	797.282.432
Inpatients			
Favipiravir	1.671.567.100	71%	2.354.319.859
Remdesivir	1.015.438.900	29%	3.501.513.448

Table 7. The results of the calculation of the Cost Effectiveness Ratio (CER) for COVID-19 patients in South Tangerang City

Pharmaceutical interventions for COVID-19	Rata-Rata Nilai		CER (IDR)
	Average of Total Direct Costs (IDR)	*Length Of Stay* (LOS)	
Favipiravir	10.355.664	6,70	1.545.621
Remdesivir	15.798.385	6,84	2.309.705

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When considering the ACER of inpatients and outpatients, it can be observed that the efficacy of the COVID-19 medication favipiravir surpasses that of remdesivir. Favipiravir demonstrates a favourable cost-effectiveness profile, characterised by a low overall direct expenditure and a high level of efficacy. In contrast, the utilisation of remdesivir is associated with a substantial overall direct expenditure coupled with limited efficacy. A research investigation carried out in Saudi Arabia examined the cost-effectiveness of treating COVID-19 patients with favipiravir in comparison to those treated with remdesivir, revealing a cost-effectiveness rate of 65.6%.[17] The study was replicated at the DR. Soetomo General Hospital to assess the efficacy of favipiravir drug therapy in comparison to remdesivir. The findings indicated that favipiravir exhibited an effectiveness rate of 85.17%, suggesting that its utilization is more economically advantageous than remdesivir.[18]

Table 7 presents data on the efficiency of interventions for COVID-19 patients, together with their corresponding average total direct medical expenses. By utilising this information, one may determine the CER. Consequently, there is no requirement to perform the calculation of the Incremental Cost Effectiveness Ratio (ICER). Based on the findings from the computation of CER, it is evident that patients administered with favipiravir exhibit a CER of IDR 1,541,021, whereas patients receiving remdesivir have a CER of IDR 2,309,705.

The CER result signifies that there is a difference in the cost of inpatient treatment between patients utilising the drugs favipiravir and remdesivir. Specifically, for each additional day of inpatient treatment, the cost for patients using favipiravir is IDR 1,545,621, but for patients using remdesivir, the cost is IDR 2,309,705.

The findings of this study are consistent with the research conducted by Halimbar, et al in 2023, which suggests that favipiravir exhibits greater cost-effectiveness compared to tremdesivir. The research conducted by Setiadi and Nur aligns with the findings of Halimbar, indicating that favipiravir exhibits superior efficacy compared to oseltamivir and remdesivir. This is evident from the observed duration of treatment, as patients receiving therapy with favipiravir experience a more rapid rate of recovery.[19]

Alternative perspectives from several studies suggest that a higher mortality rate is observed among people utilising remdesivir compared to those who experience recovery. In the interim, a greater proportion of patients who received favipiravir exhibited recovery compared to those who had mortality.[20]

A study conducted in Bali also provides evidence supporting the efficacy of favipiravir in comparison to remdesivir and oseltamivir. The research was carried out over a duration of 14 days, including a total of 192 individuals. Among them, 96 patients received favipiravir, while the remaining 96 patients were administered remdesivir and oseltamivir.

The study observed a cohort of 96 individuals who received favipiravir medication therapy and found that they exhibited improved health outcomes, namely a reduction in fever and respiratory issues, compared to those who did not receive the treatment.[21]

Conclusions

The data collected from the respondents indicates that a majority of the individuals receiving inpatient and outpatient care for COVID-19 at the South Tangerang General Hospital were female patients. Furthermore, the average age of these patients exceeded 51 years. The analysis conducted by researchers

has also examined the utilisation of COVID-19 medications, revealing that the drug Favipiravir is the predominant choice among patients, as opposed to the drug Remdesivir. The investigation yielded findings indicating that the medicine Favipiravir exhibits characteristics that render it a cost-effective option for the treatment of COVID-19. This conclusion is based on its superior efficacy and comparatively lower expenses in comparison to the drug Remdesivir. In order to expedite the rate of recovery for the patient, while simultaneously reducing the financial burden. The findings of this study may serve as a valuable resource for guiding medicine selection in the treatment of people afflicted with COVID-19 or other related illnesses.

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None Declared

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Assessment of Drug Adherence and Adverse Effects of Disease-Modifying Antirheumatic Drugs (DMARDS) in Patients of Rheumatoid Arthritis Attending a Tertiary Care Hospital in India

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Abstract

Adherence to drug treatment is one of the key factors in treating chronic diseases like rheumatoid arthritis (RA) to maintain remission and prevent functional disability. Poor medication adherence is directly associated with a worse prognosis and an increase in healthcare utilization, adding to a financial burden. Hence, the present study was proposed to assess drug adherence in diagnosed patients of RA attending a tertiary care hospital. The study was initiated after obtaining institutional ethics committee permission, and written informed consent was requested from all the eligible patients before their enrolment. This cross-sectional questionnaire-based study was conducted on RA patients attending the rheumatology outpatient department. The patient's adherence to the drugs prescribed was assessed using the 19-item Compliance Questionnaire Rheumatology (CQR), and the correlation between drug adherence with various demographic, disease, and medication-related variables was studied. After screening 103 patients, 75 patients fulfilling the selection criteria were enrolled, and their data was analyzed. The adherence measured using the CQR score was in the range of 54.39% to 68.42%, with a mean CQR score of 62.27 ± 2.76. A negative correlation was found between the CQR score and the number of ADRs ($r = -0.12$, $p>0.05$) and age ($r =-0.06$, $p>0.05$). A positive correlation was found between the CQR score and variables like sex, education, and number of medications, but none were statistically significant. Unsatisfactory compliance was evident in the present study. Therefore, integrating drug treatment with strategies to improve patient adherence may improve clinical outcomes and quality of life, reducing healthcare costs.

Keywords: adherence, compliance questionnaire, rheumatology, MMAS scale, antirheumatic drugs

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by symmetric peripheral polyarthritis.[1] If left untreated, it can progress from self-limiting arthritis to irreversible joint destruction, progressing to physical disability and death.[1,2] RA affects people worldwide, with 20 million prevalent cases and 1.2 million incident cases reported by the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017. An estimated 246 per 100,000 people suffer from RA worldwide, showing an increase of 7.4% between 1990 and 2017.[3] The burden of RA in India is also massive, with an estimated prevalence of 0.1 to 0.4%.[1]

Disease-related inefficiency in work and household activities is not just due to the physical limitations posed by RA but also emotional distress, which remarkably affects patients' health-related quality of life and productivity.[4] In the past decade, there has been a substantial change in the management of RA, with short-term use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to combat acute inflammatory response to the long-term use of disease-modifying antirheumatic drugs (DMARDs) so as to attain clinical remission, arrest the disease progression and to improve patient's quality of life.[5-7]

In addition, the biologics targeting various cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6 receptor, and B-lymphocytes have considerable potential to change the long-term outcomes in patients of RA.[8] However, adequate adherence to physician's recommendations is necessary to reach the therapeutic goals. Compliance may be defined as 'The extent to which the patient's behavior matches the prescriber's recommendations', whereas the term 'adherence,' which is often used as a substitute for compliance, may be defined as 'the extent to which the patient's behavior matches agreed recommendations from the prescriber'.[9,10]

Adherence to treatment helps achieve the therapeutic goals and is one of the key factors in treating chronic diseases like RA. However, published literature states that adherence to drugs in RA patients ranges from 30% to 100% using different methods to measure adherence.[11-15] Failing to adhere to the physician's advice often results in disease progression, poor prognosis, functional disability, additional medical therapy, and surgical intervention, contributing to increased financial burden.[16,17]

Apart from the doctor-patient relationship, multiple factors are expected to influence the nonadherence behavior to medication, such as socioeconomic profile, literacy status, patient perception of the disease, patient faith in medication, several drug-related factors like duration of the treatment, complexity of the regimen, and also disease-related factors such as the duration of disease, severity of disease, presence of comorbidities and functional disabilities.[14,18] The management of RA is thus challenging and multifaceted as it is influenced not only by the level of non-adherence but also by adverse drug reactions related to medication, a requirement of laboratory investigations, frequent follow-up, monitoring, and often patients' dissatisfaction due to natural remissions and exacerbations experienced.[17,19]

Hence, the present study was proposed to assess the treatment adherence in diagnosed patients of RA and study the correlation between drug adherence with various demographic, disease, and medication-related variables in patients receiving antirheumatic drugs in a tertiary care hospital.

Methods

This cross-sectional study was conducted at the Department of Pharmacology in collaboration with the Department of Medicine at HBT Medical College and Dr RN Cooper Municipal General Hospital, Juhu, Mumbai, Maharashtra, India. It was performed by the Declaration of Helsinki and initiated after obtaining institutional ethics committee permission. Patients attending the rheumatology outpatient (OPD) department were randomly screened for inclusion and exclusion criteria before participating. After screening 104 patients for selection criteria, 75 diagnosed patients of RA were included in the study. The selected patients were explained the purpose of the study and requested to give written informed consent before their inclusion in the study. The study was conducted between March 2020 to November 2021.

Diagnosed patients of RA attending the rheumatology outpatient department having age more than or equal to 18, of either sex receiving DMARDs for at least three months or more were included in the study. Detailed demographic profile of each patient, such as age, sex, personal habits (smoking, chewing tobacco, and alcohol consumption), duration of the disease, any comorbidity, duration of concurrent medication, and any adverse drug reactions experienced while on the treatment was recorded with the help of a case record form.

The adherence was assessed with the help of the 19-item compliance questionnaire for rheumatology (CQR), specifically developed for measuring drug adherence in patients of RA. It has a sensitivity of 98% and a specificity of 67% in detecting adherence in patients with rheumatoid arthritis. CQR is specific for measuring drug adherence in RA and is one of the validated tools to assess adherence. It is easy to use, cost-efficient, and used in some studies to calculate adherence.[11,18,20-25] It includes items scored on a 4-point Likert response scale ranging from 1 (do not agree at all) to 4 (agree very much). The score for this measure ranges from 0 (complete noncompliance) to 100 (perfect compliance).[21]

Selection Criteria

Inclusion criteria:

1. Patients of either sex, more than or equal to 18 years of age
2. Patients diagnosed with RA receiving treatment for more than three months.
3. Patients on DMARDs treatment, such as methotrexate alone or methotrexate in combination with either hydroxychloroquine and/or sulfasalazine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids for more than 3 months.
4. Patients diagnosed with RA with co-morbidities such as hypertension, diabetes mellitus, bronchial asthma, thyroid disorders, or epilepsy are well controlled with medication, as per the physician's opinion.

Exclusion criteria:

1. Patients were not willing to give informed consent.
2. Patients with any mental disorders or linguistic problems that could affect adequate understanding and response to the questionnaire.

After screening the patients for selection criteria and obtaining the written informed consent, a detailed demographic profile of each patient was recorded, such as age, sex, personal habits (smoking, chewing tobacco, and alcohol consumption), duration of the disease, any other co-morbidity, duration of concurrent medication, baseline laboratory investigations (Hemoglobin, ESR, Liver enzymes, renal function tests, rheumatoid factor) with the help of a case record form.

The patients were requested to fill up the 19-item compliance questionnaire rheumatology (CQR) questionnaire, specifically developed for measuring drug adherence in patients of RA. It has a sensitivity of 98% and a specificity of 67% in detecting adherence in patients with RA.

CQR is specific for measuring drug adherence in RA and is one of the validated tools to assess adherence. It is an easy-to-use and cost-efficient tool used in similar studies.[11,17,19,20-24] It comprises items scored on a 4-point Likert response scale ranging from 1 (do not agree at all) to 4 (agree very much). The score for this measure ranges from 0 (complete noncompliance) to 100 (perfect compliance).[20] The investigator asked each patient to respond to the questionnaire in the language they understood and about the adverse drug effects they experienced while on the treatment.

Statistical Analysis

The data collected was analyzed with the help of statistical software SPSS, version 22 for Windows. Categorical variables were represented as percentages and mean ± standard deviations. CQR score and adverse drug reactions were represented as counts and percentages. Spearman and Pearson's correlations were used to estimate the association between adherence and demographic, disease, and drug-related variables. A p-value of less than 0.05 was considered for statistical significance.

Results and Discussion

A total of 75 patients' data was considered for final analysis. The mean age was 47.9± 0.8 years. Among all patients, 70 were females, and 5 were males. A similar finding was reported by Sripreethy etal,[2] Moreland et al,[8] Nakagava et al,[10] Marras et al,[11] Bharthi etal,[12] Sharma et al,[18] van den Bemt et al.[23] Refer Table 1 for the detailed demographic characteristics of the patients.

