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Letter

Embracing Artificial Intelligence in Malaysian Pharmacy Practice: Current Landscape and Future Directions

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Artificial intelligence (AI) is gaining global attention for its potential to transform various aspects of care, including healthcare. In pharmacy, AI is establishing a foothold in clinical decision-making and medication management, and it also holds promise in pharmacovigilance, medication safety, research and development, regulatory processes, and professional education. As countries worldwide advance in these areas, Malaysia's path toward AI integration in pharmacy deserves closer examination to explore its opportunities and challenges. While the use of AI in pharmacy practice is still in an evolving stage in Malaysia, this article outlines the global application of AI in pharmaceutical care and the potential for Malaysia to adapt these advancements to enhance health screening, identify at-risk populations, optimize healthcare resource allocation, and improve access to healthcare services.

Current Applications of AI in Pharmaceutical Care

AI has been employed internationally to streamline pharmacy operations and improve patient outcomes. A recent scoping review identified three primary applications: (1) identification of atypical or inappropriate medication orders, (2) enhancement of mass screening services, and (3) improvement of medication adherence through the integration of AI in mobile applications. These applications leverage machine learning to analyze big data, supporting pharmacists in making more informed clinical decisions [1].

MedAware, for example, uses probabilistic machine learning to detect medication errors by flagging statistically outlier prescriptions, while deep learning models assist pharmacists in identifying blister-pack medications to prevent dispensing errors [2]. Conversational AI systems have also improved medication adherence, as seen in SMS-based refill reminders for Medicare patients [2].

These AI-supported interventions resonate with Geoffrey Rose's theory of preventive medicine, where both high-risk individual strategies and population-wide measures, such as AI-powered mass screening and medication adherence programs, are necessary to effectively reduce the burden of medication-related morbidity and mortality [3]. Embedding AI integration efforts within a Health in All Policies (HiAP) governance framework could further align with broader national and regional health priorities and cross-sectoral equity considerations.

In addition to supporting clinical pharmacy services, AI is increasingly transforming upstream pharmaceutical processes, including drug discovery and molecular design. Deep learning algorithms, such as generative adversarial networks (GANs) and reinforcement learning models, are now used to generate novel molecular structures with optimized pharmacokinetic profiles. For example, AlphaFold has revolutionized protein structure prediction, allowing researchers to simulate receptor conformations with higher accuracy [4]. Similarly, platforms like DeepDock and AtomNet use deep learning for ligand–protein docking simulations, enabling rapid virtual screening of large compound libraries [5]. These technologies could reduce development timelines and increase the success rate of identifying viable drug candidates, making AI an invaluable

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tool in pharmaceutical research and development (R&D).

Meanwhile, emerging innovations such as AI-guided nanorobotics present a transformative opportunity for pharmacy practice. Researchers are developing nano-scale robots capable of targeted drug delivery, where AI algorithms are used to calculate optimal dosing, control navigation through biological environments, and regulate the timing of drug release. These systems have shown promise in preclinical models for conditions such as cancer and cardiovascular disease, offering potential improvements in therapeutic precision and minimization of off-target effects [6]. Although still in the early stages of development, these technologies highlight the future trajectory of AI-integrated precision pharmacotherapy.

Challenges

In Southeast Asia, including Malaysia, the adoption of AI in pharmacy is still in its early stages. Factors such as limited infrastructure, lack of standardized electronic health records and varying levels of digital literacy among healthcare professionals are key reasons contributing to the slow uptake. Data privacy concerns, especially regarding patient information, are paramount. Therefore, it is essential to maintain public trust by ensuring compliance with regulations like the Personal Data Protection Act 2010. Additionally, the cost of implementing AI technologies can be prohibitive for smaller community pharmacies, potentially widening the gap between urban and rural healthcare services.

Another significant barrier is the lack of AI-related education and training among pharmacy professionals. A study surveying international pharmacy students revealed that while there was a positive attitude towards AI, many felt inadequately prepared to utilize such technologies in their future careers [7]. This highlights the need for curriculum reforms to incorporate AI competencies, to ensure future pharmacists are equipped with up-to-date AI skills.

Opportunities

Nevertheless, Malaysia stands at a strategic position to leverage AI in pharmacy practice, supported by its robust healthcare infrastructure and a growing pool of tech-savvy professionals. Collaborations between academic institutions, healthcare providers, pharmaceutical companies, and tech firms are fostering the development of AI tools tailored to local needs. Some pharmaceutical companies are developing advanced AI platforms, such as those used for cancer screening, which could pave the way for impactful public-private partnerships. In addition, AI-driven solutions can help address non-communicable diseases prevalent in Malaysia, such as diabetes and cardiovascular conditions, through personalized medication counselling, adherence checkers with reminders, and continuous patient monitoring.

