

Keamanan Obat Herbal: Evaluasi Perbandingan Reaksi Obat yang Merugikan di Dua Kecamatan, Kota Gorontalo

Herbal Medicine Safety: Comparative Evaluation of Adverse Drug Reactions in Two Subdistrict, Gorontalo City

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Abstrak

Seiring dengan meningkatnya tren konsumsi obat herbal di Indonesia, sangat penting untuk memahami potensi Reaksi Obat yang Merugikan (ROM/Adverse Drug Reactions, ADRs) yang dapat timbul di berbagai komunitas. Gorontalo, sebagai wilayah yang kaya akan keanekaragaman hayati, masih banyak memanfaatkan obat herbal dalam praktik sehari-hari. Penelitian ini bertujuan untuk mengevaluasi profil Reaksi Obat yang Merugikan (ROM) pada pengguna obat herbal di Kecamatan Sipatana dan Kecamatan Kota Utara, Kota Gorontalo. Penelitian ini menggunakan pendekatan deskriptif observasional, dengan pengumpulan data melalui wawancara langsung terhadap 194 responden, terdiri dari masing-masing 97 partisipan di tiap kecamatan. Data yang dikumpulkan mencakup karakteristik demografis, jenis obat herbal yang digunakan, serta manifestasi klinis dari ROM. Analisis kuantitatif dilakukan untuk menentukan frekuensi, kategori ROM berdasarkan kausalitas, dan hubungan kausal menurut *Naranjo ADR Probability Scale*. Hasil penelitian menunjukkan bahwa sebagian besar responden berada pada usia produktif (31–50 tahun), mayoritas berjenis kelamin perempuan, dan berprofesi sebagai ibu rumah tangga. Dari sembilan kasus ROM yang dilaporkan, 22,3% dikategorikan sebagai *possible*, 44,4% sebagai *probable*, dan 33,3% sebagai *definite*. Jenis herbal yang paling sering dikaitkan dengan ROM meliputi bawang putih, daun kelor, *Peperomia pellucida*, kayu bajakah, *Clinacanthus nutans*, dan daun sirsak. Manifestasi paling umum melibatkan sistem gastrointestinal seperti nyeri epigastrium, kolik, diare, serta beberapa efek metabolik dan hipoglikemik. Penelitian ini menekankan pentingnya faktor individu, dosis, lama penggunaan, serta kombinasi herbal dalam menentukan risiko ROM. Temuan ini menegaskan perlunya edukasi pasien mengenai penggunaan herbal yang aman, pemantauan klinis yang tepat, serta konsultasi dengan tenaga kesehatan sebelum mengombinasikan beberapa jenis herbal. Penelitian lebih lanjut direkomendasikan untuk mengkaji interaksi antara herbal dengan obat konvensional serta mengembangkan sistem farmakovigilans herbal berbasis komunitas. Dengan demikian, penelitian ini memberikan dasar ilmiah untuk meningkatkan keamanan penggunaan obat herbal dan mendukung praktik farmasi berbasis bukti di masyarakat.

Kata Kunci: ROM; Naranjo; Gorontalo

Abstract

Amid the growing trend of herbal medicine consumption in Indonesia, it is essential to understand the potential Adverse Drug Reactions (ADRs) that may arise across various communities. Gorontalo, a region rich in biodiversity, continues to widely utilize herbal medicines in daily practices. This study aimed to evaluate the profile of Adverse Drug Reactions (ADRs) among herbal medicine users in the Sipatana and Kota Utara sub-districts of Gorontalo City. A descriptive observational approach was employed, with data collected through direct interviews with 194 respondents, comprising 97 participants from each sub-district. Collected data included demographic characteristics, types of herbal medicines used, and clinical manifestations of ADRs. Quantitative analyses were conducted to determine the frequency,

ADR categories based on causality, and causal relationships according to the Naranjo ADR Probability Scale. The results indicated that most respondents were of productive age (31–50 years), predominantly female and housewives. Among the nine reported ADR cases, 22.3% were classified as possible, 44.4% as probable, and 33.3% as definite. The herbs most frequently associated with ADRs included garlic, moringa leaves, *Peperomia pellucida*, Kayu Bajakah, *Clinacanthus nutans*, and soursop leaves. The most common manifestations involved the gastrointestinal system, such as epigastric pain, colic, diarrhea, as well as certain metabolic and hypoglycemic effects. The study emphasizes the importance of individual factors, dosage, duration of use, and herbal combinations in determining ADR risk. These findings underscore the need for patient education on safe herbal use, appropriate clinical monitoring, and consultation with healthcare professionals before combining multiple herbs. Further research is recommended to examine interactions between herbs and conventional drugs and to develop community-based herbal pharmacovigilance systems. Consequently, this study provides a scientific basis to enhance the safety of herbal medicine use and support evidence-based pharmacy practice in the community.