Based on the duration of the disease, patients were divided into three groups: 50 patients with a duration of the disease more than or equal to 3 years, 24 patients with a duration between 2-3 years, and one with less than 1 year of duration. With regards to medication use, it was found that 5 or more than 5 antirheumatic drugs were prescribed to 10 patients. In contrast, most patients (N=60) received 2-4 antirheumatic drugs, and 5 patients were prescribed only one.

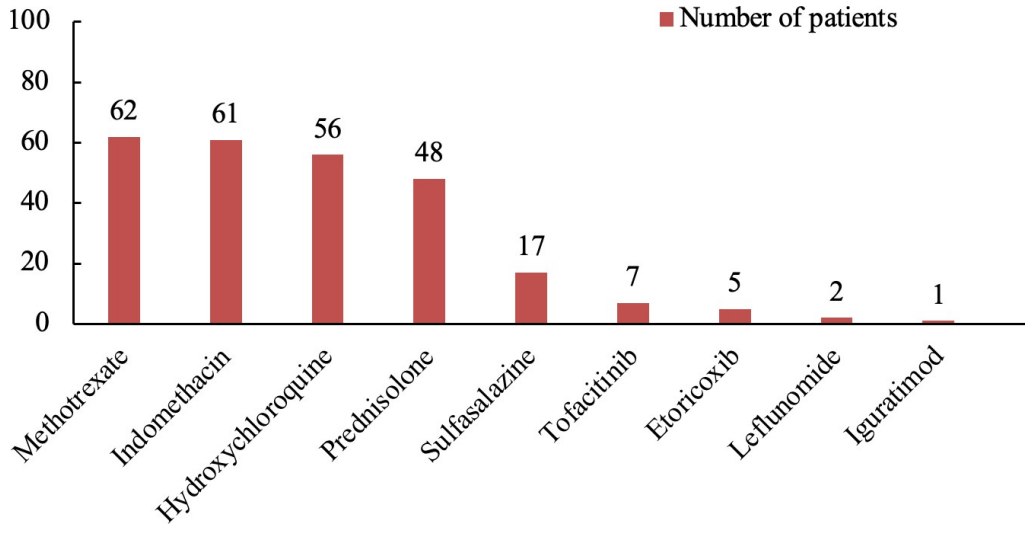

Figure 1. Distribution of Antirheumatic Drugs Prescribed to Patients

Table 1. Details of Patients' Demographic Characteristics

Demographic profile		Number of patients N (%)
Gender	Male	05 (6.7)
	Female	70 (93.3)
Age (years)	20-40	15 (20)
	41-60	43 (57.3)
	>60	17 (22.7)
Level of education	Primary	25 (33.3)
	Secondary	46 (61.3)
	Graduation & above	4 (84)
Employment status	Employed	11(14.7)
	Unemployed	01(1.3)
	Housewife	63 (84)
Personal history	Smoking	00
	Alcohol	01 (1.32)
	Tobacco	14 (18.7)
	None	60 (80)
Co morbidities	None	47 (60)
	Hypertension	16 (21.3)
	Hypertension & Diabetes mellitus	03 (4)
	Hypothyroidism	07 (9.3)
	Anemia	02(2.7)

*Others- One patient each of hyperlipidemia, Liver disease, Lung fibrosis, spondyloarthropathy

Table 2. Level of Adherence in Patients based on CQR Score

CQR score (N=75)	
Range	54.39% to 68.42%
Mean ± SD	62.27% ± 2.76
Median	63.16%
CQR adherence categories	N=75
≥60%	57(76%)
50-60%	18(24%)

Table 3. Distribution of Different Types of ADR Experienced by the Patients

Types of ADR	N (%)	Types of ADR	N (%)
Dryness of mouth	23 (30.7)	Urticaria	8 (10.7)
Loss of hair	20 (26.7)	Rashes	6 (8)
Weakness	14 (18.7)	Fatigability	5 (6.7)
Epigastric pain	12 (16)	Vomiting	4 (5.3)
Loss of appetite	11 (14.7)	Diarrhoea	4 (5.3)
Nausea	10 (13.3)	Blurring of vision	4 (5.3)
Weight gain	9 (12)	Breathlessness	3 (4)
Oral ulcers	8 (10.7)	Stomatitis	2 (2.7)

Fig. 1 depicts the distribution of frequency of antirheumatic drugs prescribed. The adherence was measured using CQR score which revealed the adherence to prescribed medication in RA patients in the range of 54.39% to 68.42%, with the mean CQR score of 62.27 ± 2.76% and having the median of value of 63.16% (Table 2). On assessing adverse drug reactions (ADR) it was observed that 31 (41.3%) patients reported one ADR, 2-4 ADRs were reported by 36 patients (N=36, 48%) and 5 or more than 5 ADRs were reported by 8 patients (N=8, 10.7%). Distribution of different types of ADR experienced by the patients is shown in Table 3.

Out of 75, 60 patients were on two or more 2 drugs, which included methotrexate, hydroxychloroquine, indomethacin, prednisolone, and sulfasalazine, being prescribed in different combinations to different patients based on the disease presentation and clinical response. These medications shared some common ADRs hence causality assessment was not possible. Further, the focus of this study was to find out the correlation between drug adherence behavior and ADR experience.

The correlation between drug adherence and ADRs experienced was not found to be statistically significant implying that the adherence behavior was independent of the ADRs experienced. Other studies also have reported similar findings.[17,23,24] This could possibly be because patients are forced to take the drug despite experiencing the adverse effects due to the functional disability and health-related quality of life affecting their day-to-day activities. On the other hand, some of them take drugs during acute exacerbations, whereas some avoid taking medication, particularly during remission, due to perceived ADRs affecting their adherence behavior.

On assessing the correlation of various demographic variables such as age, sex, level of education, and disease variables such as number of RA medications, number of drugs prescribed, and duration of disease with the adherence level as calculated using CQR score, was not found to be statistically significant. Negative correlations were found between CQR score with age ($r = -0.06$, $p>0.05$) and number of ADRs ($r= -0.12$, $p>0.05$). A positive correlation was found between CQR score and variables like sex, education and number of medications but were not statistically significant. (Table 4)

This could be attributed to various factors such as, beliefs of patient on the doctor, treatment provided, their experience on the benefit obtained following drug treatment or ADRs experienced. This study was conducted at a public hospital in India where the patients seeking medical treatment come from low socioeconomic status, having lack of information about the disease, its complications and limited understanding of efficacy of drugs. As the patient load is very high even doctors have limited time to communicate information with regards to the disease and drugs. These factors may be perceived as a potential barrier to drug adherence as it was found to be less than satisfactory. This finding was in accordance in the systematic review published by Annalieke et al.[14]

Other studies carried out with a similar objective also reported similar findings.[23,24] In contrast to this, study conducted by Bharthi et al[12] and Wabe et al[17] showed improvement in adherence with increasing age. The level of education also did not correlate with the adherence to drugs, indicating that even highly educated individuals may have less than satisfactory drug compliance. This may be due to a lack of information about medication fear of adverse effects, or a hectic lifestyle, which leads to missed doses and poor adherence, all of which warrant further investigation.

Adherence to prescribed medication is one of the key factors that influence the disease outcome in many chronic diseases.Asystematic review of factors associated with adherence to pharmacological treatment for RA patients reported that adherence rates varied between 49.5% and 98.5%, depending on the definition and method used.[14] In this study, based on CQR score, the adherence score was less than satisfactory, consistent with similar studies that used CQR as a measure of medication adherence in RA patients.[11,14,15,17,20,23,24]

The questions in the CQR are directed towards gathering patients' information on general attitudes or habits towards taking antirheumatic drugs and perhaps ignorance about the disease drugs, which may be the reason for poor adherence in our setting.

In RA patients, adherence to the treatment recommended often retards the disease progression, thereby improving the quality of life of patients with a considerable reduction in healthcare expenditures. Given the benefits of adherence in managing chronic diseases, physicians must emphasize drug adherence right from the first consultation. Regarding the questions used in the CQR, for item number 16, which stated, 'I use dose organizer for my medication,' we found all patients answered that they did not use dose organizer, which could have influenced the final CQR score. This response was expected in our country, as dose organizer is neither popular nor advertised in our setting, and people rely on their close-knit social contacts and family members besides themselves to remind them to take the medication.

Other factors which may reduce patient adherence to drug treatment may include the cost of the drugs, which could be studied by correlating the monthly income of patients with the CQR scores. On analysis of ADRs experienced, we could not attribute causality of a specific adverse effect to a particular drug as patients were prescribed more than one drug.

Conclusion

The mean CQR score was 62.27 ± 2.76%, reflecting less than satisfactory adherence in the present study. No statistically significant correlation was identified between the CQR score and various demographic, disease, and drug-related variables. Improvement in adherence behavior needs integrating

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Table 4. Correlation of CQR Score with Various Demographic and Disease Variables

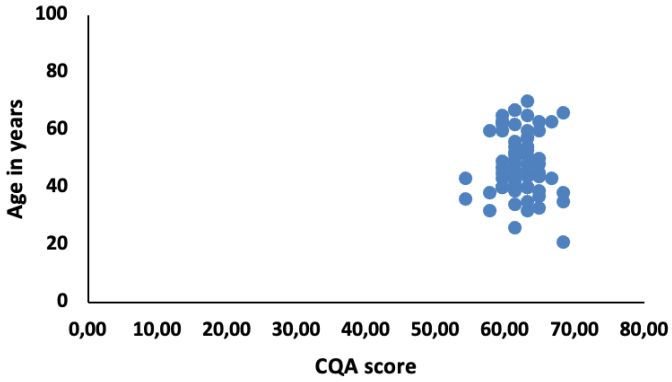
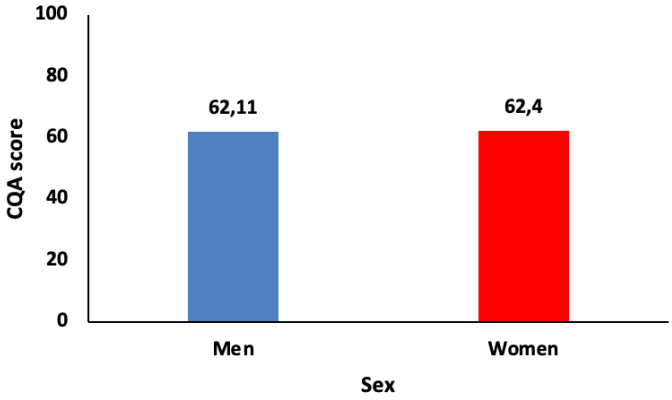
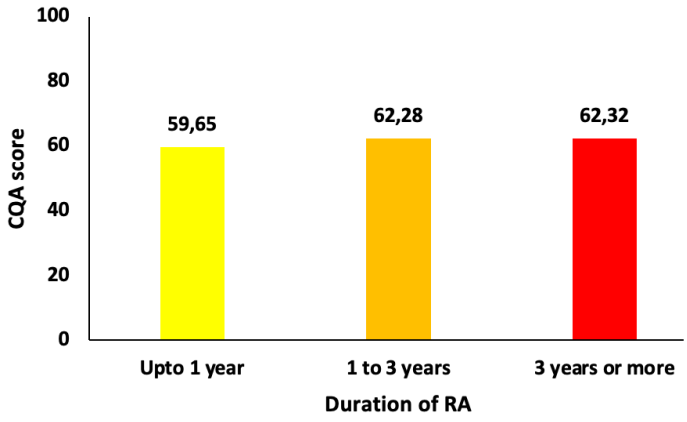
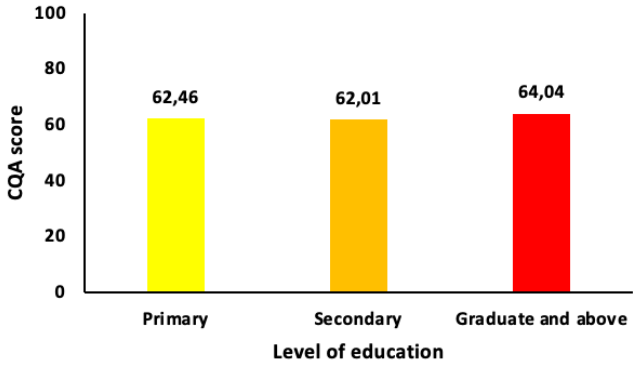
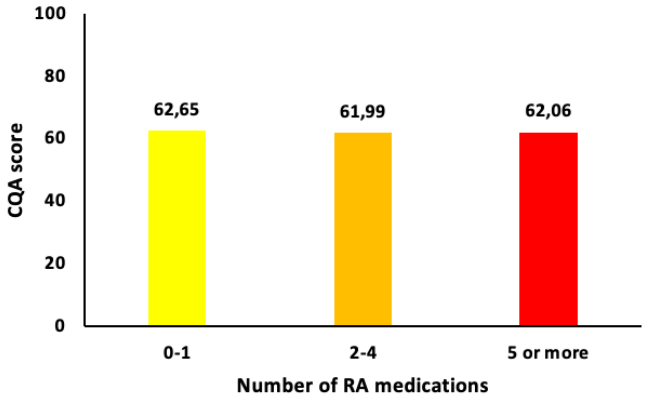
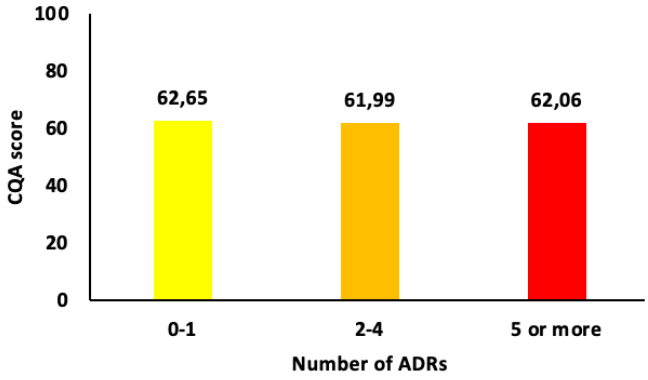
Variable	R	p-value	Graph
Age	-0.06	0.6332	
Sex	0.02	0.84612	
Duration of disease	0.00	0.9661	

Table 4. Correlation of CQR Score with Various Demographic and Disease Variables (cont...)