Moreover, AI-driven predictive analytics has the potential to reshape population health by identifying individuals at risk of chronic disease or readmission, enabling earlier and more targeted clinical interventions. These predictive tools align with population health management approaches by stratifying populations based on risk profiles, allowing health systems to prioritize patient outreach, tailor treatment strategies, and allocate resources more efficiently [8].

While AI offers diverse opportunities, it is crucial to consider Malaysia's unique healthcare landscape. Rural and underserved regions continue to face disparities in access to pharmaceutical services due to workforce shortages and infrastructure gaps. In this context, AI can serve as a powerful enabler of equitable care. For example, AI-powered telepharmacy platforms could facilitate remote medication reviews and pharmaceutical consultations, while chatbot-based tools may help improve health literacy and medication adherence. Additionally, predictive analytics could assist the Ministry of Health in anticipating medicine demand trends and optimising national supply chain distribution systems. These applications align with national digital transformation efforts outlined in the Malaysia Digital Economy Blueprint (MyDIGITAL), which envisions an inclusive, digitally empowered healthcare ecosystem. By integrating pharmacy-specific AI innovations into this broader agenda, Malaysia can bridge the urban–rural divide and modernise pharmaceutical care delivery in both public and private sectors [9].

Future Directions

To fully realize the benefits of AI in pharmacy practice, a comprehensive and multi-faceted approach is required (Figure I). First, there must be deliberate efforts in policy development. While AI continues to advance rapidly, it is worth noting that currently, there is no comprehensive, up-to-date legislation in place to regulate its use in healthcare. Establishing clear guidelines and regulatory frameworks to govern the use of AI in healthcare is essential. These frameworks should prioritize ethical considerations, data privacy, accountability, and patient

Figure I: Future directions for AI in Pharmacy Practice in Malaysia.

safety, ensuring that AI tools are implemented responsibly and

in ways that enhance the standard of care. Transparent policies empower practitioners and institutions to adopt AI-driven solutions with greater confidence by reducing legal ambiguity.

Equally important is the integration of AI-related education and training into pharmacy curricula. Future pharmacists must be equipped not only with clinical and pharmacological knowledge but also with digital literacy and a foundational understanding of AI technologies. Pharmacy programs should embed modules that teach students about the applications, limitations, and ethical use of AI. Additionally, continuous professional development (CPD) initiatives should be introduced to upskill current practitioners, enabling the existing workforce to adapt to technological advancements and engage with AI systems responsibly in daily practice.

Research and development efforts must also be actively encouraged to explore the efficacy, safety, and outcomes associated with AI applications in pharmacy. To ensure AI innovations are evidence-based and practically beneficial to both patients and practitioners, efforts should focus on supporting pilot projects, clinical trials, and interdisciplinary collaborations among pharmacists, data scientists, and healthcare providers. Future evaluations could adopt established public health implementation frameworks, such as RE-AIM, to assess AI interventions, ensuring they achieve meaningful patient outcomes.

Implementing AI in pharmacy practice often involves significant upfront investments in infrastructure, training, and system integration, making cost-effectiveness analysis essential. These evaluations would benefit from established Health Technology Assessment (HTA) principles to ensure the cost-effectiveness of AI-driven pharmacy solutions in resource-constrained environments. AI itself can support these evaluations by automating data extraction from electronic pharmacy records, stratifying patients by clinical risk, and running predictive models to estimate cost and outcome impacts.

Conclusion

The integration of AI into Malaysian pharmacy practice offers transformative potential for individual patient care and broader public health outcomes. By improving medication safety, expanding access to rural communities, and strengthening pharmacovigilance, AI can play a pivotal role in supporting Malaysia's national healthcare goals. However, equitable implementation, robust data governance, and interdisciplinary collaboration among policymakers, pharmacists, and public health experts are essential to maximize the benefits of implementing AI in pharmacy practice. Strategic investments in AI today can pave the way for a more efficient, equitable, and resilient pharmaceutical care system in Malaysia.

CONFLICT OF INTEREST

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Letter

Pharmacist Advocacy in Pre-Exposure Prophylaxis (PrEP) Implementation amidst Religious Debate in Malaysia

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The advent of Pre-Exposure Prophylaxis (PrEP) marks a pivotal moment in the global fight against HIV. Offering up to 99% efficacy in preventing sexual transmission with consistent use, PrEP, typically a daily oral dose of tenofovir/emtricitabine, empowers HIV-negative individuals at substantial risk to protect themselves [1]. Malaysia, recognizing this potential, has initiated PrEP pilot programs and integrated it into national health guidelines, aiming to curb new infections, particularly among key populations [2,3]. However, the rollout of this biomedical intervention occurs within a unique socio-religious landscape where Islamic perspectives profoundly shape health behaviours and policy acceptance. For pharmacists on the front lines of dispensing medication and counselling patients, understanding these perspectives is not just relevant but essential.