Keywords: *ADR's, Naranjo, Gorontalo.*

BACKGROUND

Indonesia has a long history of utilizing natural or herbal medicines. Since ancient times, the people of the archipelago have been familiar with various plants and food ingredients believed to possess properties for maintaining health and treating illnesses. The use of natural resources, particularly plants, has become an integral part of traditional healing practices passed down from generation to generation. The tradition of using herbal remedies serves not only as a means of therapy but is also closely tied to cultural values, beliefs, and social practices. One of the most well-known examples is the use of jamu by the Javanese people, which continues to be an important part of Indonesia's traditional medicine system.

The phenomenon of herbal medicine use is not limited to Indonesia but is also a growing trend in many countries around the world. The concept of “back to nature”—returning to the use of natural ingredients believed to have fewer side effects than modern medicines—has driven an increase in herbal product consumption. The relatively high cost of modern medicines, limited access to healthcare services, and the ease of obtaining herbal ingredients locally further strengthen the preference for traditional remedies. According to Lee et al. (2018), approximately 80% of the world's population still relies on traditional medicines for primary healthcare needs, and nearly 25% of modern medicines are derived from natural sources. Data from the Secretariat of the Convention on Biological Diversity (CBD) reported that the global sales value of traditional medicines reaches 60 billion US dollars annually. In Indonesia, surveys indicate that 59.12% of the population consumes jamu, with 95.6% reporting health improvement benefits (Oktarlina et al., 2018).

Despite the increasing use of herbal medicines, concerns remain regarding their safety. Many people assume that herbal products are completely safe simply because they are plant-based. However, similar to modern medicines, improper use of herbal products can cause side effects or Adverse Drug Reactions (ADRs). ADRs are unwanted responses to a drug at doses used for disease prevention or treatment, potentially impacting patient quality of life and leading to morbidity and mortality (BPOM, 2019; Schatz and Weber, 2015). Research conducted at the Einstein Medical Center in Philadelphia revealed that the use of herbal medicines and dietary supplements can cause irreversible liver damage. In Indonesia, studies have reported that 19% of herbal medicine users experienced ADRs with a likelihood classified as possible, presenting symptoms such as dizziness, nausea, and abdominal pain (Kurniawati, 2021).

One of the main challenges in herbal medicine utilization is the limited availability of systematic safety data based on scientific research. Most efficacy claims are still based on empirical evidence, and many raw materials have not undergone standardization. Therefore, a structured safety monitoring system is essential, particularly through pharmacovigilance studies. Pharmacovigilance is the science and practice concerned with the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems (BPOM, 2020). This system plays an important role in identifying ADRs that may not have been detected during initial evaluation and clinical trials, recognizing risk factors, quantifying risks, and communicating safety information to healthcare professionals and the public.

One method widely used in pharmacovigilance studies is the Naranjo Algorithm—a questionnaire-based instrument consisting of 10 questions to assess the likelihood that a drug caused an ADR. Each answer is assigned a score, and the total score is used to classify ADRs into categories: definite, probable, possible, or doubtful

(Muthaharah, 2017). This algorithm has been officially adopted in Indonesia and serves as a valuable tool for ensuring the safe use of medicines, including herbal products.

Amid the growing trend of herbal medicine consumption in Indonesia, it is crucial to understand the potential ADRs that may occur within various communities. Gorontalo, as a region rich in biodiversity of medicinal plants, has communities that continue to rely heavily on herbal remedies in their daily lives. However, comparative studies on the safety of herbal medicine use across different urban areas in Gorontalo remain scarce. Sociocultural factors, access to health information, and consumption habits may all influence the risk of ADRs.

The present study, entitled “Herbal Medicine Safety: Comparative Evaluation of Adverse Drug Reactions in Two Subdistrict, Gorontalo City”, aims to conduct a comparative assessment of ADRs among herbal medicine users in two Subdistrict in Gorontalo City. Using the pharmacovigilance approach with the Naranjo Algorithm, this research seeks to identify the association between herbal medicine use and ADRs. The findings are expected to provide a clearer understanding of the safety profile of herbal medicines at the community level, serve as a basis for public health interventions to minimize ADR risks, raise awareness about safe herbal medicine practices, and inform evidence-based health policy development.

METHODS

This study employs a descriptive approach with a cross-sectional design. Primary data were collected directly from respondents through questionnaires prepared by the researcher. The research was conducted in Sipatana Subdistrict, and Kota Utara Subdistrict, Gorontalo City, Gorontalo Province, from January to June 2025.

The study population includes all residents aged 17 to 65 years who reside in Kelurahan Tanggikiki. The sampling technique used was purposive sampling, which involves selecting samples deliberately based on specific criteria relevant to the research objectives. The inclusion criteria were residents who had used herbal medicine within the last six months, were willing to participate as respondents, and domiciled in the study area. Exclusion criteria included herbal medicine users who did not complete the questionnaire and those unwilling to participate as respondents. Since the total population size is unknown, the sample size was determined using the Lemeshow formula. This formula considers a 95% confidence level with a Z-value of 1.96, an assumed herbal medicine user proportion of 0.5, and a precision level of 0.10. Based on these calculations, a sample size of 96.04 was obtained, rounded up to 97 respondents.