Variable	R	p-value	Graph
Education status	0.03	0.81862	
Number of RA medications	0.10	0.3898	
Number of ADRs	-0.12	0.309	

drug therapy with innovative technologies, spreading awareness of the disease, effectiveness of drug therapy, and addressing patient's apprehensions and concerns. It may change their attitude towards adherence behavior and thereby improve the quality of life of RA patients.

Therefore, physicians need to integrate drug therapy with an individualistic approach addressing patients' apprehensions and beliefs to improve drug adherence, thereby improving the quality of life in RA patients

Limitations

The larger sample size could have given a better insight into the correlation of CQR score with the patient, disease, and drug-related variables.

Conflict of Interest

None declared

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FABP4 and Metabolite Profile in Lipopolysaccharide-Induced Mice Model Treated with *Moringa oleifera* Ethanol Leaf Extract

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Abstract

Sepsis, a life-threatening organ dysfunction resulting from a dysregulated host response to infection, induces changes in blood cells and metabolic alterations. Fatty acid binding protein 4 (FABP4), a lipid chaperone predominantly expressed in adipose tissue, is modulated in sepsis and may contribute to metabolic and immunologic changes. *Moringa oleifera* (*M. oleifera)* leaf extract (MOLE) is known to modulate immune system activity, but its potential for treating acute inflammatory conditions like sepsis remains unclear. This study investigates the ability of MOLE to modulate metabolite and hematological profiles in lipopolysaccharide (LPS)-induced sepsis in mice. Thirty-five male Swiss Webster mice (*Mus musculus*) were divided into five groups, including healthy control pre-treated with 0.5% carboxymethyl cellulose (CMC), an LPS-induced negative control, an LPS-induced positive control treated with dexamethasone (DMX) 7mg/KgBW/day and two MOLE treatment groups with doses of 5.6 and 11.2 mg/20 gBW. Mice received MOLE pre-treatment for three days before LPS induction. Three hours post-LPS injection, the LPS-induced group exhibited leukopenia (1.4 [0.9-2.5] x109 cells/L) and a 68.3% increase in triglyceride levels. However, the MOLE-treated group showed improved erythrocyte levels compared to the positive control group; [(9.9(9.3-10.0) x1012 cell/L) vs (7.7(7.0-9.0) x1012 cells/L), $p<0.05$]. The study suggests that MOLE administration may positively impact sepsis conditions, particularly by enhancing RBC levels. Further research with an extended observation period is recommended to address limitations in metabolite level assessment.

Keywords: *Moringa oleifera,* fatty acid binding protein – 4 (FABP-4), metabolite profiles, hematological profiles, lipopolysaccharide

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Introduction

Sepsis, a life-threatening condition,[1] is associated with various cellular changes, including the induction of free radicals, an imbalance in oxidation reactions, and a decline in liver energy metabolism.[2] At the symptomatic level, sepsis triggers inflammatory reactions such as hypothermia or hyperthermia, tachycardia, tachypnea, and changes in white blood cell (WBC) count.[1,3] This imbalance results in a systemic response,[4] causes damage to cells and organs.[5] Sepsis also affects metabolic homeostasis, mainly carbohydrate and lipid metabolism. Cytokine activation, such as TNF-α, IL-6, and IL-1β, plays a significant role in these conditions. Additionally, sepsis affects energy and lipid metabolism.[6,7] TNF-α, similar to cachetin, is believed to increase lipolysis during sepsis. IL-1β and IL-6 work together to induce a hypermetabolic state.[7]

Mitochondrial damage is considered a primary cause of metabolic disorders in sepsis, influencing the metabolism of all macronutrients. Carbohydrate metabolism experiences intensified glycolysis, leading to increased lactate formation due to the failure to introduce pyruvate into the tricarboxylic acid cycle. In lipid metabolism, sepsis induces lipolysis in adipose tissue, resulting in elevated levels of fatty acids and triglycerides in the blood. Simultaneously, disrupted energy substrate utilization may lead to the accumulation of lipids and their toxic metabolites.[6]

Moreover, adipocyte tissue undergoing lipolysis releases fatty acid binding protein 4 (FABP4) acting as an adipokine. FABP4 is expressed by adipocytes and macrophages, playing a crucial role in insulin resistance and atherosclerosis development, especially in metaflammation. During inflammatory states, FABP4 is expressed by macrophages upon LPS administration. In our previous study, there were alterations in pro-inflammatory cytokines, and increased glycogen and triglycerides in the heart of LPS-induced mice. Additionally, a decrease in blood glucose levels and an increase in triglyceride and non-esterified fatty acid (NEFA) levels were observed in mice induced with LPS.[8]

The shift from chemical to traditional treatments has led to extensive studies on herbal plants, revealing their immunomodulatory potential in optimizing the immune system during disruptions like infections and inflammation. We previously demonstrated the efficacy of cogon grass (*Imperata cylindrica*) roots extract in ameliorating sepsis conditions, as evidenced by improvements in hematological parameters (lymphocytes, monocytes, and platelets), immunological factors (TNF-a and GPx3), and metabolite levels (FABP4). This observed effect is attributed to the presence of flavonoids in the extract, known for their potential anti-inflammatory properties.[9]

The flavonoid content is also found in other plants, including *M. oleifera*.[10] *M. oleifera* is monogeneric genus *Moringa* within the *Moringaceae* family, gaining widespread recognition since the conference held in 2001 in Tanzania. Subsequent studies have explored the potential of *M. oleifera*, particularly in the field of health, owing to its abundance of bioactive compounds such as vitamins, carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins, saponins, oxalates, and phytates. Among the numerous compounds found in *M. oleifera*, quercetin is believed to play a role in inhibiting NF-ĸB activation in the inflammatory process.[11]

M. oleifera leaves extracts (MOLE) inhibit the production of human macrophage cytokines

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like tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and IL-8, induced by cigarette smoke and LPS. Furthermore, *M. oleifera* and isothiocyanate concentrates may decrease gene expression and the production of inflammatory markers in RAW macrophages. In particular, they attenuate the expression of inducible nitric oxide synthase (iNOS), IL-1β, and the production of NO and TNFα at 1 and 5μM.1[1,12] Further study indicate MOLE has the potential to reduce triglyceride levels, glucose levels[11,13,14] also increase hemoglobin levels, and reduce granulocyte presentation in mice models of chronic inflammation due to a high-fat diet[15] and diabetes.[11,13,14] However, there have been no studies related to MOLE in sepsis model mice. Thus, the study aimed to determine the effect of MOLE on FABP4 concentration, metabolite profile and hematological profile in sepsis model mice.

Methods

Ethical consideration

Considering the Declaration of Helsinki for the welfare of animals used for research,the Research Ethics Committee Universitas Padjadjaran Bandung has approved the experimental animal protocol (Approval No. 959/UN6.KEP/EC/2022).

Extract and Drug Preparation

M. oleifera leaf powder, approximately 1 kg in quantity, was obtained from PT. Moringa Organik Indonesia. The extraction process involved maceration using a 1:3 ratio of 96% ethanol (Merck, USA) to water for 24 hours, followed by filtration. This procedure was repeated three times. The resulting filtrate was homogenized and subjected to rotary evaporation until it reached one-third of the initial volume.

Subsequently, the filtrate was frozen at −20°C for 24 hours and further desiccated through freeze-drying until it transformed into a greenish concentrate (approximately 1.8 g). The resultant extract was stored in a refrigerator for subsequent applications in treatment as previously described.[16]

The utilization of carboxymethyl cellulose (CMC) as a solvent for MOLE at the optimal concentration of 0.5% involved dissolving it in distilled water.[17] The administration of MOLE, based on previous studies, comprised an initial dose of 5.6 mg/20g body weight (BW) [MOLE1] and a second dose of 11.2 mg/20gBW [MOLE2], each dissolved in CMC 0.5%.16 LPS from Escherichia coli O111 : B4 (Sigma-Aldrich, US), at a dosage of 10 mg/kgBW, diluted in 10 ml phosphate-buffered saline (PBS).[9,18] Dexamethasone, sourced from PT. Harsen, Jakarta, Indonesia, was administered at a dose of 7 mg/kg/BW/day.[19]

Model dan Research Design

The male Swiss Webster mice (*Mus musculus*), belonging to the normal species, which are intended for induction with LPS at a dosage of 10 mg/kg body weight, were procured from D'Wistar Company (Bandung, Indonesia). The selection criteria include an age range of 4-6 weeks and a body weight within the range of 20 – 25 gram. All efforts were made to relieve any pain and distress of the animals by strictly following the procedures. The mice were acclimatized for two weeks in the laboratory. They were then kept in cages at the animal laboratory of Universitas Padjadjaran at a controlled room temperature and on a 12 hours light/12 hours dark cycle. The mice were provided regular food, drinking water ad libitum, and observed daily to confirm lack of behavior.

A randomized post-test control group design was used. The number of samples for each treatment group was determined using the Federer formula [(n-1)(t-1) ≥ 15; n ≥ 5]. The

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mice were divided into the following five experimental groups (5-7 mice per group; 35 mice total): group 1 (healthy control) and group 2 (negative control) were treated with (CMC), group 3 (positive control) was treated with CMC and DMX, while group 4 and 5 (treatment group), were treated with MOLE1 and MOLE2, respectively, for three days. On the third day, mice were fasted overnight. Groups 2, 3, 4 and 5 were injected intraperitoneally with LPS. At 3 hours after injection, blood were collected from the abdominal vein, then inserted into the K3-EDTA tube and SST tube.

Measurement of blood parameters

The whole blood in the K3-EDTA tubes was is mixed with the anticoagulant ethylenediaminetetraacetic acid (EDTA). EDTA prevents blood clotting by binding to calcium ions, crucial for the coagulation process, thereby inhibiting the coagulation cascade and maintaining the blood in a liquid, non-clotting state.[15,20–24] The processed blood is then analyzed using the Mindray BC20s hematology analyzer, following the manufacturer's protocol.

The Mindray BC20s utilizes the volumetric impedance method to measure the quantity and characteristics of blood cells. The analyzer draws a small volume of anticoagulated whole blood through an aperture. As cells pass through this aperture, they disrupt an electric current. The resulting impedance changes are proportional to the volume and number of cells passing through, allowing for the quantification of leukocyte (WBC), erythrocyte (RBC), and thrombocytes (PLT), also known as platelets).

Blood parameter tests in this study including WBC, differential count (lymphocyte, granulocyte or neutrophil and mid-range counts or MID encompass cells like monocytes, eosinophils, basophils, blasts, and other precursor white cells falling within a specific size range,[25] PLT, RBC, hematocrit (HCT), hemoglobin (HB), mean corpuscular hemoglobin concentration (MCHC), mean platelet volume (MPV), and red distribution width concentration (RDWC), mean platelet volume (MPV), platelet disribution width concentration (PDWC) dan plateletcrit (PCT).