The intersection of PrEP with Islamic jurisprudence has sparked considerable debate, leading to divergent formal religious opinions even within Malaysia. This divergence stems from the application of established Islamic legal principles to this novel preventative technology. Central to Islamic bioethics is the concept of the core objectives of Islamic law (maqasid al-Shariah), particularly the preservation of life (hifz al-nafs) [4]. This principle strongly supports medical interventions that prevent disease and save lives. Furthermore, principles like public interest (maslahah) justify actions benefiting the community's well-being, such as controlling infectious diseases. Islam generally encourages seeking treatment and prevention, viewing health as a blessing to be protected [4].

However, PrEP often involves contexts related to behaviours Islam prohibits, such as extramarital or homosexual relations. This triggers the application of counter-principles like blocking the means to perceived wrongdoing (sadd al-dhara'i), where permissible actions might be forbidden if likely to lead to a prohibited outcome. The core tension arises in weighing these principles: does the imperative to save lives and prevent public health harm (reflecting public interest) outweigh the concern that PrEP might inadvertently facilitate or condone prohibited acts (reflecting the principle of blocking the means)? This jurisprudential tension manifested clearly in 2023, with differing religious rulings issued by Malaysian state authorities (Table I). The Perlis State Fatwa Committee declared PrEP permissible (harus) for administration by health practitioners, including accessibility for the LGBT community [1,2]. Their reasoning prioritized harm reduction, concluding through a comparative analysis (or weighing process, muwazanah) that the harm (mafsadah) of unchecked HIV transmission was greater than the potential harm of PrEP misuse encouraging illicit acts. This ruling invoked the principle of choosing the lesser of two evils (irtikab akhaff al-dararain) [1].

Conversely, state religious authorities in Kedah, Selangor, and Sabah, along with the Penang Mufti, expressed prohibitive or restrictive views, particularly concerning PrEP provision to LGBT individuals [1,5]. These rulings prioritized the principle of blocking the means, fearing PrEP would act as a pathway (dhari'ah) to encourage prohibited sexual behaviours. They argued that providing PrEP to these groups could be interpreted as condoning actions contrary to the fundamental objectives of Islamic law, defining the primary harm to be avoided as moral transgression rather than physical disease [1]. Some, like the Penang Mufti, suggested limiting PrEP only to contexts deemed licit, such as within a marriage where one partner is HIV-positive [5].

This divergence presents significant challenges for pharmacists and the healthcare system. Pharmacists may face ethical dilemmas when dispensing PrEP, caught between national health guidelines promoting access based on risk [3] and potentially restrictive state-level religious interpretations. Patients seeking PrEP might encounter stigma or refusal, leading to unequal access depending on their location or the provider's interpretation. This situation underscores the need for clarity and support for healthcare professionals navigating

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Table I: Summary of Recent Malaysian State Fatwa Opinions on PrEP [1]

Component	Admission value	Discharge value	Reference range
Perlis State Fatwa Committee	Permissible (Harus) for administration, including accessibility for LGBT.	Preventing greater harm (HIV spread) outweighs potential lesser harm (encouraging illicit activity)	Forbidden for users to promote homosexuality/free sex. Applicable to high-risk groups including LGBT.
Kedah State Fatwa Department	Prohibited provision to LGBT individuals.	Apprehension about exacerbating adultery/homosexual acts. Prioritizes avoiding moral harm over reducing HIV transmission.	Prohibition specifically targets the LGBT community.
Selangor State Fatwa Department	Advised against dispensing PrEP to homosexuals (interpreted as prohibition).	Facilitating PrEP for LGBT is seen as condoning behaviour contrary to *Maqasid al-Shariah*.	Advisory/prohibition specifically targets homosexuals/LGBT individuals.
Sabah State Mufti	Against providing PrEP to the LGBT community (inferred).	Echoes Selangor: Facilitating PrEP for LGBT might condone behaviour antithetical to *Maqasid al-Shariah*.	Implied prohibition targets the LGBT community.
Penang State Mufti	Advised against dispensing PrEP to homosexuals. Agrees with Selangor.	Providing PrEP to LGBT encourages 'deviant' behaviour.	Limited to specific licit contexts (e.g., HIV-negative wife of HIV+ husband); excludes homosexuals.
Perlis State Fatwa Committee	Permissible (Harus) for administration, including accessibility for LGBT.	Preventing greater harm (HIV spread) outweighs potential lesser harm (encouraging illicit activity)	Forbidden for users to promote homosexuality/free sex. Applicable to high-risk groups including LGBT.

these sensitive interactions. Pharmacists require the competency to provide accurate medical information and non-judgmental counselling while being aware of and respecting the diverse religious concerns patients might have.

It is worth noting that Islamic jurisprudence in Malaysia has previously accommodated harm reduction strategies, offering a meaningful parallel to the current debate surrounding PrEP. The national harm reduction program, comprising methadone maintenance therapy and needle and syringe exchange programs, is a key example. When first introduced in 2005, these interventions faced significant public and religious concern. Some stakeholders viewed them as potentially inconsistent with Shariah principles and associated them with external, non-traditional public health models [6].