The variables studied include independent and dependent variables. The independent variables comprise respondents' characteristics such as age, gender, education, and occupation. The dependent variables consist of the profile of herbal medicine usage and the causality of adverse drug reactions (ADRs) assessed using the Naranjo algorithm.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software with two types of analysis. First, univariate analysis aimed to describe the frequency distribution and percentage of each variable, both independent and dependent. Second, bivariate analysis was conducted to examine the relationship between independent and dependent variables using the Chi-Square test. Results were considered statistically significant if the p-value was less than 0.05.

The bivariate analysis focused on three aspects: the relationship between respondents' characteristics and the profile of herbal medicine use, the relationship between respondents' characteristics and the causality of herbal medicine ADRs, and the relationship between the profile of herbal medicine use and the causality of ADRs according to the Naranjo method. With this research design and analysis, the study is expected to provide a comprehensive overview of the safety of herbal medicine use and the factors influencing the occurrence of adverse reactions among residents in two Subdistrict of Gorontalo City.

RESULT AND DISCUSSION

The findings of the study regarding Adverse Drug Reactions in the two sub-districts of Gorontalo City can be described as follows:

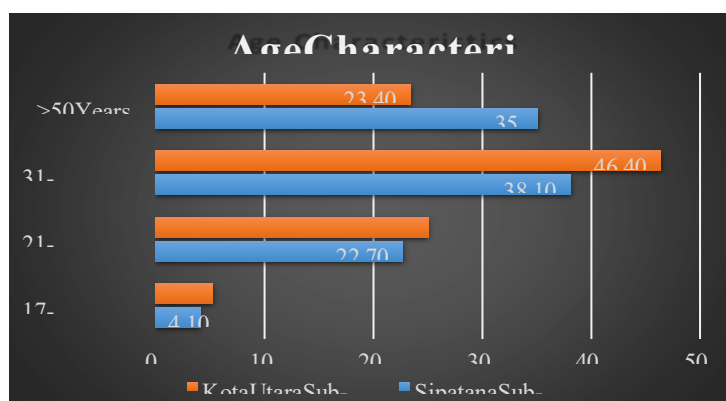
1. Respondent Characteristics

The respondents who reported the use of herbal medicines in this study consisted of 97 participants each from Sipatana Sub-district and Kota Utara Sub-district. The demographic characteristics of respondents from both sub-districts are presented in Table 1 below:

Table 1. Characteristics of Research Respondents

Characteristics	Amount			
	Sipatana Sub-district		Kota Utara Sub-district	
	Amount	Percentage	Amount	Percentage
1) Age				
17-20 Years Old	4	4,1%	5	5,2%
21-30 Years Old	22	22,7%	24	25 %
31-50 Years Old	37	38,1%	45	46,4%
>50 Years Old	34	35,1%	23	23,4%
Total	97	100%	97	100 %
2) Gender				
Women	64	66%	53	54,7%
Men	33	34%	44	45,3%
Total	97	100%	97	100 %
3) Occupation				
College student	4	4.1%	6	6,2%
Self-employed	13	13.4%	14	14,4%
Government Employees	11	11.3%	4	4,1%
Housewife	44	45.4%	42	43,3%
Farmers/Laborers/Drivers/Etc	25	25.8%	31	32%
Total	97	100%	97	100%

In terms of age distribution, the 31–50 year age group represented the majority in both sub districts, accounting for 38.1% in Sipatana and 46.4% in Kota Utara. This finding suggests that individuals in the productive age group tend to have the most extensive experience in using herbal medicines. Furthermore, the proportion of respondents aged above 50 years was also relatively high, comprising 35.1% in Sipatana and 23.4% in Kota Utara, indicating that older adults likewise represent a significant group of herbal medicine users

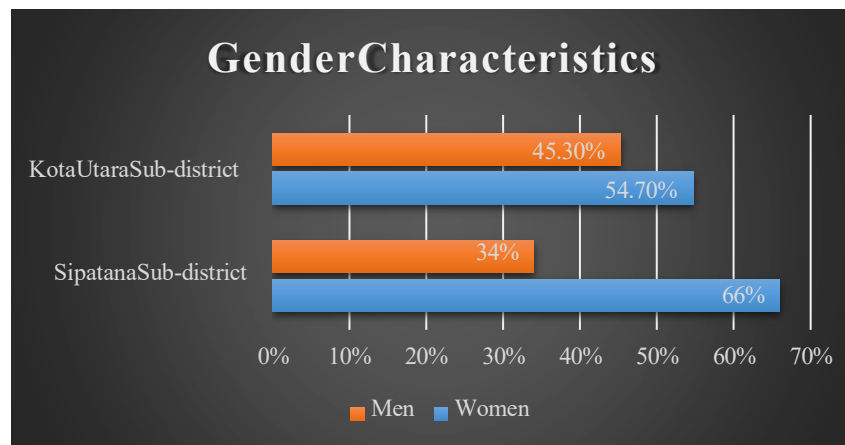
**Figure 1.** Age Characteristics of Research Respondents

The findings of this study indicate that the 31–50 year age group constitutes the majority of herbal medicine users in both sub-districts, followed by those aged above 50 years. This result is consistent with the study conducted by Rikomah (2020), which reported that respondents over the age of 30 demonstrated the highest level of knowledge regarding herbal medicines, with a proportion of 30.05%. This trend may be explained by the fact that as individuals grow older, the quality of their knowledge tends to increase, supported by both formal education and accumulated life experience.