Measurement of metabolite parameters

The serum in the serum separator tube (SST) tube is separated using centrifugation at 1,500g for 15 minutes at 4°C, and were stored at 80°C for metabolite examination. Metabolites measured include FABP4, NEFA, Triglycerides and Glucose.[8,9,16] FABP4 levels in the samples were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits Mouse FABP4 ELISA Kit (Fine Biotech, Wuhan, China) according to the manufacturer's protocol. NEFA, Glucose and Triglyceride levels in the samples were measured using commercial colorimetric assay kit (Elabscience, United State and DiaSys Diagnostic Systems GmbH, Germany) according to the manufacturer's protocol.

Statistical analysis

Statistical analyses were performed using the GraphPad Prism version 8.0.1 (244) for Windows (GraphPad Software, Inc. CA). All of the data were submitted to the Shapiro-Wilk test of normality. Data are shown as Mean ± SD, on normally distributed, variables using ANOVA One Way and Tukey's test as post hoc. Whereas non-parametric variables are shown as median (min-max) values using Kruskal-Wallis and Dunn's test as post hoc.

Results and Discussion

Numerous methods exist for establishing sepsis models in experimental animals, with among the most frequently employed being cecal ligation and puncture (CLP) and LPS induction.

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In our study, the LPS induction method was chosen based on several advantages, including (1) a simpler technique,[26] (2) the formation of an inflammatory response resembling the response to a direct infection,[27] and (3) higher reproducibility with a faster recovery time.[26] The LPS dose used in this study aligns with previous studies, specifically 10 mg/kgBW.[8,9] As an initial observation, mice induced with LPS exhibited conditions such as lethargy, curling up, and clustering, indicative of behaviors aimed at maintaining body heat.[28] The post-LPS induction observation period in our study was conducted for 3 hours. This choice was made to spesifically target early onset of sepsis and focus on the inflammatory response. However, a few parameters exhibited different results when compared to previous studies that utilized longer durations for post-LPS induction observation.

WBC parameter, typically used as a reference for sepsis conditions, manifests conditions such as leukocytosis or leukopenia.1 In our study, leukopenia occurred, wherein the leukocyte levels were significantly lower in LPS treatment-only group compared to healthy group [1,4 (0,9-2,5) x109 cells/L vs 9,2 (5,7-11,8) x109 cells/L, $p<0,05$]. Furthermore, the results of the WBC differential count indicated a significant decrease in absolute counts of lymphocytes and granulocytes, with a simultaneous significant increase in mid-range relative count.

The reduction in lymphocyte absolute count was observed between the healthy group and the LPS treatment-only group and MOLE2 treatment group [6.9(4.7-9.7) x109 cells/L vs. 0.95(0.6-2.2) x109 cells/L and 0.9(0.3-2.0) x109 cells/L, $p<0.05$]. A decrease in granulocyte absolute count was also noted between the healthy group and the LPS treatment-only group and positive control group [1.3(0.9-2.9) x109 cells/L vs. 0.2(0.2-0.5) x109 cells/L and 0.2(0.1-0.7) x109 cells/L, $p<0.05$]. Meanwhile, an increase in mid-range relative count occurred between the healthy group and the LPS treatment-only group and MOLE^2 treatment group [1.3(1.2-1.5) x109 cells/L vs. 19.5(14.5-23.3) x109 cells/L and 18.6(14.5-25.6) x109 cells/L, $p<0.05$].

Our research reveals a decrease in WBC counts, consistent with findings reported in numerous prior studies related to the ability of endotoxins to induce inhibition of hematopoiesis processes through the administration of bacterial endotoxin[29] or LPS induction.[30] In other experimental animals, apart from mice, this commenced within the first hour following LPS induction and escalated after 8 hours post-induction.[36,37] The reduction in WBC count (leukopenia) correlates with a decrease in the number of circulating lymphocytes and monocytes[30] due to the migration of bloodstream into tissues. This is evidenced by absolute lymphocyte count data, whereas there were no differences in mid-range absolute count, and a significant increase in mid-range relative count was observed. This difference is presumed to be a result of the overall decrease in WBC count that occurred across all treatment groups due to LPS induction.

Therapeutic administration of MOLE in immunomodulated mice trials increased WBC count.[32] Meanwhile, in the administration of MOLE with sub-acute toxicity, here was an increase in WBC count.[33] The administration of MOLE without specific conditions in mice showed a significant increase in WBC count.[34] This condition aligns with the improvement trend observed after mice were provided with MOLE therapy in this study.

The RBC parameter showed a significant increase in treated with MOLE1 compared to positive control [(9,9 (9,3-10,0) x1012

cells/L vs (7,7 (7,0-9,0) x1012 cells/L), p<0,05]. RBC count in mice tends to increase after endotoxin induction,[35] providing significant results with MOLE therapy. This is consistent with previous research conducted on healthy mice[34,36] and mice induced with cyclophosphamide as an immunomodulation condition, which experienced an increase in RBC count.[32] However, there were no significant differences observed in platelet levels among the treatment groups (Table 1).

In our previous study, it was observed that there is a propensity for a reduction in WBC parameters, alongside an elevation in RBC and PLT parameters following *M. oleifera* therapy administered to a mouse model with a high-fat diet (HFD).[15] In the other hand, *M. oleifera* can increase WBC and decreased RBC and PLT in parasite infection.[37] These indicate that the difference of hematological parameter might be influenced by varying inflammatory conditions and disease background.

Metabolically, a significant 68.3% increase in blood triglyceride levels was observed in the LPS treatment-only group compared to healthy group (Figure 1.D). Elevated triglyceride levels have also been documented in various condition such as cholera, polymicrobial infections, and sepsis.[38–40] Previous research has identified triglyceride levels as predictive of sepsis-related mortality.[39,40] Sepsis triggers the release of catecholamines, which contribute to the liberation of free fatty acids through adipose tissue lipolysis. The liver metabolizes these free fatty acids, releasing them as triglycerides in lipoproteins.[2]

In gram-negative bacteria-induced sepsis (LPS), high doses (50ug/100gBW), lead to decrease Lipoprotein Lipase (LPL) activity in adipose tissue, diminishing catabolism and clearance of triglyceride-rich lipoproteins in the bloodstream.[2,38,41] Conversely, at low doses (100ng/100gBW), there is stimulation of de novo liver fatty acid synthesis and lipolysis.[38] This stimulation results in elevated blood triglyceride levels (hypertriglyceridemia).[42,43] Lipoproteins, particularly those containing large triglycerides (chylomicrons and VLDL), may function as an innate immune response to lipopolysaccharide-induced sepsis.[7,11] These lipoproteins can bind to lipopolysaccharides (LPS) to form lipoprotein-LPS or chylomicron-LPS complexes.[2,38] This binding modulates the immune response and inhibits LPS-induced toxicity. The chylomicron-LPS complex can inhibit nitric oxide (NO) production[45,46] y hepatocytes, suggesting that the chylomicron-LPS bond can inhibit the nuclear factor kappa-B (NF-ƘB) pathway and prevent liver damage.[2]

Additionally, glucose levels exhibited a significantly reduction of 71.8% in the positive control group, 74.9% in MOLE1-treated group and 66.2% in MOLE2-treated group compared to the healthy group (Figure 1.C). Previous studies have reported a substantial decrease in glucose levels[26] within the first 3 hours following endotoxin (LPS) administration,[47] persisting from 6 to 24 hours.[48] Dexamethasone therapy in other groups showed a decreasing trend within the 6 to 24 hours timeframe, with a slight increase at 12 hours post-induction.[48]

The decline in blood glucose levels is linked with the release of inflammatory cytokines. IL-1 is a prerequisite for hypoglycemia in LPS-induced mice, with IL-1α, β and TNF-α inducing hypoglycemia due to LPS induction.[49] This observation is consistent with research by Schmidt et al which revealing that TNF-α, IL-1β and INF-γ decrease the regulation of sodium-glucose co-transporter (SGLT)-2, SGLT-3, glucose transporter (GLUT)-2 and Na-K-ATPase, while SGLT-1 and GLUT-1 activity increased.

Table 1. Results of Hematological Parameter Examination Conducted using Hematology Analyzer (Mindray BC20s)

Parameter	Group				
	Healthy	LPS-only	LPS-DMX	LPS-MOLE1	LPS-MOLE2
Leukocyte					
WBC (10^9/L)	9.2(5.7-11.8)[ab]	1.4(0.9-2.5)[a]	1.5(0.9-3.8)	2.2(1.3-3.8)	1.3(0.5-3.9)[b]
Lymph (10^9/L)	6.9(4.7-9.7)[ab]	0.95(0.6-2.2)[a]	1.0(0.6-2.4)	1.5(0.8-2.1)	0.9(0.3-2.0)[b]
Mid (10^9/L)	0.1(0.1-1.4)	0.2(0.0-0.3)	0.3(0.0-0.7)	0.2(0.0-0.4)	0.2(0.1-0.7)
Gran (10^9/L)	1.3(0.9-2.9)[ab]	0.2(0.2-0.5)[a]	0.2(0.1-0.7)[b]	0.4(0.2-0.4)	0.3(0.1-0.7)
Lymph%	83.4(49.8-88.1)	68.5(58.2-91.7)	75.5(57-91.6)	75.6(60.5-88.7)	56.5(45.4-67.8)
Mid%	1.3(1.2-1.5)[ab]	19.5(14.5-23.3)[a]	16.7(4.8-20.9)	11.8(8.8-17.5)	18.6(14.5-25.6)[b]
Gran%	15.2(10.7-28.8)	12.4(9.2-23.2)	13.1(6.6-22.1)	12.2(6.2-23)	25.7(6.6-34.2)
Erytrocyte					
RBC (10^{12}/L)	7.9(7.4-8.3)[a]	8.3(7.5-9.1)	7.7(7.0-9.0)[b]	9.9(9.3-10.0)[ab]	8.5(8.0-8.9)
HGB (g/dL)	12.1(11.6-14.2)[a]	13.4(11.9-13.9)	14.0(11.7-15.7)	14.9(13-15.8)[a]	14.6(13.6-14.8)
HCT (%)	38.3(34.9-41.1)[a]	44(37.6-49.5)	46.4(38.4-53.0)	48.8(44.0-52.7)[a]	46.7(43.7-50.1)
MCV (fL)	48.2(47.0-50.9)[a]	52.8(49.7-59.6)	53.6(50.2-56.2)	44.15(43-50.7)[b]	54.9(53.2-56.2)[ab]
MCH (pg)	15.9(14.6-17.6)	16.0(15.2-16.8)	16.2(14.9-17.4)	14.6(13.2-16.8)	16.6(16.2-18.3)
MCHC (g/L)	328.5(304-346)	294(281-337)	303.5(287-310)	304.5(295-313)	308(288-335)
RDW-CV (%)	15.4(13.4-18.5)	16.2(13.2-17.7)	14.9(14.0-17.5)	16.5(13.6-21.6)	15.9(12.6-16.7)
RDW-SD (fL)	26.1(23.1-31.4)	30.5(23.2-33.9)	29.2(24.9-33.8)	28.6(24.4-33.5)	31.4(24.3-32.6)
Thrombocyte					
PLT (10^9/L)	480(162-781)	482(311-805)	516.5(364-835)	454(205-737)	614(182-921)
MPV (fL)	6.6(5.5-6.8)	6.0(5.9-6.6)	6.4(5.7-7.0)	6.6(5.7-7.0)	6.2(5.8-6.9)
PDW	15.0(14.7-15.0)	15.2(14.8-16.5)	15.1(14.8-15.6)	15.3(14.7-15.9)	15.0(14.8-15.3)
PCT (mL/L)	3.7(2.8-6.8)	2.9(2.1-5.0)	3.4(2.5-4.9)	1.7(0.4-4.5)	3.8(1.1-5.3)

LPS decreased leukocyte parameter in a sepsis mouse model
LPS increased mid-range relative count in a sepsis mouse model
Treatment of MOLE, increased erythrocyte parameter in sepsis mouse model
Data are represented as the median(min-max), n = 5 per group.
Kruskal-Wallis and post-hoc Dunn's test were performed for difference between median
a-b: Similar superscript in the same line indicate significant statistical differences ($p<0.05$)