Nevertheless, the Malaysian government proceeded, driven by the urgency of a growing public health crisis: a rapidly escalating HIV epidemic, largely fueled by injecting drug use and disproportionately affecting the Malay Muslim population. The justification for this policy was twofold. From a scientific standpoint, clear evidence supported the effectiveness of these harm reduction strategies. From an Islamic ethical lens, the policy was grounded in the principles of necessity and the prevention of greater harm. This framing helped bridge religious and medical perspectives, leading to the argument that safeguarding life and containing the epidemic took precedence over concerns about permissiveness. This viewpoint gained traction among policymakers and religious leaders, and evaluations later confirmed the program's success, showing it was highly cost-effective and had prevented an estimated 12,000 new HIV infections by 2015 [6]. This experience illustrates a key lesson: when faced with pressing public health needs, Malaysia has demonstrated the capacity to adopt pragmatic, evidence-based approaches that align with both scientific evidence and Islamic ethical values.

As Malaysia considers its path forward with PrEP, the experience of Indonesia offers a particularly relevant and instructive comparison. Operating in a socio-political climate where discussions about sexuality remain sensitive, Indonesia has nonetheless made pragmatic progress in advancing HIV prevention through the implementation of a national PrEP program. Initiated as a pilot in 2021 and expanded in subsequent years, the program moved forward without being stalled by prolonged public religious contention [7]. This does not suggest that religious perspectives are unimportant. Rather, it highlights how public health interventions can proceed when they are guided by the principle of necessity and when engagement with religious and community stakeholders is grounded in shared goals of harm reduction and preserving life.

Indonesia's experience underscores that progress is possible even in culturally and religiously sensitive environments. For Malaysia, the lesson is not to sideline religious perspectives but to engage them constructively. Policymakers, healthcare professionals, religious authorities, and community stakeholders must collaborate to resolve inconsistencies, seeking common ground rooted in the shared objectives of preserving life and safeguarding public health. Open and respectful dialogue should guide policies toward equitable PrEP access, anchored in clinical necessity and population health needs, while remaining attuned to the religious and cultural values of local communities.

While jurisprudential debates offer important ethical guidance, the successful implementation of PrEP in Malaysia ultimately depends on the capacity and empowerment of frontline healthcare providers, particularly pharmacists. Their challenges extend far beyond navigating religious sensitivities and are deeply embedded in the structural and systemic constraints of the healthcare system. Many pharmacists face capability gaps, including limited training in PrEP-specific clinical knowledge and a lack of confidence in conducting sensitive sexual health counselling [8]. Opportunity-related barriers include insufficient infrastructure, such as private counselling areas, and competing demands from high workloads. Motivation gaps may arise from personal reservations about PrEP's perceived social implications, alongside limited financial incentives in the private sector, where time-intensive clinical services are often undervalued. Therefore, even with the recent publication of the National Guidelines on HIV PrEP Program Implementation [9], overcoming these deep-seated challenges related to capability, opportunity, and perception remains the primary hurdle for successful implementation.

These overlapping constraints place pharmacists in a difficult ethical and professional position. They are expected to deliver evidence-based care in line with national guidelines that support PrEP access for at-risk populations, yet must navigate powerful forces including community stigma, institutional ambiguity, and restrictive state-level religious rulings. This conflict creates a climate of fear around PrEP dispensing, particularly in conservative regions, where concerns about social or legal repercussions are heightened. To move forward, there is an urgent need for clear national policy alignment, legal protections, and professional support systems that affirm the pharmacist's role as a legitimate provider of HIV prevention services. Investing in targeted training, safe practice environments, and policy clarity is essential to unlocking pharmacists' full potential in advancing equitable PrEP delivery in Malaysia.

Moving beyond a superficial call for "non-judgmental counselling" requires more than good intentions. It demands a structured, evidence-informed training framework that equips pharmacists to navigate complex and sensitive health conversations with confidence, empathy, and cultural humility. While Malaysian pharmacists are highly trained in pharmacology and medication management, most have not received adequate preparation in delivering person-centred care for socio-ethical health issues such as HIV prevention and sexual health. These topics are often perceived as taboo and are not routinely addressed in pharmacy curricula or continuing professional development. As a result, pharmacists may feel unprepared to counsel patients effectively, particularly when religious and cultural values are deeply intertwined with health behaviours.

To address this critical competency gap, training for pharmacists must be standardized and strengthened. While the Ministry of Health provides some training for its pharmacists, especially in primary care, a mandatory training module should be introduced to systematically include all pharmacists involved in PrEP service delivery, particularly community pharmacists. This recommendation is not merely theoretical but supported by both local and international evidence. A quasi-experimental study in Malaysian tertiary hospitals has demonstrated that a structured communication skills training program grounded in the Four Habits Model and incorporating motivational interviewing significantly improved pharmacists' communication behaviours [10]. These included the ability to greet patients warmly, explore how their conditions affect daily life, and support emotional expression. This model, already validated in the local context, offers a strong foundation for developing a PrEP-specific training module that incorporates culturally sensitive and religiously respectful communication strategies.