Furthermore, Fonda et al. (2014) stated that adulthood is a period during which individuals are more responsive to information obtained from various sources. In addition, Sitepu et al. (2024) emphasized that within the age range of 25–35 years, individuals tend to be more socially active, frequently engage in reading activities, and possess stable intellectual abilities, problem-solving skills, and verbal capacities. These observations suggest that individuals in the productive age group have a greater capacity to process health-related information, including knowledge about the use of herbal medicines.

In addition, a study by Andriati and Wahjudi (2016) demonstrated that Indonesian society continues to maintain a strong cultural attachment to the use of jamu, resulting in the widespread use of traditional medicines across different age groups. This is particularly relevant in Gorontalo Province, where the community still upholds longstanding cultural traditions. Similarly, Stevani et al. (2020) reported that elderly populations remain active users of traditional medicines.

With regard to gender, female respondents dominated in both sub-districts, accounting for 66% in Sipatana and 54.7% in Kota Utara. This tendency may be associated with the role of women as primary caretakers of family health, who often seek alternative forms of treatment, including the use of herbal medicines.



These findings are consistent with the study by Indrayani and Shakila (2025), which reported that out of 88 respondents, 55.7% were women. Female respondents were more likely than men to utilize medicinal plants for self-medication, reflecting their greater concern for health. This result is further supported by Ernawati et al. (2020), who noted that women tend to be more health-conscious and therefore demonstrate a stronger willingness to seek knowledge compared to men. Moreover, women who are married are often regarded as the guardians of family health, which encourages them to continuously pursue safe and beneficial knowledge to maintain the well-being of their family members.

In terms of occupation, housewives constituted the largest group in both sub-districts, accounting for 45.4% in Sipatana and 43.3% in Kota Utara. This finding reinforces the data on the predominance of female respondents and their central role in managing family health. The result is consistent with the study by Akarsu et al. (2020), which stated that women tend to exhibit higher levels of concern and vigilance compared to men. Such characteristics enable women to be more cautious in considering and making health-related decisions, particularly with regard to the use of traditional medicines for their families.

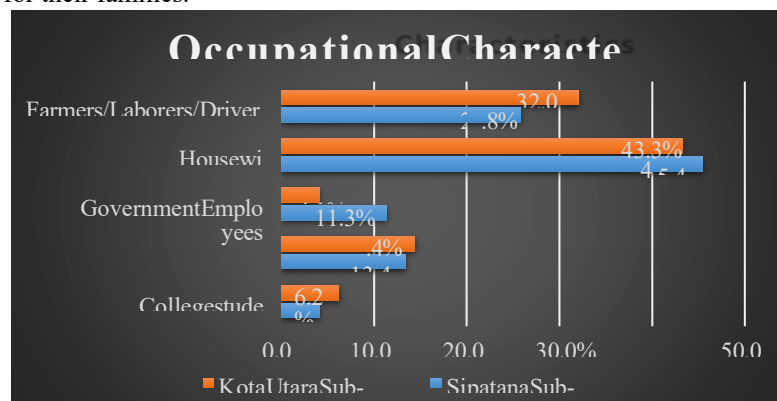


Figure 3. Occupational Characteristics of Research Respondents

The study conducted by Supardi and Susyanty (2010) emphasized that being a housewife is strongly correlated with the use of traditional medicines. According to their research, different types of occupations may influence an individual's knowledge and attitudes; however, knowledge can also be acquired through daily life experiences, which is highly relevant to the activities of housewives.

The findings of this study are also consistent with those of Medisa et al. (2020), who reported that housewives (41.7%) dominated as users and demonstrated knowledge of herbal medicines. Furthermore, research by Oktarlina et al. (2018) supports this argument, revealing that 69.1% of their respondents were women. Their study also explained that female respondents exhibited a higher level of willingness and positive response to being research subjects, which indicates their openness to information, including knowledge related to traditional medicines.