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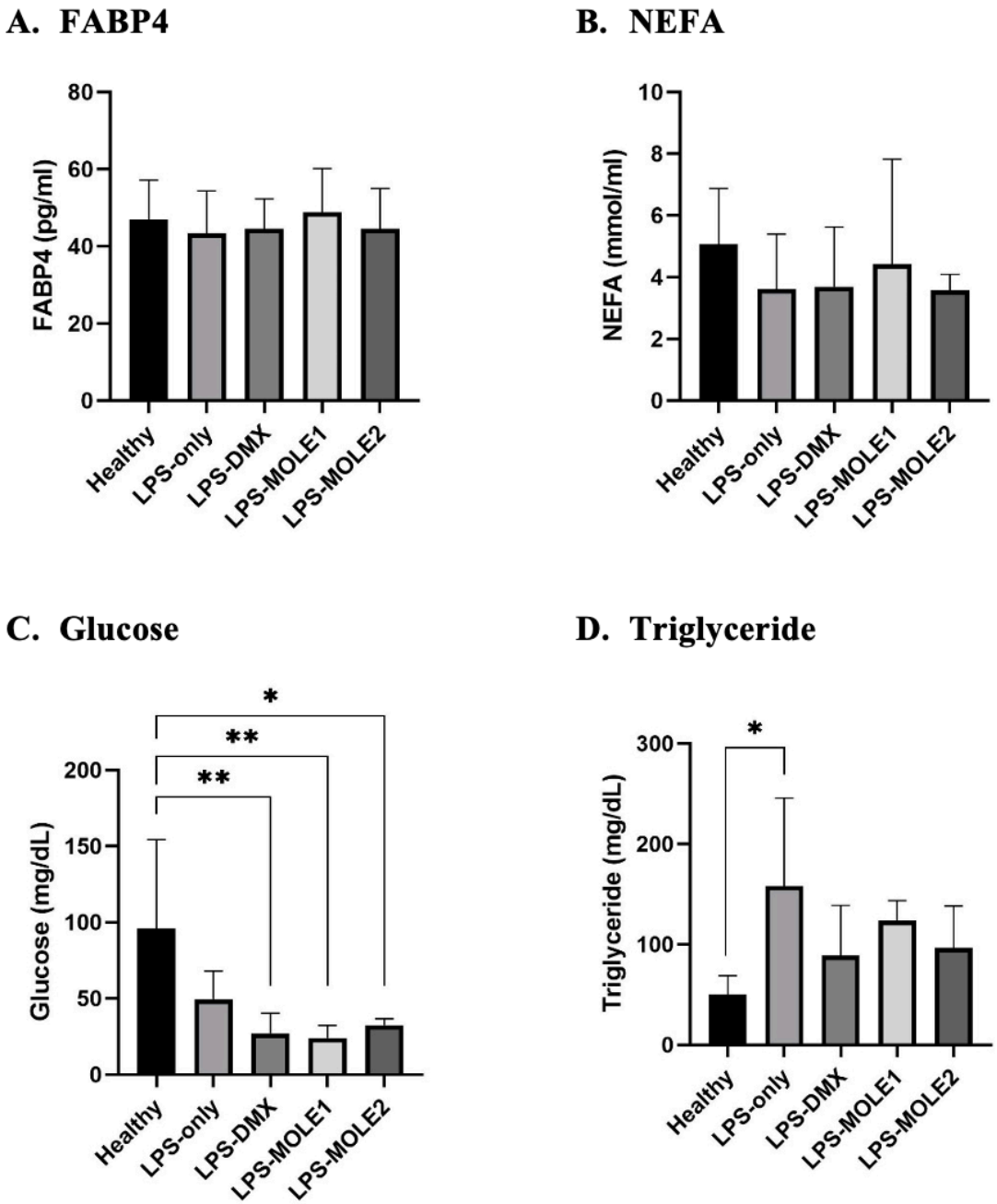

Table 1. Results of Hematological Parameter Examination Conducted using Hematology Analyzer (Mindray BC20s)

IL-6 inhibits of SGLT-2 and GLUT-2 activity and IL-1β reduces Na-K-ATPase activity in in vitro studies.[48] The use of glucocorticoids like dexamethasone as anti-inflammatories reverses changes in glucose transport activity by suppressing the spread of inflammatory cytokines in the NF-ƘB pathway.[48,50–52]

In this study, there were no significant difference in the levels of FABP4 and NEFA; only a trend towards a decrease was observed among the treatment groups (Figure 1.A. and 1.B.). This finding contrasts with prior research that reported an increase in FABP4 levels after 8 hours[9] and an increase in FABP4 mRNA after 12 hours[53], as well as an increase in NEFA after 12 hours post-LPS induction.[8] However, there is research indicating a significant decrease in FABP4 gene expression after 12 hours post-LPS induction.[8] These differences are presumed to be associated with distinct inflammatory conditions between the early and later stagesThe unbalanced secretion of cytokines such as IL-10 and TNF-α as seen in sepsis, increases insulin resistance, affecting adipocyte cells that become insensitive to insulin. Such conditions can induce lipotoxicity and hinder insulin's ability to stimulate the absorptivity of NEFA cells, generated by the lipolysis cycle of triglycerides, leading to the inhibition of lipolysis of endogenous triglycerides into NEFA.[54]

M. oleifera identified as having major components isoquercetin and quercetin-3-O-malonylglucoside inhibits adipogenesis by suppressing marker CCAAT / enhancer-binding protein beta (C/EBPβ), adiponectin, FABP4, peroxisome proliferator-activated receptor (PPAR)-γ,[13,55] fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC),[56] resulting in reduced cellular lipid level (triglycerides, LDL and VLDL).[57] The extract enchances lipolysis by inhibits α-glucosidase, and lipase[56] increasing phosphorylation of AMP-activated protein kinase α (AMPKα) and ACC,55 and activating uncoupling protein 1 (UCP1), sirtuin 1 (SIRT1), PPARα, and Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α). It also induces the antioxidant enzyme heme oxygenase-1 (HO-1).[58] *M. oleifera* exhibits potential in improving glucose tolerance, reducing blood glucose levels, and demonstrating antidiabetic effects,[59–61] possibly due to quercetin,[62] myricetin[11] and isothiocyanate.[57] which have anti-diabetic effects.[61]

The compound (4-[2-o-Acetyl-alpha-l-rahamnoslyloxy)benzyl]thiocynate isolated from *M. oleifera* effectively inhibits nitric oxide in Raw264.[7] cells.[20,44] Active compounds such as tannins, phenols, alkaloids, flavanoids, carotenoids β-sitosterol, vanillin, and moringin have anti-inflammatory properties.[61] MOLE treat atopic dermatitis[20,45] protection against oxidative stress from methotrexate[20,46] and exhibits antioxidant potential against diclofenac sodium-induction liver toxicity.[20.47] Bioactive components contribute to reactive oxygen spices (ROS).[12,61,66–68]

The aqueous extract capturis free radicals,[59,61] while kaempferol, isoquercetin, astragalin, and crypto-chlorogenic acid act as an antioxidant.[61,69,70] Additionally, *M. oleifera* acts as an oxidative and inflammatory marker, inhibiting IKBα phosphorylation, preventing nuclear translocation and suppressing inflammatory proteins such as TNF-α, cyclooxygenase-2 (COX-2), IL-6, and inducible nitric oxide synthase (iNos) offering therapeutic potential for as obesity, arthritis, cancer, diabetes, and ulcers.[61]

Although previous research supports the elevation of certain metabolites in sepsis, our study yields conflicting results with some of those findings. The limitation of this study lies

in the brief duration of observing the effect of LPS-induced sepsis in mice, compared to prior studies that conducted observed for 8 to 12 hours.[8,9] Additionally, the duration of therapy with *M. oleifera* is believed to influence anti-inflammatory, antioxidant, and immunomodulatory cabilities. Therefore, further understanding of these mechanisms could aid in the development of therapeutic strategies to address complications induced by sepsis.

Conclusion

In this study, we established that MOLE has the potential to change metabolite and hematological parameters in a sepsis mouse model. This suggests that *M. oleifera* may ameliorate sepsis by reducing glucose levels and downward trend triglyceride levels, as well as by increasing erythrocyte parameters, and upward trend leukocyte parameters, FABP4 levels, and NEFA levels.

Further understanding of the mechanisms involved in the metabolic and inflammatory effects of *M. oleifera* is needed. This requires continued exploration of the NF-ĸB pathway and other metabolic markers associated with sepsis by period. Our findings have the potential of *M. oleifera* as an herbal medicine for sepsis.

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Conflict of Interest

None declared

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Off-Label Drug Use in Acute Respiration Infection Patient at Pangandarn Hospital, Pangandaran District, West Java - Indonesia

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Abstract

Acute respiratory infections (ARIs) are infectious diseases of the upper or lower respiratory tract that cause a spectrum of illnesses from mild to severe infections. ARI is one of the leading causes of death in children in developing countries. The high incidence of ARI in children results in the use of off-label drugs. Off-label medicine is the use of drugs outside the provisions of the license relating to dose, age, route of administration, contraindications. This study aims to determine the use of off-label drugs in children with a diagnosis of ARI at Pandega Pangandaran Hospital, Pangandaran District, West Java - Indonesia. This study was an observational study with a cross sectional design and data collection was done retrospectively using Chi-square data analysis with a significance level of 0.05. Of the 84 patients who fit the inclusion criteria, there was an off-label drug use of 16.01% with the categories of off-label age (11.16%), off-label dose (4.37%), and off-label indication (0.48%) while in the category of route of administration and contraindications no off-label drug use was found. The most common type of off-label drug used was cetirizine antihistamine. Based on the results, pharmacist's supervision related to the risk of drug use is strongly recommended.

Keywords: Acute respiratory infection, pediatric, off-label drugs

Introduction

Acute respiratory infections (ARIs) are infectious diseases of the upper or lower respiratory tract that can produce mild to severe illness depending on the causative agent, host, or environmental variables. According to the World Health Organization, ARI is one of the top causes of morbidity and mortality from infectious diseases globally, with newborns, children, and the elderly bearing the greatest risk.[1]

One of the leading causes of death in children in developing countries is ARI, because they can cause respiratory failure and renal failure, especially in children.[2] According to the 2018 health profile data results, the prevalence of ARI in Indonesia was 20.54% of 1000 toddlers. West Java Province is among those with a high incidence of ARI, with a rate of 14.7%, which is greater than in other provinces.[3]

Off-label medication is the off-label use of drugs related to dose, age, route of administration, contraindications, and indications that are not mentioned in the product labeling approved by the Food and Drug Administration (FDA).[4] Off-label use of drugs may increase the risk of adverse drug events (ADEs) or unintended drug effects, which are medication-related side effects that occur in patients, such as adverse drug

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reactions (ADRs) and medication errors. Off-label use of medications in children may increase the likelihood of medication errors.[5] Knowing that pediatric patients have physiologically rudimentary organs and that differences in pharmacokinetic responses between pediatric patients and adults must be considered, off-label use of drugs involves a higher risk of unwanted side effects compared to on-label use of drugs.[6] Therefore, this study aimed to determine the use of off-label drugs in pediatric patients with ARI at Pandega Pangandaran Hospital, Ciamis, West Java Indonesia. This study was conducted in the hope of providing information regarding the use of off-label drugs and reducing the risk of drug use.

Methods

This is an observational study with a descriptive-quantitative research design and a cross-sectional approach, and the data was collected retrospectively at Pangaran Hospital, Pangandaran District, West Java - Indonesia from medical record data containing information on name, age, gender, and diagnosis. In addition, data collection was also sourced from drug prescriptions of patients diagnosed with ARIs aged 0-12 years from January to December 2022.

The sampling technique used in this study was purposive sampling. Informed consent is not required because this study uses a retrospective method for data collection. No medical interventions were performed during the study. All ethical considerations were followed and patient files were processed anonymously. The Ethics Committee of Bakti Tunas Husada Tasikmalaya University approved the research protocol.

We consulted literature such as the National Drug Information Center, the Indonesian Pediatric Association Health Sciences Specialty Formulary, the British National Formulary for Children (BNF), and the Drug Information Handbook (DIH) 21st edition to identify drug prescriptions. Data were analyzed using chi-square in SPSS Statistics version 26.

Research ethics clearance has been obtained from the Research Ethics Commission of the Health Research Ethics Commission of Bakti Tunas Husada University Tasikmalaya with No.015/E.01/KEPK-BTH/II/2023.

Results and Discussion

Data from a total of 84 pediatric patients were collected in this study. With a total of 206 prescriptions, there are 33 prescriptions (16.01%) are included in off-label drugs. Table 1 shows the demographic information for the study subjects. There were 50 males (59.52%) and 34 females (40.48%) among the participants. The largest number was 13.10% in patients aged 1 to 12 years, followed by 86.90% in patients aged 1 to 12 months. The common cold was the most common diagnosis in this study (59.5%).

According to Setyaningrum et al.'s report, there is an overwhelming prevalence of off-label medication use among pediatric demographics, with an incidence rate of incidence rate of 21%. Furthermore, off-label pharmaceutical usage has been reported to be especially widespread in pediatric patients in the early stages of development. As a result, it is critical to monitor the dangers associated with off-label pharmaceutical usage closely, particularly when given to children.[7] As can be seen from Table 2, the off-label drug's use of 16.01% with the categories of off-label age (11.16%), off-label dose (4.37%), and off-label indication (0.48%) while in the category of route of administration and contraindications no off-label drug use was found.