International models also provide useful benchmarks. In New Zealand, pharmacists must complete a comprehensive training program before offering PrEP [11]. This curriculum covers not only clinical aspects but also techniques for taking a sexual history, addressing stigma, and delivering inclusive, respectful care. For Malaysia, any such adaptation must meaningfully integrate Islamic ethical principles and religious considerations. For example, discussions on abstinence, moral responsibility, and harm prevention could be framed within Islamic values such as preservation of life and public interest. In doing so, PrEP counselling becomes not just a clinical task but a moral engagement, one that aligns pharmacists' professional responsibilities with the broader religious and ethical fabric of Malaysian society.

Drawing from both local evidence and international best practices, a robust and contextually grounded PrEP training module for Malaysian pharmacists should be developed collaboratively. This initiative should involve the Ministry of Health, professional societies, academic institutions, and relevant community organizations, including faith-based and key population groups. The objective is to ensure pharmacists are equipped not only with clinical knowledge but also with the cultural, ethical, and communication competencies required to deliver PrEP services effectively, sensitively, and responsibly. The proposed training module should cover the following core components:

- Clinical Competency: Comprehensive, up-to-date knowledge on PrEP use, including indications for daily and on-demand regimens, baseline and follow-up testing

(e.g., HIV, renal function, hepatitis B), side effect management, and drug interaction monitoring.

- Advanced Communication Skills: Training using role-play and standardized patient scenarios rooted in motivational interviewing. Emphasis on open-ended questioning, active listening, rapport-building, and creating safe spaces for discussions on sexual health and risk behaviours.

- Cultural and Religious Competency: Education on the varying religious interpretations of PrEP within Malaysia, grounded in local fatwa analyses. The aim is not to turn pharmacists into religious authorities but to prepare them to counsel patients with respect and sensitivity. This includes framing PrEP within Islamic principles such as preservation of life and public interest.

- Referral Network: Guidance on establishing effective referral pathways to PrEP-affirming general practitioners, sexual and reproductive health clinics, mental health professionals, and community-based organizations, including those that offer faith-sensitive support.

By investing in such a comprehensive program, Malaysia can elevate the pharmacist's role from medication dispenser to trusted public health provider. This ensures that PrEP services are not only clinically sound but also ethically grounded, culturally respectful, and responsive to the needs of diverse communities. Standing at this critical intersection between healthcare delivery and religious ethics, pharmacists, by promoting patient-centred care and cultural humility, can significantly influence PrEP acceptance and effective use, ultimately contributing to Malaysia's broader goal of HIV eradication.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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Case Study

Atypical Manifestations of Bupropion Overdose: A Case Report from A Public Hospital in Macao

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ABSTRACT

Bupropion is a monocyclic antidepressant that is structurally similar to amphetamine and inhibits the reuptake of dopamine and norepinephrine, with negligible effects on serotonin. It is primarily prescribed for treating major depressive disorder, attention deficit hyperactivity disorder, as well as for smoking cessation. Although several cases of massive bupropion overdose have been reported worldwide, certain manifestations, such as hypokalemia, are relatively rare. In this report, we present the case of a 20-year-old female student with a past medical history of major depression who was brought to the emergency department (ED) due to intentional ingestion of 9 g of bupropion. She experienced cardiac toxicities and persistent hypokalemia. Following five days of intensive care unit (ICU) admission with supportive care, she eventually recovered and was discharged from the hospital with psychiatric follow-up arranged.

INTRODUCTION

Bupropion is a monocyclic aminoketone structurally analogous to amphetamine. Its primary mechanism of action involves the inhibition of dopamine (DA) and norepinephrine (NE) reuptake, with only minimal effects on serotonin transport [1-2]. As a highly lipophilic compound, bupropion undergoes extensive stereoselective metabolism, yielding three major active metabolites: hydroxybupropion, threohydrobupropion, and erythrohydrobupropion [3]. It is thought that these metabolites might exhibit potency of up to 25–50% of that of bupropion, as shown in an animal model [4,5].

Clinically, bupropion is widely used for treating major depressive disorder, anxiety disorders, and attention deficit hyperactivity disorder (ADHD), as well as for smoking cessation, owing to its favorable tolerability profile [6]. However, overdose frequently precipitates seizures, tachycardia, and agitation [7]. Severe cases may progress to status epilepticus, life-threatening arrhythmias, and cardiogenic shock [8]. The onset of neurological symptoms necessitates urgent intervention to prevent cardiopulmonary arrest secondary to hypoxia and metabolic acidosis.

Bupropion hydrochloride is available in three oral formulations: immediate-release (IR; administered three times daily), sustained-release (SR; twice daily), and extended-release (XL; once daily) [3]. Despite its widespread use, documented cases of bupropion overdose in Macao remain exceedingly rare. This report describes a patient who ingested a large quantity of SR bupropion but achieved full recovery following prompt and targeted medical management.