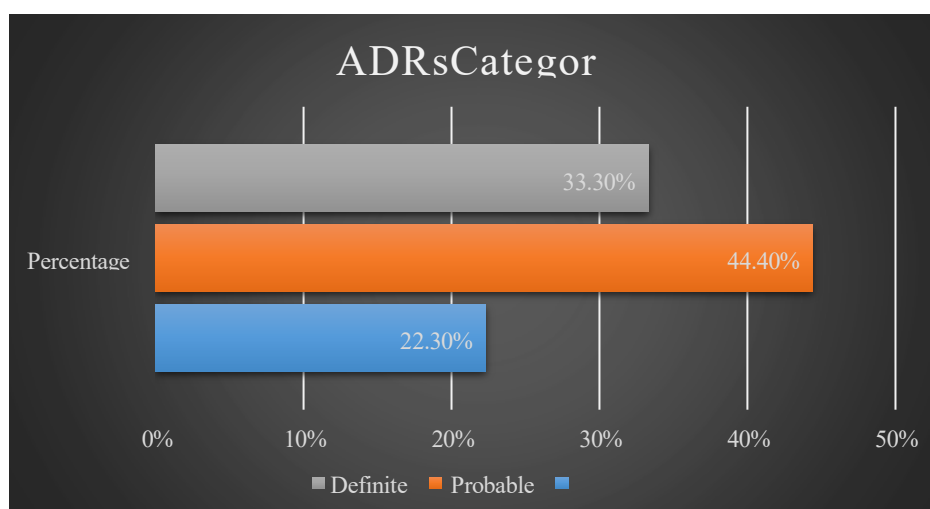
2. Profile of Adverse Drug Reactions Among Herbal Medicine Users in Sipatana and Kota Utara Sub-districts, Gorontalo City

This study involved the collection of data on Adverse Drug Reactions (ADRs) among herbal medicine users in two sub-districts of Gorontalo City, namely Sipatana and Kota Utara. Based on the data obtained, a total of nine (9) ADR reports met the inclusion criteria, comprising four (4) reports from Sipatana and five (5) reports from Kota Utara.

Table 2. . Incidence of Adverse Drug Reactions (ADRs) Associated with Herbal Medicines in Sipatana and Kota Utara Sub-districts

Subject	Therapy	Incidents of Adverse Drug Reactions (ADRs) of Herbal Medicines			Types of herbal medicines
		Manifestasion	Score	Category*	
Sipatana Sub-district					
S22	Weight Gain	Diarrhea	4	Possible	Healthy Weight Gain Herbal Medicine
S84	Joint Pain	Dizziness & Hypoglycemia	8	Probable	Amuralin
S92	Hypertension	Heartburn Pain	9	Definite	Bajaka Wood
S96	Kidney stones	Heartburn Pain	9	Definite	Kejibeling Leaves
Kota Utara Sub-district					
S1	Hypertension	Throat Dryness	4	Possible	Garlic
S5	Diarrhea	Abdominal cramping	8	Probable	Cinnamon & Lemon Water
S9	Hypercholesterolemia	Abdominal cramping	7	Probable	Garlic&AppleCider Vinegar
S59	Diabetes Mellitus	Heartburn Pain	9	Definite	Moringa Leaves, Chinese BetelLeaf
S60	Diabetes Mellitus	Kidney stones	8	Probable	Moringa leaves, Chinese betelleaves, soursop leaves

The distribution of ADR categories showed that most reports were classified as probable, with four cases (44.4%), followed by definite with three cases (33.3%), and possible with two cases (22.3%). The herbal products most frequently recorded in the ADR reports included garlic (*Allium sativum*), moringa leaves (*Moringa oleifera*), and *Peperomia pellucida* (two reports each), as well as several other medicinal plants, herbal preparations, and traditional jamu products.



The reported clinical manifestations primarily involved gastrointestinal symptoms, including epigastric pain (3 reports) and abdominal cramping (2 reports). Other manifestations identified included diarrhea, dizziness, hypoglycemia, dry throat, and a case of nephrolithiasis, which warrants particular attention for further evaluation.

Based on Table 2, the first case in Sipatana Sub-district involved diarrhea occurring after patient S22 consumed Jamu Gemuk Sehat as a therapy for weight gain. This reaction was categorized as a possible ADR. Although there was a clear temporal relationship between the consumption of the herbal preparation and the onset of diarrhea, other potential causes such as dietary factors or gastrointestinal infection could not be entirely ruled out. This type of jamu typically contains ingredients such as *Curcuma xanthorrhiza* (temulawak), turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), aromatic ginger (*Kaempferia galanga*), papaya leaves (*Carica papaya*), and nutgrass (*Cyperus rotundus*), which are known to stimulate digestion and enhance intestinal motility. These effects may be intensified when consumed in large doses or on an empty stomach, thereby increasing the risk of diarrhea. Several traditional formulations have indeed been reported to accelerate gastrointestinal transit or alter gut microbiota composition, ultimately leading to increased bowel frequency (Cziple et al., 2022).