Table 1. Demographic Data of the Study Subjects

Characteristics	Frequency	Percentage (%)
Gender		
Male	50	59.52
Female	34	40.48
Age		
Neonates (0-28 days)	0	0
Infants (1-12 months)	11	13.10
Children (1 year-12 years)	73	86.90
Diagnoses		
Common cold	50	59.50
Asthma	27	32.10
Bronchopneumonia	4	4.80
Pneumonia	2	2.40
Bronchiolitis	1	1.20

Table 2. Distribution of Off-label Drug Use

Category	Frequency	Percentage (%)
Age	23	11.16
Dosage	9	4.37
Indication	1	0.48
Contraindication	0	0
Route of administration	0	0
Total	33	16.01

Off-label use of drugs in the age category is a drug that is used outside the permitted age range. There were 23 cases of use of off-label drugs in this study; the findings are similar to the study conducted by Tuloli in that the use of offline drugs is mostly given to children under the age of 12 years, especially in children under 2 years of age.[8]

Off-label drug prescribing is more common in pediatric patients because special formulations for children are still very limited, while clinical trials for licensed drugs are mostly conducted in children. Cetirizine is the most widely used off-label drug in the age category. The chi-square test analysis showed that there was no association between gender and off-label drug use in this age group, with a significance value of 0.161>0.05 (Table 3).

Cetirizine is not suggested for children under the age of two, according to the BNFC (British National Formulary Children) 2019–2020. According to Tan Rou et al.'s study, the use of antihistamine-containing drugs in children should be limited as there is a high risk of ADR in children.[9]

Cetirizine will cause restlessness, insomnia, and drowsiness if it is given to children under the age of 2 years. BNFC 2019-2020 also advises refusing to give salbutamol to children under 2 years old due to their later onset of action and higher rate of side effects. Oral bronchodilators are not recommended for use compared to inhaled counterparts. Hypokalemia, hypoglycemia, tachycardia, anxiety, and other consequences may occur with low-risk ingestion.[10]

The National Drug Information Center states that children above the age of 6 years should only use Symbicort®. The safety and efficacy of Symbicort® use in children younger than 6 years old is yet unknown. Budesonide and formoterol fumarate dihydrate, which are utilized in Symbicort®, are asthma controllers that require daily administration over an extended period to produce and preserve a controlled asthmatic state.

Triamcinolone can exhibit anti-inflammatory activity so that it can be used in asthma management. Triamcinolone cannot be used in children under 6 years old, according to the BNFC 2019-2020. Side effects of triamcinolone can cause headaches and visual disturbances.[11] Statistically, for children (aged 2–11 years), the rate of off-label prescribing is high, which is concerning as several studies have reported that off-label prescribing is a risk factor for adverse reactions.[12]

The off-label dosage category refers to drugs that are administered without following the dosage listed in the distribution license. In the data obtained, there were nine cases of off-label use of ambroxol. The official dose of ambroxol, according to PIONAS, is at the age of 2–6 years, 15 mg/2.5 mL given 2-3 times a day, and for ages 6–12 years, 15 mg/5 mL. In this study, the use of ambroxol at the age of 1 year and 4 months was given 15 mg/5 mL every three times a day, and at the age of 7 years, 15 mg/2.5 mL every three times a day. The side effects of ambroxol are nausea, vomiting, stomach discomfort, and dry mouth.[13]

Off-label drug use in pediatric patients is necessitated by the limited availability of medicines that are specifically marked for use in this population. Therefore, determining the appropriate dose for children sometimes involves extrapolation from adult dosing guidelines, which can result in underdoses and overdoses.[14] Which may result in underdoses and overdoses. Administration of insufficient or excessive doses of drugs insufficient or excessive poses a significant health risk for children.

Lower doses may compromise the effectiveness of treatment, but administration of excessive doses of a drug may increase the risk of toxicity.[15] According to the findings of the chi-square test analysis, there is no correlation between gender and the use of off-label drugs in the dosage category, with a significance value of 0.149 > 0.05 (Table 4).

Off-label usage of a drug occurs when it is used outside of the indications specified on the drug's brochure or when it isn't released in compliance with the BPOM distribution permit. The drug that was prescribed with an off-label indication in this study was zinc, which is an official indication.[9]

Zinc is a drug to treat diarrhea in children, but in this study, it was given in chidlren with ARI. In general, zinc is used to help speed up the healing of children's diarrhea. But according to Rerksuppaphol's research, zinc can reduce inflammation, decrease airway obstruction, and reduce chest tightness, a high respiratory rate, and hypoxia.[16]

Table 3. Profile of Off-label Drug Use: Age Category

Drugs Name	Authorized use	Off-label Usage	Gender		*P-(Value)*
			F	M	
Cetirizine HCl	Children under the age two years are not recommended	Given to children aged 4 months, 11 months, and 1 year	**6**	**8**	0,161
Salbutamol	Children under the age two years are not recommended	Given to children aged 8 months and 1 year	**0**	**4**	
Symbicort®	Not suggested for children under the age of six	Given to 4-year-olds and 5-year-olds	**0**	**3**	
Triamcinolone	Not suggested for children under the age of six	Given to 4-year-olds and 5-year-olds	**0**	**2**	
Total			**6**	**17**	

Table 4. Profile of Off-label Drug Use: Dose Category

Drugs Name	Authorized use	Off-label Usage	Gender		*P-(Value)*
			F	M	
Ambroxol	15mg/5ml 2-3 times daily	15mg/2,5 ml 3 times daily	**6**	**3**	0,149
Total			**6**	**3**	

Table 5. Profile of Off-label Drug Use: Indication Category

Drugs Name	Authorized use	Off-label Usage	Gender		*P-(Value)*
			F	M	
Zinc	Relieves the symptoms of diarrhea in children	Used for patients with ARI	**1**	**0**	1000
Total			**1**	**0**	

Side effects of zinc should be monitored as they may cause temporary abdominal discomfort.[17] Based on the chi-square test analysis results, with a significance value of 1000 > 0.05, there is no relationship between gender and off-label drug use in the indication category (Table 5). Of-label use of drugs in children is common globally, as well as in Indonesia. The term "off-label" refers to the unapproved use of approved medications, and it may seem like a nearly simple concept. Prescribing and dispensing medications with pre-existing off-label regimens remains a problem today, primarily due to unmet clinical demands. Off-label techniques are necessary in some treatment domains. Thus, the physicians face challenges with this practice.[18]

Since the right to information and informed consent are components of the patient's rights, parental informed consent is a crucial component of the off-label process in pediatrics. From a liability standpoint, it is preferable to obtain informed permission.[19] The informed consent of the patient was mandated in many European nations (including the UK, France, Italy, the Netherlands, and Sweden) in addition to the off-label use.[20]

The limitation of the research is that there was not any further conversation with the doctors; accordingly, the reasons for using off-label medications are unknown. The other drawback is that this investigation was limited to respiratory medications rather than all drugs. It's challenging to compare the results of this study with those of others due to limited research location. However, it's crucial to acknowledge the uniqueness of this study and recognize the valuable insights it can provide to the research community.

Conclusion

It can be concluded that there is still off-label use of drugs on pediatric patients with a diagnosis of ARI at Pandega Pangandaran Hospital, West Java - Indonesia in the period 2022. The categories are off-label age 23 cases (11.16%), off-label dose 9 cases (4.37%) and off-label indication 1 case (0.48%). Based on the results of this study, it is known that the use of off-label drugs in children is still quite high, so supervision related to the risk of drug use needs to be carried out by pharmacists.

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Conflict of Interest

None declared

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The Effect of Ashitaba (*Angelica keiskei* (Miq.) Koidz.)) Sap on the Total Cholesterol Levels of Cisplatin-Induced Wistar Rats

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Abstract

Cisplatin is a platinum-based anticancer drug that, in long-term use, causes nephrotoxicity due to oxidative stress and increases total cholesterol and triglycerides in animal models. *Angelica keiskei* (Miq.) Koidz., (*A. keiskei*) or Japanese celery ashitaba, has been reported for its antioxidant and nephroprotective activity. This study aims to determine the activity of *A. keiskei* sap on total cholesterol levels of cisplatin-induced Wistar rats. The sap of *A. keiskei*- was freeze-dried until a yield of 3.62% w/v was obtained. The fat content in *A. keiskei* sap powder was obtained at 7.36%. A total of 60 g of *A. keiskei* sap powder was macerated with 96% ethanol solvent (1:10) for 5 x 24 h until the ethanol extract of *A. keiskei* sap (ASEE) of 82.08% w/w was obtained. The pharmacology activity was conducted on male Wistar rats, which were divided into 5 groups, namely normal (treated with CMC Na 0.3%), negative (nephrotoxicity induced with cisplatin 5 mg/kg BW), positive (nephrotoxicity induced with cisplatin 5 mg/kg BW and treated with quercetin 20 mg/kg BW), and two test groups which were nephrotoxicity induced with cisplatin 5 mg/kg body weight and treated with ASEE 1000 mg/kg BW, and ASEE 1500 mg/ kg BW. It was found that neither dose of ASEE altered the total cholesterol levels in cisplatin-induced male Wistar rats and could maintain the cholesterol levels in the normal range.

Keywords: *Angelica keiskei* sap, cholesterol, cisplatin

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Introduction

Cisplatin is one of the most potential and widely used drugs for the treatment of various types of cancer such as testicular, ovarian, breast, bladder, lung, cervical, and several others.[1] Cisplatin works by cross-binding purine bases by interfering with the mechanism of deoxyribonucleic acid (DNA) formation, thereby causing DNA damage.[2] In using cisplatin, the process of mitosis does not occur, causing cytotoxic and apoptosis.[3]

Long-term use of cisplatin and excessive doses can cause toxicity including nephrotoxicity, ototoxicity, hepatotoxicity, hematological, gastrointestinal, and metabolic disorders, e.g., abnormal cholesterol levels.[4–6] Nephrotoxicity on rat-induced cisplatin has been reported for an increase in total cholesterol and triglyceride levels.[7] Metabolic testing such as total cholesterol levels can be used as a biomarker of nephrotoxicity caused by kidney injury due to cisplatin use.[5]

Angelica keiskei (Miq.) Koidz., or Japanese celery ashitaba, contains flavonoids such as quercetin and luteolin, polyphenols, and chalcone compounds including xanthoangelol, 4-hydroxyderricin, and isobavachalcone.[8,9] Flavonoid compounds found in *A. keiskei* have been reported for their activity as antioxidants.[10] The reported pharmacological activities of *A. keiskei* include nephroprotective, antiobesity, antidiabetic, anti-inflammatory, antitumor, and anti-hyperlipidemia.[10–16] This study aims to provide the effect of ethanol extract of *A. keiskei* sap (ASEE) on the cholesterol levels of cisplatin-induced Wistar rats to ensure its safety for dyslipidemia patients.

Methods

1. Equipment

The equipment used was a freeze dryer (Ihanil, Vac 8), rotary evaporator (IKA RV 10), Soxhlet apparatus, desiccator, centrifuge (Hettich EBA 280), multimode reader (Tecan, Infinite 200PRO NanoQuant), glassware (Pyrex), oral sonde, spuit (Terumo), restrainer, and rat cages.

2. Materials

The sap of *A. keiskei* was collected from Mount Rinjani, Sembalun, Lombok-Indonesia. Taxonomic determination (Number.2847/ITI.C11.2/TA00/2023) was conducted by a certified botanist at the Bandung Institute of Technology (ITB), ethanol 96% (pharmaceutical grade), carboxymethyl cellulose sodium CMC Na (pharmaceutical grade), hexane (Merck), cisplatin (PT. Kalbe Farma - Indonesia), quercetin (Sigma Aldrich, CAS No.849061-97-8), ketamine (Ket-A-100 Agrovet market), Cholesterol kit (Linear Chemicals, SLU).