CASE PRESENTATION

A 20-year-old Asian female (70kg), a college student with a past medical history of major depression and a previous drug overdose involving dextromethorphan, presented to the emergency department (ED) 90 minutes after intentionally ingesting sixty 150-mg sustained-release bupropion tablets (total dose: 9 grams). Upon arrival, she was afebrile (37.4 °C), fully conscious with a Glasgow Coma Scale (GCS) score of

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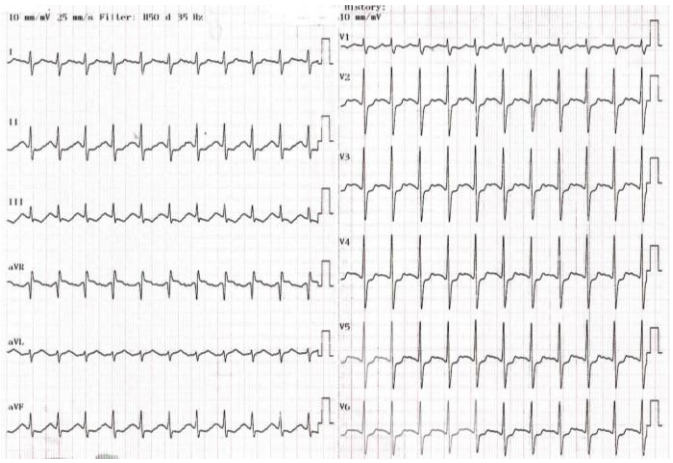

Figure I: ECG on arrival to the ED.

15, and hemodynamically stable with a blood pressure of 109/64 mmHg. She exhibited agitation and a noticeable hand tremor. The physical examination was otherwise unremarkable. The initial electrocardiogram (ECG) revealed sinus tachycardia at a rate of 123 beats per min (bpm) (Figure I), and the prominent R wave in the lead aVR suggested terminal 40 ms right axis deviation (T40msRAD).

Given the short interval post-ingestion and the high seizure risk from this massive amount, the attending emergency physician decided to proceed with early intubation for airway protection at the ED. Activated charcoal was promptly administered after intubation for gastro-intestinal decontamination. She was then transferred to the high dependency unit (HDU) followed by the intensive care unit (ICU) for close monitoring and management of potential complications. Later, toxicology screening was negative for salicylate and acetaminophen. The urine drug screen was negative for benzodiazepines, amphetamine, as well as tricyclic antidepressants. About 11 hours after admission to the ED, a follow-up ECG showed a widened QRS complex (140 ms) with a more prominent R wave in lead aVR (Figure II).

A single dose of intravenous sodium bicarbonate was administered, and a subsequent ECG revealed no further QRS widening (120 ms). Arterial blood gas (ABG) analysis showed no significant acidosis. Laboratory results indicated moderate hypokalemia with a potassium level of 3.0 mmol/L (Table I).

During the first two days of her ICU admission, hypokalemia persisted, with potassium levels dropping to a low of 2.5 mmol/L. Concurrently, spot urine analysis showed an elevated potassium concentration of 150 mmol/L, above the reference range of 25-125 mmol/L. Therefore, supplemental potassium

Figure II: ECG showed prolonged QRS interval and prominent R wave during observation.

Table I: Pertinent laboratory value.

Component	Admission value	Discharge value	Reference range
pH	7.415	7.338	7.35-7.45
pCO_2	37.5	42.7	35-45 mmHg
pO_2	97.4	111↑	80-100 mmHg
HCO^{3-}	23.5	22.0	22-26 mmol/L
Anion Gap	12.5↑	12.0	4.0 -12 mmol/L
Hemoglobin	12.8	11.5	11.5-17.4 g/dL
Sodium	140	138	136-145 mmol/L
Potassium	3.0↓	3.9	3.5-5.1 mmol/L
Chloride	104	104	98-107 mmol/L
Calcium	2.37	2.31	2.15-2.5 mmol/L
Phosphorus	0.89	1.12	0.81-1.45 mmol/L
Magnesium	0.85	0.85	0.70-0.91 mmol/L
Albumin	50	42	35-52 g/L
Glucose (random)	7.13	4.9	≤ 11.1 mmol/L
Urea	2.3	1.3↓	2.1-7.1 mmol/L
Serum creatinine	64	49	45-84 µmol/L
Total bilirubin	7	6	< 15 µmol/L
Aspart. Aminotransferase (AST)	13	10	≤32 U/L
Alanine Aminotransferase (ALT)	4	6	≤33U/L

chloride was administrated until the patient's status stabilized. Fortunately, she was successfully extubated two days later and gradually recovered before being transferred to a general medical ward. By day 5 of admission, she requested to be discharged against medical advice (DAMA) without any sequelae. A psychiatric consultation was conducted before discharge, and follow-up was arranged for ongoing care.