Given its classification as possible, a dechallenge approach—discontinuing the consumption of the herbal preparation—may help establish a clearer causal relationship. If symptoms improve within a few days, this would strongly suggest that the jamu contributed to the onset of diarrhea. Nevertheless, additional assessments, such as dietary evaluation, stool examination to exclude infection, and review of other medications or supplements, remain necessary to eliminate alternative explanations. This approach is consistent with the WHO-UMC causality assessment method, in which clinical and laboratory evidence may strengthen the ADR classification from possible to probable (WHO-UMC, 2013; Cziple et al., 2022).

The second case, involving subject S84 in Sipatana Sub-district, presented with dizziness and hypoglycemia following the consumption of Amuralin for joint pain. These symptoms were most likely attributable to contamination or adulteration of the product with undeclared pharmaceutical substances, such as sulfonylureas (e.g., glibenclamide/glyburide), which can lower blood glucose levels, or other agents that reduce blood pressure, thereby causing hypoglycemia and/or hypotension leading to dizziness (HSA Singapore, 2018; Hayes et al., 2022). The ADR classification as probable remains appropriate when there is a clear temporal relationship between product intake and symptom onset, as well as improvement upon discontinuation (dechallenge). However, laboratory verification of the product sample (e.g., sulfonylurea screening using LC-MS/MS) and documentation of blood glucose levels during the episode are required to confirm causality, in addition to excluding alternative explanations such as concomitant prescription drugs, alcohol consumption, or predisposing medical conditions for hypoglycemia (Kuramoto et al., 2015).

The third case involved subject S92, who developed epigastric pain after consuming kayu bajakah (*Spatholobus littoralis*) as a therapy for hypertension. This reaction was classified as a definite ADR, indicating a strong causal relationship between the herbal intake and the onset of symptoms. Kayu bajakah contains a variety of phytochemical compounds, including flavonoids, tannins, saponins, alkaloids, polyphenols, and steroids, which may provide therapeutic benefits but also carry the potential for adverse effects (Mahfudh et al., 2024).

The symptom of epigastric pain was primarily associated with the tannin content of kayu bajakah. Tannins, particularly when consumed in high doses or over prolonged periods, may cause gastric mucosal irritation through several mechanisms: (1) increasing epithelial permeability and triggering a localized inflammatory response (Gu et al., 2023); (2) interacting with mucosal proteins, thereby disrupting the protective gastric barrier (Chung et al., 2010); and (3) influencing gastric acid secretion, which in certain individuals may exacerbate dyspeptic symptoms (Kitay et al., 2019). The risk is further heightened when the herbal preparation is ingested on an empty stomach.

In patients with hypertension, the use of antihypertensive agents such as diuretics or calcium channel blockers may further increase susceptibility to gastric irritation (Bavishi and Dupont, 2011). This is relevant because such combinations have the potential to modify gastrointestinal responses, although specific evidence regarding interactions with kayu bajakah remains limited.

This case highlights the importance of patient education regarding dosage, mode of consumption, and potential adverse effects of kayu bajakah, particularly among individuals with chronic conditions such as hypertension. The classification of causality as definite should be supported by documentation of a dechallenge (symptom improvement following discontinuation of the herbal remedy) and a rechallenge (symptom recurrence upon re-exposure), as well as additional diagnostic evaluations when necessary.

The final case in Sipatana Sub-district was a definite ADR, presenting as epigastric pain following the consumption of keji beling (*Clinacanthus nutans*) for kidney stone therapy. This classification indicates a strong causal relationship between the herbal product and the gastrointestinal complaint. Keji beling is known to contain flavonoids,

phenolics, tannins, saponins, steroids, and alkaloids, which may provide therapeutic benefits but also pose potential adverse effects on the gastrointestinal tract (Sabindo et al., 2024; Chia et al., 2021).

The most plausible mechanisms underlying the epigastric pain associated with keji beling involve several interrelated pathways. First, tannins may bind to gastric mucosal proteins, thereby disrupting the protective barrier, increasing epithelial permeability, and triggering localized inflammation in the epigastrium (Chung et al., 1998; Gu et al., 2023). Second, saponins and certain phenolic compounds may influence gastric acid secretion, which in susceptible individuals can exacerbate dyspeptic symptoms. Third, alterations in the gut microbiota and the formation of pro-inflammatory metabolites may further potentiate gastrointestinal irritation (Chung et al., 1998; Chia et al., 2021). The risk of epigastric pain is heightened when keji beling is consumed in concentrated preparations, over prolonged periods, or on an empty stomach.