3. Procedure

3.1 Extraction

Approximately 2L of *A. keiskei* sap was freeze-dried at a temperature of -80°C to obtain yellow sap powder *A. keiskei*. The sap powder was macerated in 96% ethanol solvent (1:10) for 5 x 24 hours. The filtrate was collected and evaporated at a temperature of 60°C, with 85 rpm for 1 hour until a thick extract of ASEE was obtained.[13]

3.2 Determination of Fat Content on Sap Powder A. keiskei

Approximately weight of 1g of the sap powder was wrapped in filter paper and put into a Soxhlet flask. The hexane solution was added to the Soxhlet flask and the mixture was heated for 6 hours, then was evaporated at 105°C until a crude fat was obtained. The flask containing the crude fat was cooled in a desiccator and weighed (Soxhlet method: SNI 01-2891-1992).

$$\% \text{ fat} = \frac{\text{Weight of fat}}{\text{Weight of sample}} \times 100\% \quad (17)$$

3.3 Animal Acclimatization

The experiment was carried out on 25 male Wistar rats (*Rattus norvegicus*), aged between 6-8 weeks, and weighed between 200-220 g. The study was approved by the Research Ethics Committee of Padjadjaran University (Document No. 1241/UN6.KEP/EC/2023). The rats are placed in plastic tub cages with net-shaped wire lids and cage mats using clean rice husks which are replaced every 2 days. Animals were given a light-dark cycle for 12 hours and given standard feed and ad libitum drinking water. The standard pellet feed used low fiber (5%), protein (20%), and fat (5–10%).

3.4 The Effect of ASEE on the Total Cholesterol Level of Wistar Rats

The male Wistar rats were distributed randomly into five groups (5 rats each), and were treated as follows:

- The normal group was orally given a 0.3% CMC Na suspension for 10 days.
- The negative group was given CMC Na 0.3% orally for 10 days.
- The positive group was given 20 mg/kg of quercetin BW orally for 10 days.
- Treatment 1 group was given an ASEE dose of 1000 mg/kg BW orally, 1 time a day for 10 days.
- Treatment 2 was given an ASEE dose of 1500 mg/kg BW orally, 1 time daily for 10 days.

All groups, except the normal group, were nephrotoxicity-induced using cisplatin 5 mg/kg BW intraperitoneally on day 7.

At the end of the experiment, rats were sequentially sedated with ketamine at a dose of 100 mg/kg BW.[18] Blood samples of as much as 3 mL were taken in the caudal vein of the mouse's tail. Each blood sample obtained from each mouse was collected into a plain sample vial with a capacity of 4 mL that was clearly labeled.[19]

The serum was separated by centrifugation at 11,000 rpm for 10 minutes to measure the total cholesterol level. 10 µL of serum and standard 1 mL of reagent each were added and incubated for 10 min at room temperature. Absorbance was measured at 500 nm using a multimode reader. The absorption results were calculated using the following formula:

$$\text{Cholesterol Total } \left(\frac{\text{mg}}{\text{dl}}\right) = \frac{\text{A Sample}}{\text{A Standard}} \text{ x C Standard}$$

3.5 Data Analysis

Data analysis was performed using GraphPad Prism 8.1.2. The difference in the nephroprotective activity ratio of test animals was analyzed using the one-way analysis of variance (ANOVA) test at a confidence level of 95%. The Bonferroni test determined the mean significant difference between each group with $p < 0.05$.

Results and Discussion

1. Extraction and Fat Content

The sap of *A. keiskei* used in this study was obtained from the stem part of the plant. The characteristics of *A. keiskei* sap include liquid, solid yellow, and slightly sticky. From the freeze-drying process, dry powder of *A. keiskei* sap was obtained by 72.4 g with a yield of 3.62% w/v. This result was smaller than other studies on *A. keiskei* sap obtained a yield of 4.20% w/v.[13] The *A. keiskei* sap powder has a yellow and specific odor. The maceration yielded 49.25 g (82.08% w/w) ASEE.

A. keiskei contains several phytonutrients, including protein, sugar, and electrolytes such as calciums, ferric, pottasium, magnesium, and natrium.[20] A smaller fat content of 7.36% was obtained in our ASEE compared to a previous study, which was 12%.[21] It was reported previously that the sap of *A. keiskei* contains flavonoids, polyphenols, and chalcone compounds.[8,9,13] Thus, confirming its potential pharmacology activity is necessary.

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A small increase in total cholesterol levels was observed in the rats treated with ASEE, although not significantly when compared to the negative group (cisplatin 5 mg/kg BW) (Fig.1). In the positive group, quercetin 20 mg/kg BW could reduce the total cholesterol levels, although not significantly when compared to the negative group (cisplatin 5 mg/kg BW) (Fig.1). However, the success of the induction is proven by comparing the data of the negative control group with that of the normal group.

2. The Effect of ASEE on Total Cholesterol Levels of Wistar Rats

A small increase in total cholesterol levels was observed in the rats treated with ASEE, although not significantly when compared to the negative group (cisplatin 5 mg/kg BW) (Fig. 1). In the positive group, quercetin 20 mg/kg BW could reduce the total cholesterol levels, although not significantly when compared to the negative group (cisplatin 5 mg/kg BW) (Fig. 1). However, the success of the induction is proven by comparing the data of the negative control group with that of the normal group. The use of cisplatin in excess doses leads to nephrotoxicity.[22] Poor kidney function generates lipid metabolism disorders, including increased total cholesterol, triglycerides, and changes in lipoprotein composition, which can later develop into vascular disease.[23]

Rats treated with cisplatin 5 mg/kg BW intraperitoneally did not experience an increase in cholesterol when compared to the normal group. The dose used for induction should likely be higher. A previous study described that cisplatin at a dose of 5 mg/kg BW was reported to accumulate mostly in the inner cortex and corticomedullary junction of the rat kidney, which is the location of proximal and distal tubules (on day 5). However, when a lethal dose was used (16 mg/kg BW) cisplatin was detected in renal columns (on day 3).[24,25] Moreover, cisplatin at a dose of 20 mg/kg BW can inhibit fatty acid oxidation in animal models.[6]

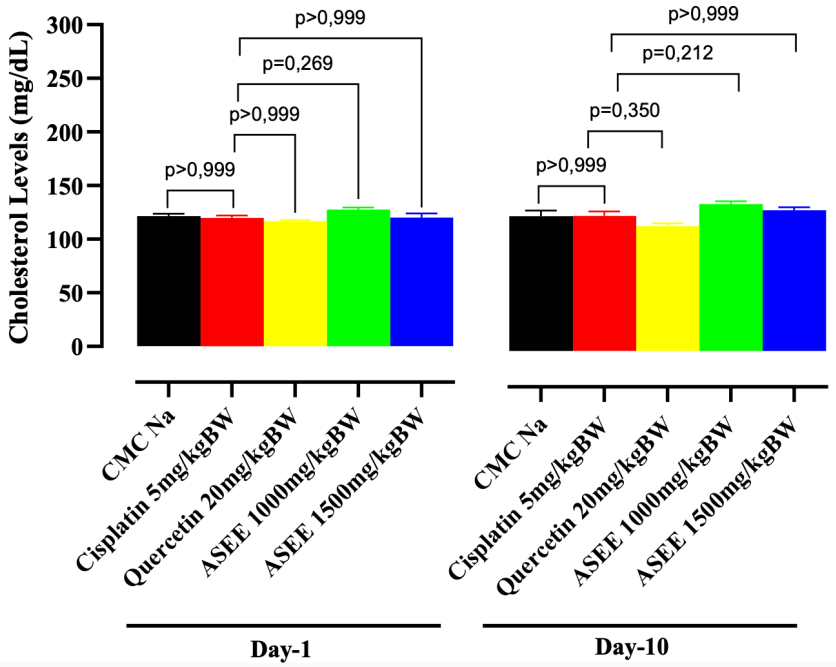

Figure 1. The Statistical Analysis Result on the Effect of ASEE on the Serum Total Cholesterol Level of Cisplatin-Induced Rats at Day 1 and Day 10

Table 1. The Effect of ASEE on the Serum Total Cholesterol Level of Cisplatin-Induced Rats at Day 1 and Day 10

Groups	Total Cholesterol (mg/dL)	
	Day-1	Day-10
Normal (CMC Na 0.3%)	123.23 ±0.80	125.60 ±2.89
Negative (Cisplatin 5 mg/kg BW)	119.86 ±2.35	125.83 ±2.39
Positive (Quercetin 20 mg/kg BW)	116.76 ±1.05	116.60 ±2.48
Treatment 1 (ASEE 1000 mg/kg BW)	127.62 ±1.97	137.05 ±2.43
Treatment 2 (ASEE 1500 mg/kg BW)	120.11 ±2.65	131.18 ±2.74

In this study, neither dose of ASEE altered the total cholesterol levels of cisplatin-induced male Wistar rats. They maintained the cholesterol levels in the normal range (<200 mg/dL). Conversely, a previous study reported that treatment with *A. keiskei* sap dose of 1000 mg/kg BW resulted in increased total cholesterol levels significantly compared to normal groups.[26] Interestingly, a clinical trial described that adult participants consuming *A. keiskei* (Chalcurb®) 220 mg/capsule showed no significant changes in total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and overall glucose levels (fasting glucose and HBA1c).[12]

Previous studies described that isoflavones, flavones, and flavanones could reduce blood cholesterol levels by inhibiting cholesterol synthesis and increasing LDL receptor expression.[27,28] It was suggested that this pharmacology activity may resulted from the effect of flavonoids on SREBP-2.[29–32]

Conclusion

The ethanol extract of dry sap powder of *Angelica keiskei* (Miq.) Koidz. (ASEE), or Japanese celery ashitaba, collected from Mount Rinjani, Sembalun, Lombok-Indonesia, contained 7.36% of fat. In this study, both doses of ASEE (1000 mg/kg BW and 1500 mg/kg BW) did not alter the total cholesterol levels of cisplatin-induced male Wistar rats and maintained the cholesterol levels in the normal range (< 200 mg/dL). It is obvious that ASEE is safe to be consumed by patients with dyslipidemia, however, further studies on the molecular pathway affected by ASEE are interesting to explore.

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Conflict of Interest

The authors declare no conflict of interest.

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Lacked of Breast Cancer Awareness of Indonesian Rural Women: a Descriptive Study to Adult Women in District Pangandaran, Indonesia

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Abstract

Breast cancer remains a significant global health challenge, particularly in low and middle-income countries like Indonesia. Patients with advanced metastatic breast cancer have a dismal prognosis. A cancer promotion program's failure can be attributed to low awareness of breast cancer. This descriptive study aimed to evaluate breast cancer awareness among adult women in District Pangandaran, Indonesia. Data was gathered in July 2018 from 189 individuals using a verified Breast Cancer Awareness Measure instrument developed by Cancer Research UK. Results revealed a concerning lack of awareness among participants regarding various breast cancer risk factors, symptoms, and screening practices. Additionally, reluctance to seek medical help due to fear of diagnosis was observed, particularly among housewives without health insurance. These findings highlight the urgent need for comprehensive health programs to enhance breast cancer awareness and promote early detection strategies tailored to the Indonesian population, especially in rural areas. Healthcare providers and public health workers play a vital role in this effort, along with implementing innovative health promotion policies by the government to improve cancer prevention programs.

Keywords: Breast cancer awareness, rural women, Indonesia, Pangandaran, health promotion, public health intervention.

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Introduction

Breast cancer continues to pose a significant public health challenge, with 2.09 million new cases and 627,000 fatalities reported globally each year.[1] It ranks as the second most frequently diagnosed cancer worldwide, affecting populations across low and middle-income countries.[2] While early detection and effective treatment options exist for breast cancer, survival rates remain disproportionately low in developing nations. This is often attributed to factors such as limited awareness, inadequate screening programs, and challenges in accessing timely and standardized care. A substantial portion of breast cancer-related deaths, particularly in low- and middle-income countries, can be linked to insufficient access to early detection methods and treatment. The implementation of systematic mammography screening, which is considered a crucial tool for early detection, is often hindered by issues of affordability and feasibility in these regions.[3]

As an alternative, breast self-examination (BSE) offers a cost-effective and less invasive approach to detecting potential abnormalities.[4] While the effectiveness of BSE remains a topic of debate within medical circles, it nonetheless offers distinct advantages. Engaging in regular self-examination not only promotes heightened awareness of breast health among women but also empowers them to take proactive measures for their well-being. Furthermore, it encourages individuals to promptly seek assistance from healthcare professionals upon noticing any concerning changes, potentially facilitating earlier diagnosis and intervention.[2,5]

The early identification, treatment, and prevention of breast cancer are significantly bolstered by widespread public awareness of the disease. Unlike some other cancers, breast cancer holds a high potential for successful treatment when detected at an early stage. To effectively plan comprehensive health programs and campaigns for early detection and treatment, it is imperative to first assess the current levels of cancer awareness within communities of women nationwide.[2] Study showed that breast cancer awareness is influenced by various factors including socioeconomic factors, affordability to facilities and health personnel, social activities, and personality.[6]

In that case, women residing in rural areas encounter distinct obstacles and limitations concerning awareness and early detection of breast cancer. These challenges encompass restricted access to healthcare facilities, a lack of education and knowledge regarding breast cancer, cultural taboos, and financial constraints.[2] Research indicates a pervasive lack of awareness among women globally, with particular prevalence among Asian populations. A cross-sectional study conducted by Norlaili AA et al. in 2013 examined five rural districts in Malaysia, revealing a correlation between higher levels of education and increased awareness of breast cancer among women.[3] Notably, women from rural areas typically had lower levels of education. This study aimed to investigate the level of knowledge, confidence, and behavioral patterns related to breast cancer among women in Indonesia, with a specific focus on suburban areas. The findings from this research are anticipated to be utilized by healthcare professionals and governmental bodies to enhance the effectiveness of health programs tailored to address breast cancer awareness and prevention within the Indonesian population, particularly in suburban regions.