DISCUSSION

Bupropion was initially approved as an antidepressant in 1986. However, it was temporarily withdrawn from the market due to a higher-than-expected incidence of seizures occurring at therapeutic doses. It was reintroduced in 1989 at a lower recommended maximum dose of 450 mg/day [9]. Over the past decade, the prescription rate of bupropion has significantly increased for the treatment of major depressive disorder and as an aid in smoking cessation, especially for patients who want to minimize the risk of antidepressant-induced sexual dysfunction [6].

The patient reported a sudden onset of mood disorder and consequently ingested 60 tablets of SR bupropion, which is 20 times the maximum recommended dose, in an attempt to alleviate her symptoms. Upon her arrival at the ED, additional drug screening tests were performed, all of which returned negative results. The lack of a clinical assay to measure bupropion concentration in plasma or urine significantly limited the ability to confirm the diagnosis through standard methods. However, the patient's clinical presentation, characterized by agitation, tremor, tachycardia, and ECG abnormalities, was consistent with a bupropion overdose. These observations led to the establishment of the diagnosis.

Management of bupropion overdose primarily involves close monitoring and supportive care, given the absence of a specific antidote. In general, with sustained-release formulations, the onset of toxicity may be delayed [10]. Understanding the pharmacokinetic properties is crucial for providing better clinical outcomes. Based on the pharmacokinetic parameters of SR bupropion, it normally takes about 3 hours to reach peak plasma concentration after absorption [6]. This makes gastrointestinal decontamination (e.g. activated charcoal) extremely important in the management of overdose with sustained-release formulations, as long as the risk of aspiration is balanced. Since she was brought to the ED about 1.5 hours after ingestion, gastrointestinal decontamination with activated charcoal may still been beneficial. Consequently, she was intubated for airway protection (as agitation, tremor, and prolonged QRS all predicted a high risk of convulsion) and sedated with benzodiazepine (i.e. midazolam) due to the substantial risk of pulmonary aspiration and seizure. Interestingly, despite bupropion's potential to cause seizures in a dose-dependent manner [10], no seizures were noted throughout her hospital stay. We attribute this outcome to early aggressive management, including prompt benzodiazepine administration.

Bupropion-induced QRS prolongation has been reported and may not respond to sodium bicarbonate, as the cardiotoxicity does not appear to be primarily mediated by sodium channel blockade. Instead, it is thought to result from impaired gap junction communication [11]. However, in our case, both terminal 40 ms RAD and QRS widening were observed and appeared responsive to intravenous sodium bicarbonate.
A recent report also suggests that bupropion may have sodium channel-blocking effects [12]. Therefore, we propose that sodium bicarbonate can be considered as a potential treatment in bupropion overdose patients who exhibit a typical sodium channel blockade ECG pattern and are at high risk of clinical deterioration.

On the other hand, bupropion undergoes extensive liver metabolism to produce several active metabolites, which are then mainly eliminated by the kidneys. For patients with normal hepatic and renal function, the elimination half-life ($t_{1/2}$) of bupropion and its primary active metabolite, hydroxybupropion, is approximately 21 hours and 20 hours, respectively [3]. In light of the linear elimination kinetics of bupropion and its metabolites [13], 94 to 97% of the drug is eliminated after 4 to 5 half-lives [14]. In other words, 4-5 days after ingestion, the plasma concentrations of bupropion will fall below a clinically relevant level. This could explain why the patient fully recovered after this 5-day hospitalization.

Interestingly, despite the absence of gastrointestinal symptoms or other identified causes, the patient's plasma potassium levels remained consistently low, reaching a nadir of 2.5 mmol/L. Additionally, the high urine potassium level suggests significant urinary potassium loss. Notably, hypokalemia is not frequently reported as a toxic effect of bupropion overdose. A retrospective analysis of bupropion overdoses found hypokalemia in only three out of five patients [15].

The exact mechanism by which bupropion may cause hypokalemia is still not well understood, and further research is needed to establish this association. Given the persistent low potassium levels and the risk of life-threatening complications such as dysrhythmias and status epilepticus, admitting the patient to the ICU for close monitoring and management of the electrolyte disturbance is deemed necessary.

CONCLUSION

This case demonstrates several atypical manifestations of bupropion overdose, including persistent hypokalemia with urinary potassium loss, ECG abnormalities responsive to sodium bicarbonate, and the absence of seizures despite massive ingestion. It is important to note that supportive care remains essential. Early aggressive management, including airway protection and benzodiazepine administration, likely contributed to the patient's favorable outcome. Further research is needed to clarify the mechanisms underlying bupropion-associated hypokalemia and cardiotoxicity.