Patient-related factors also play a critical role, as the use of diuretics or adjuvant therapies for nephrolithiasis may alter gastric motility and render the mucosa more susceptible to irritation. Moreover, the timing of ingestion (e.g., before meals) and duration of use (chronic consumption) may further increase the likelihood of persistent irritation and symptomatic manifestations. Given that this case is classified as a definite ADR, establishing causality requires documentation of dechallenge (symptom improvement following discontinuation of the herbal product), while supportive diagnostic evaluations such as endoscopy would strengthen the causal association between *C. nutans* and epigastric pain. From a clinical perspective, patients should be advised to temporarily discontinue the herbal remedy, record the dosage and formulation used, monitor organ function, and consider referral if symptoms persist. The first case in Kota Utara District involved a complaint of dry throat following the consumption of garlic for blood pressure reduction in subject S1. This event was categorized as a possible ADR, as there was a clear temporal association between exposure and symptom onset; however, alternative causes such as dehydration, concomitant medication use, or upper respiratory tract infection could not be completely excluded. Garlic contains volatile organosulfur compounds, such as allicin and diallyl disulfide, which are easily vaporized and may irritate the oral and pharyngeal mucosa either through direct contact or after systemic absorption. Reported adverse effects include burning sensation, irritation, and even mucosal ulceration, particularly when consumed in concentrated or raw form (Tesfaye, 2021; Muniz et al., 2021).

Dry throat may also arise through indirect mechanisms, including acid reflux that produces a sensation of dryness or burning in the pharynx; allergic reactions or hypersensitivity to *Allium* components that trigger inflammatory responses; and alterations in the oral microbiota following exposure to volatile sulfur compounds (Walaa et al., 2024; Verma et al., 2024).

To ascertain the underlying cause, it is recommended to temporarily discontinue garlic consumption (dechallenge) and monitor for symptom improvement, while documenting the formulation and pattern of use and excluding other potential contributing factors. Should the symptoms persist, allergy testing or referral to a specialist may assist in further substantiating or refuting the causal association.

The second reported case involved a patient who developed severe abdominal colic following the ingestion of a mixture of cinnamon powder (*Cinnamomum* spp.) and citrus juice (Subject S5). Symptoms appeared within 2–4 hours after consumption and markedly improved within 24–36 hours upon discontinuation, with only oral rehydration therapy provided as supportive care. The clear temporal relationship and resolution after dechallenge support the classification of this event as a probable adverse drug reaction (ADR) according to the WHO-UMC and Naranjo criteria (WHO UMC, 2013; Naranjo et al., 1981).

Pharmacologically, cinnamon contains cinnamaldehyde, an agonist of the TRPA1 channel expressed in the enteric nervous system and intestinal epithelium. TRPA1 activation may enhance intestinal motility, secretion, and visceral pain sensitivity, which, in susceptible individuals or at high doses, can lead to hypermotility, cramping, and diarrhea (Hajimonfarednejad et al., 2019; Tekulapally et al., 2024; Manneck et al., 2021). Safety reviews have likewise documented gastrointestinal complaints—including nausea, abdominal pain, and diarrhea—associated with short- to medium term use at higher doses (Hajimonfarednejad et al., 2019).

Orange juice contains fructose and has high osmolality. In individuals with limited fructose absorption capacity, ingestion of orange juice may induce osmotic diarrhea and gas production via colonic fermentation, leading to distension and cramping (Heyman et al., 2017; DiNicolantonio et al., 2015). The American Academy of Pediatrics guidelines do not recommend fruit juices for acute diarrhea, as they may exacerbate stool frequency and volume. Controlled clinical trials have demonstrated greater fecal losses in groups receiving juice compared with water (Heyman et al., 2017; Valois et al., 2005).

This, the combined pro-motility and secretory effects of cinnamaldehyde and the osmotic impact of fructose in orange juice likely explain the rapid onset of colic and diarrhea in this case. The absence of stronger alternative causes, the consistent temporal relationship, and symptom resolution upon discontinuation support the classification

of causality as probable (WHO-UMC, 2013; Naranjo, 1981). Documentation of such cases is crucial for pharmacovigilance of natural products and functional foods.

The third case involved a patient (S9) who experienced colicky abdominal pain after consuming a mixture of garlic (*Allium sativum*) and apple cider vinegar (ACV) for cholesterol reduction. Symptoms appeared several hours after ingestion and resolved within 48 hours following discontinuation. This temporal pattern aligns with the Naranjo ADR Probability Scale criteria, classifying the reaction as probable (Naranjo et al., 1981). Garlic contains organosulfur compounds such as allicin and ajoene, which are beneficial for lowering cholesterol and triglyceride levels (NCCIH, 2025). However, these compounds can also irritate the gastrointestinal tract, leading to abdominal pain, nausea, bloating, or diarrhea (McWhorter, 2025; Higdon, 2005). This irritant effect likely contributed to the colicky abdominal pain experienced by the patient.

Apple cider vinegar (ACV) contains acetic acid, which increases gastric acidity and delays gastric emptying. This can result in sensations of fullness, nausea, bloating, or cramping (Hlebowicz et al., 2007). High-dose ACV consumption has also been associated with esophageal irritation (Hill et al., 2005) and hypokalemia, which may trigger muscle cramps or weakness (Lhotta et al., 1998).

Regarding their therapeutic effects, clinical trials have shown that garlic can moderately reduce total cholesterol and LDL levels. Apple cider vinegar has also been reported to lower total cholesterol and triglycerides, although its effects on LDL and HDL are inconsistent (Du et al., 2024). Consequently, the combination of mucosal irritation from garlic and delayed gastric emptying induced by ACV likely precipitated colicky abdominal pain in the patient. Recommended management includes temporary discontinuation of both substances, symptomatic treatment for abdominal pain, and improvement of the patient's dietary habits.