Methods

Study Design

This research conducted a descriptive, cross-sectional analysis aimed at evaluate the level

of breast cancer awareness among women aged 16 to 65 residing in the suburban area of Cijulang sub-district, Pangandaran district, within the West Java Province of Indonesia. During July 2018, data was gathered from 189 participants using a validated tool provided by Cancer Research UK to assess Breast Cancer Awareness. Data collection involved visiting participants' homes and utilizing a validated, adapted version of the Breast Cancer Awareness Measure (Breast-CAM), which had been translated into Indonesian. The study was conducted with the approval of the ethical research committee of Universitas Padjadjaran (approval number: 422/UN6.KEP/EC/2018), and prior informed consent was obtained from all participants before conducting interviews.

Sampling and Sample size

Cluster random sampling was employed for the sampling methodology, wherein participants were grouped based on their residential areas, specifically categorized according to the seven villages within the Cijulang sub-district: Batukaras, Ciakar, Cibanten, Cijulang, Kertayasa, Kondangjajar, and Margacinta. This study focused on three of these villages, namely Cijulang, Kondangjajar, and Margacinta. A total of 189 subjects were included in the data collection process.

Data Collecting and Analysis

The data collected underwent recording and tabulation using Microsoft Office Excel 2010, followed by analysis through descriptive methods. Presentation of the data was achieved through frequency and percentage distributions, facilitating a clear understanding of the findings.

Results and Discussion

Demographic Characteristic of The Study Population

The subjects' average age was approximately 39.9 years. Predominantly, the participants identified as Sundanese, comprising 93.7% of the sample. Additionally, a significant majority resided in their own homes (95.8%) and were situated within a 5-kilometer radius of a healthcare facility (94.2%). Furthermore, the vast majority reported not smoking (97.4%) and had not previously received a breast cancer diagnosis (82%). Regarding educational attainment, more than half had lower levels of education (58.2%), and a majority identified as housewives (53.4%). The majority also derived their income from non-permanent employment (58.7%) and possessed health insurance (52.4%) (Table 1).

Research indicates that a person's occupation and level of education significantly influence the prognosis of breast cancer, impacting factors like the stage at diagnosis and treatment strategies. Typically, individuals with higher education levels exhibit smaller tumor sizes, a greater likelihood of early breast cancer detection, and improved treatment outcomes compared to those with lower education levels. Moreover, diverse occupational groups exhibit varying breast cancer outcomes; for example, professionals may experience a higher prevalence of early-stage breast cancer, necessitating different treatment approaches compared to manual laborers or other occupational cohorts.[7] However, in our study, we did not explore the relationship between participants' educational backgrounds or occupations and their breast cancer education or awareness levels. Further investigation is warranted to delve deeper into these associations.

Awareness of Breast Cancer Among Suburban Women

In order to evaluate the breast cancer awareness levels of the subjects, they were questioned about five specific aspects, which encompassed (1) their knowledge regarding breast cancer signs and symptoms, (2) the

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regularity of breast self-examinations, (3) their confidence in identifying any changes in their breasts, (4) awareness of age-related risks, and (5) comprehension of lifetime risks associated with breast cancer. An asterisk serves as a symbol denoting that the participant possesses a strong comprehension of the pertinent question (Table 2).

Our research findings indicate a significant lack of awareness regarding breast cancer among Indonesian suburban women. The participants in our study demonstrated a lack of understanding concerning the age-related risk factors associated with breast cancer, as well as an underestimation of the lifetime risk of developing the disease, as highlighted in Table 2. These findings align with similar studies, which have also identified limited knowledge among subjects regarding both age-related and lifetime breast cancer risks.[8–11] Additionally, it was observed that the majority of subjects were unaware of the role of family history and previous instances of breast cancer in their medical history as contributing factors to their risk. This contrasts with research conducted among high-risk populations, where participants were found to be knowledgeable about the significance of family history and past breast cancer diagnoses as risk factors.[8]

Introducing breast cancer symptoms and providing training on how to conduct breast self-examinations (BSE) from a young age could significantly improve breast cancer awareness among women. In developed countries, a notable 82% of women engage in routine BSE.[12] This heightened awareness is largely attributed to the guidance and encouragement provided by healthcare professionals, with 69.9% of women receiving coaching on BSE and 78.3% being encouraged to perform regular self-examinations during their teenage years.[12] Unfortunately, our study revealed that our subjects seldom conducted BSE and were primarily aware of lumps or thickening in the breast, neglecting other potential symptoms in the nipple, armpits, and breast skin, as detailed in Table 2. These findings underscore the critical need to educate suburban communities and implement government-sponsored early cancer detection programs.

Suburban Women's Awareness of Breast Cancer Symptoms and Risk Factor Variables

The participants' understanding of breast cancer symptoms was evaluated through a task requiring them to identify such symptoms. Analysis of the data revealed that fewer than 30% of the subjects were able to correctly identify breast cancer symptoms other than a lump in the breast, as illustrated in Table 3. This observation suggests a notable deficiency in the subjects' awareness regarding breast cancer symptoms.

Furthermore, the majority of subjects displayed limited awareness concerning the risk factors associated with breast cancer, as depicted in Table 4. It is noteworthy that only a small proportion of participants, amounting to 10.6%, acknowledged a recent history of breast cancer as one of the risk factors for the disease, indicating a significant gap in their understanding of breast cancer risk factors.

Fortunately, Indonesian suburban women have shown knowledge of several risk factors related to breast cancer, such as drinking alcohol and not exercising. Compared to other organs, the breast is especially susceptible to the cancer-causing properties of alcohol.[13] Even yet, studies have suggested that moderate physical activity, such brisk walking, may reduce the incidence of breast cancer, especially in postmenopausal women. This is due to the fact that exercise helps lower hormone levels, including progesterone and estrogen in the blood, which are associated with an increased risk of breast cancer.[14-15]

Table 1. Demographic Profile of the Study Population

Potential Determinants		(n = 189)	%
Age (year old)	<20	17	9.0
	21-40	85	45.0
	41-60	76	40.2
	>61	11	5.8
Ethnicity	Sundanese	177	93.7
	Javanese	9	4.8
	Other	3	1.6
Residence	private house	181	95.8
	Rent a house	5	2.6
	Rent a room	3	1.6
Distance to healthcare	<5 km	178	94.2
	5-10 km	10	5.3
	>11 km	5	2.6
Formal Education	Lower than high school	110	58.2
	High school	61	32.3
	Graduate school	18	9.5
Source of income	Parent or children	8	4.2
	Spouse	10	5.3
	Pension	8	4.2
	Fixed employment	50	26.5
	Non-permanent employment	111	58.7
	No income	2	1.1
Insured	Yes	99	52.4
	No	89	47.1
	Do not know	1	0.5
Job	Housewife	101	53.4
	Trader/Merchant	23	12.2
	Teacher	12	6.3
	Student	14	7.4
	Farmer/gardener	15	7.9
	Others	19	10.1
	Out of employ	5	2.6
Tobacco smoking	Yes	5	2.6
	No	184	97.4
Have been diagnosed with breast cancer	Yes	3	1.6
	No	155	82.0
	Do not know	31	16.4

Table 2. Understanding of Breast Cancer Among Suburban Women

Variables		n = 189	%
Knowledge of symptoms	>5 non-lump symptoms*	46	24.3
	1–4 non-lump symptoms	43	22.8
	Do not know	100	52.9
Frequency of breast checking	At least once a week or once a month*	40	21.2
	At least once every 6 months	9	4.8
	Rarely or never	140	74.1
Confidence to detect any changes in breast	Fairly-to-very confident*	75	39.7
	Slightly-to-not at all confident	82	43.4
	Do not know	32	16.9
Knowledge of age-related risk	Woman aged 70-year-old*	1	0.5
	Woman aged 50-year-old	13	6.9
	Woman aged 30-year-old	45	23.8
	Others	81	42.9
	Do not know	49	25.9
Knowledge of lifetime risk	1 in 8 women*	26	13.8
	1 in 3 women	21	11.1
	1 in 100 women	30	15.9
	1 in 1000 women	19	10.1
	Do not know	93	49.2

Table 3. Percentage of Participants Familiar with All Potential Breast Cancer Symptoms

Variables	n=189	%
Nipple position changes	36	19.0
Pulling in of nipple	37	19.6
Breasts or armpit pain	55	29.1
Breast skin Puckering or dimpling	36	19.0
Nipple discharge or bleeding	45	23.8
A lump on or thickening in the breast	77	40.7
Nipple rash	40	21.2
Breast skin Redness	46	24.3
A lump or thickening under an armpit	49	25.9
Change in the shape of the breast or nipple	45	23.8
Change in the size of the breast or nipple	48	25.4

Obstacles Encountered in Accessing Medical Assistance

During breast self-examination (BSE), abnormalities were detected in the breasts of 41 subjects. Remarkably, half of these individuals did not seek consultation with a medical doctor for further assessment, as outlined in Table 5. Additionally, it was noted that nearly half of the subjects expressed concerns regarding potential findings during medical consultations, with 53.66% indicating worry, as shown in Table 5.

Many women who become aware of their health issues often seek medical attention to confirm a diagnosis.[16] However, there are numerous obstacles to accessing healthcare services, particularly for conditions like cancer. Our findings revealed that a significant number of subjects avoided visiting a doctor, with one of the primary reasons being concern over potential diagnoses. This aligns with previous research indicating that the fear of what a doctor might uncover is a commonly cited barrier to seeking medical help.[17] Additionally, half of the subjects were housewives without health insurance, relying on unstable income from non-permanent jobs. These factors could also hinder their willingness to seek medical attention and become informed about breast cancer signs and symptoms. It is worth noting that in low-income countries, individuals often prioritize securing funds for basic necessities over healthcare, contributing to low health awareness levels.[18]

Several studies have identified common obstacles that can impact breast cancer education and awareness among women across diverse population. Firstly, there is a significant lack of knowledge and awareness, particularly within underserved communities. Secondly, individuals may face perceived barriers such as shyness, fear, and cultural attitudes, which can deter them from seeking information about breast cancer. Thirdly, socio-cultural factors, such as fear of screening, lack of social support, and adherence to cultural norms, can obstruct access to information and preventive measures. Additionally, logistical challenges like transportation issues, lack of paid time off (PTO), and childcare responsibilities can prevent individuals from attending educational sessions. Moreover, financial constraints and disparities in healthcare access and delivery further exacerbate these barriers to breast cancer education and awareness.[19-21] These factors were also identified in our research study. By recognizing and addressing these common barriers through customized educational programs, culturally sensitive awareness campaigns, improved resource accessibility, and enhanced healthcare system support, there is potential to enhance breast cancer education and awareness, particularly among suburban women.

Additional efforts such as educational interventions, community-based programs within primary healthcare settings, implementation of school-based educational initiatives targeting adolescents to raise breast cancer awareness, and the establishment of peer support groups can be integrated into educational programs and community outreach endeavors.[22,23] Public health workers are especially pivotal in these endeavors, given the prevalence of housewives among the women studied. Moreover, healthcare providers should actively participate in research endeavors aimed at advancing breast cancer treatment, interventions, and the promotion of effective strategies alongside educational initiatives. Lastly, it is advised that the government implement innovative health promotion policies to bolster cancer prevention programs.

Conclusion

This study reveals a concerning lack of awareness among women regarding various risk factors associated with breast cancer, including age-related risks, lifetime risks, as well as past medical history, hereditary factors, hormonal influences, and lifestyle choices. Notably, a majority of subjects not only infrequently performed breast self-examinations but also avoided seeking medical attention due to concerns about potential diagnoses.

These findings underscore the urgent need for healthcare providers to prioritize raising awareness of breast cancer among Indonesian suburban women. Public health workers, in particular, play a crucial role in this effort, given that many of the women in the study were housewives. Furthermore, healthcare providers should actively engage in research aimed at improving breast cancer treatment, interventions, and promotion of effective strategies, in addition to education initiatives. Lastly, it is recommended that the government implement innovative health promotion policies to enhance cancer prevention programs.

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Conflict of Interest

The authors declare that they have no competing interests.

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