The fourth case in Kota Utara District involved a patient (S59) with diabetes mellitus who experienced epigastric pain each time they consumed a combination of moringa leaves (*Moringa oleifera*) and sirih cina (*Peperomia pellucida*) as a traditional therapy. Symptoms occurred consistently with ingestion, resolved upon discontinuation, and recurred upon re-exposure. According to the Naranjo ADR Probability Scale, this reaction is classified as definite, as the causal relationship is clearly established (Naranjo et al., 1981).

Moringa leaves contain flavonoids, saponins, alkaloids, and glycosides, which can lower blood glucose by enhancing pancreatic insulin secretion and sensitivity (Kasolo et al., 2010). However, studies have reported that high-dose consumption of moringa leaves may irritate the stomach, causing nausea, dyspepsia, and epigastric pain due to increased gastric acid secretion (Stohs and Hartman, 2015).

Peperomia pellucida also contains flavonoids, alkaloids, tannins, and polyphenols, which have hypoglycemic and anti-inflammatory properties (Khan and Omoloso, 2002; Olajide et al., 2000). However, tannins and polyphenols can irritate the stomach, particularly in individuals with sensitive gastric mucosa (Hidayati, 2021). Concurrent consumption of both plants may potentiate their irritant effects, resulting in epigastric pain. The presence of positive dechallenge and rechallenge further strengthens the causal relationship (Naranjo et al., 1981). Recommended management includes discontinuation of the herbal preparations, administration of gastric analgesics, and reassessment of diabetes management using evidence-based therapies. If the patient wishes to continue traditional therapy, close monitoring and regular consultation with healthcare professionals are strongly advised.

The final case involved a patient with diabetes mellitus (S60) who experienced severe flank pain and was subsequently diagnosed with kidney stones. The patient had a habitual intake of herbal preparations including moringa leaves (*Moringa oleifera*), sirih cina (*Peperomia pellucida*), and soursop leaves (*Annona muricata*) for glycemic control. According to the Naranjo ADR Probability Scale, this case is classified as a probable ADR, as there was a clear temporal relationship between herbal consumption and symptom onset, with improvement observed upon discontinuation (positive dechallenge) (Naranjo et al., 1981).

Moringa leaves are known to lower blood glucose through flavonoids, alkaloids, and saponins (Kasolo et al., 2010). However, their calcium and oxalate content may promote the formation of calcium oxalate crystals, a primary cause of kidney stones (Stohs and Hartman, 2015). *Peperomia pellucida* exhibits antihyperglycemic and anti-inflammatory effects (Khan and Omoloso, 2002), but it also contains oxalates that can increase the risk of nephrolithiasis, particularly in cases of low fluid intake (Hidayati, 2021). Soursop leaves (*Annona muricata*) exert antidiabetic effects by enhancing insulin sensitivity and reducing oxidative stress (Moghadamtousi et al., 2015); however, long-term consumption may impair renal function and elevate uric acid levels, further increasing the risk of kidney stone formation (Gavamukulya, 2014).

This case illustrates that although herbal preparations are often perceived as safe and beneficial, excessive consumption or the combination of multiple plants may produce undesirable effects. The patient's kidney stones were likely influenced by the oxalate content of moringa and *Peperomia pellucida*, as well as the potential nephrotoxicity of

soursop leaves. Therefore, it is essential for patients with diabetes to use herbal therapies cautiously, maintain adequate fluid intake, and consult healthcare professionals before combining various herbal products.

CONCLUSION

This study demonstrates that the use of herbal medicines in the Sipatana and Kota Utara sub districts of Gorontalo City can result in Adverse Drug Reactions (ADRs) classified as possible (22.3%), probable (44.4%), and definite (33.3%). Risk factors include being of productive age, female gender, and employment as a housewife, reflecting their role in family health management. The most frequently implicated herbs were garlic, moringa leaves, *Peperomia pellucida*, Kayu Bajakah, *Clinacanthus nutans*, and soursop leaves, with gastrointestinal and metabolic manifestations. These findings highlight the importance of patient education, appropriate dosing, clinical monitoring, and consultation with healthcare professionals before combining multiple herbal products.

RECOMMENDATIONS

Based on the findings of this study, it is recommended to conduct broader follow-up research on the safety and Adverse Drug Reaction (ADR) profiles of herbal medicine users across various regions. Future studies should include quantitative analyses of dosage, duration of use, and interactions between different herbs as well as with conventional drugs. The development of community-based herbal pharmacovigilance systems is also encouraged to enhance ADR reporting. Continuous education for the public and healthcare professionals on safe herbal use, identification of patient-specific risk factors, and experimental research on the biological mechanisms of herbal side effects will strengthen scientific evidence and promote safe usage.

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