CONFLICT OF INTEREST

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Case study

Therapeutic Drug Monitoring of Vancomycin in an Adult Patient with Augmented Renal Clearance - A Case Report

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Keywords: Vancomycin; augmented renal clearance; therapeutic drug monitoring

Background: Augmented renal clearance (ARC) significantly affects the pharmacokinetics (PK)/ pharmacodynamics (PD) of vancomycin, causing sub-therapeutic serum concentrations and thus leading to treatment failure and bacterial drug resistance. Therapeutic Drug Monitoring (TDM) is important to ensure adequate therapeutic exposure of vancomycin and to minimize the risk of toxicity. A 29-year-old gentleman was admitted to the Intensive Care Unit (ICU) and was diagnosed with *Corynebacterium striatum* bacteremia. Intravenous (IV) vancomycin 1.75g stat and 1g BD was started on this patient who showed ARC (CrCl >130 ml/min) prior to and during treatment with IV vancomycin. The vancomycin trough level (C_{trough}) was successfully increased to the therapeutic range (15–20 mcg/mL) following dosage adjustment based on Therapeutic Drug Monitoring (TDM). **Conclusion:** Increasing dosing frequency, prolonged infusion time and frequent TDM can be utilized as a strategy to achieve therapeutic trough levels (C_{trough}) of vancomycin in patients with augmented renal clearance (ARC). The estimated half-life may serve as a valuable parameter for optimizing therapeutic regimens; further research is necessary to validate this hypothesis.

INTRODUCTION

Vancomycin is a hydrophilic glycopeptide antibiotic that demonstrates first-order kinetics [1]. It is eliminated renally, with 80-90% excreted unchanged in the urine [1]. Vancomycin has been used in gram-positive bacterial infections and exhibits both concentration- and time-dependent activity [1]. Owing to its narrow therapeutic range, with serious consequences coming along with both subtherapeutic and supratherapeutic levels, Therapeutic Drug Monitoring (TDM) is needed to develop an individualized dosing strategy. Augmented renal clearance (ARC) is typically defined as creatinine clearance (CrCl) higher than 130mL/min and has a significant impact on pharmacokinetics/ pharmacodynamics (PK/PD) of renally excreted antimicrobials with time-dependent activity and short half-lives, often observed in critically ill patients [2]. ARC has been associated with increased vancomycin clearance, leading to sub-therapeutic serum concentrations and may result in treatment failure and drug resistance [2]. In response to this, clinicians may increase the dose of vancomycin to ≥4g/ day, which is associated with higher likelihood of vancomycin-induced nephrotoxicity [3]. We report a case of an adult patient with augmented renal clearance (ARC) who successfully achieved a therapeutic vancomycin trough concentration (C_{trough}) through calculation and estimation guided by Therapeutic Drug Monitoring (TDM), without evidence of vancomycin-induced nephrotoxicity.

This study has been approved by National Medical Reseach Register, Malaysia with NMRR ID-25-01879-YBN. Written consent and publication consent were obtained from the patient to publish his case.

CASE PRESENTATION

A 29-year-old male (weight: 68 kg; height: 1.70 m) with a medical history of childhood bronchial asthma, short bowel syndrome, anemia (vitamin B12 and iron deficiency), and eczema was admitted to the hospital with a chief complaint of fever, rashes over the body associated with generalized itchiness for 2 weeks, dizziness, and leg cramps for 1 week. He was transferred to the Intensive Care Unit (ICU) from the general medical ward for respiratory support following a drop in Glasgow Coma Scale (GCS) to E1V3M4. He was managed as a case of meningoencephalitis.

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The patient was also noted to have electrolyte disturbances secondary to short bowel syndrome, complicated by thrombocytopenia and anemia. A septic workup was conducted, and blood culture and sensitivity results identified *Corynebacterium striatum*, which was sensitive to vancomycin. Intravenous (IV) vancomycin was initiated at a loading dose of 1.75 g, followed by 1g twice daily (b.i.d.). In the ICU, the patient was intubated and received fluid resuscitation. Prior to the initiation of intravenous (IV) vancomycin, this patient's serum creatinine level was between 67.4 and 79 µmol/L; his estimated creatinine clearance (CrCl), calculated using the Cockcroft-Gault formula, ranged from 118 to 141 mL/min.

Management and outcome

The assay used to measure the serum concentration of vancomycin was the homogeneous particle-enhanced turbidimetric inhibition immunoassay (PETINIA). The serum trough concentration (C_{trough}) of vancomycin was taken prior to the administration of the fourth dose of the new dosage regimen. The creatinine clearance of the patient was calculated using the Cockcroft-Gault formula on the same day that TDM was performed. The formula in the vancomycin chapter of the Clinical Pharmacokinetic Handbook, 2nd Edition, was adopted to calculate half-lives of vancomycin and to give a recommendation for the new dosing regimen, as shown below [4]:

$$C_{max} = C_{min} + \frac{Dose\ (mg)}{Vd\ (L)}$$

$$k_e = \frac{In\ C_{max} - In\ C_{min}}{T}$$

$$t_{1/2} = \frac{0.693}{k_e}$$

$$New\ dose = \frac{C_{min}\ target\ \times Vd\ (L) \times (1 - e^{-k_eT})}{e^{-k_eT}}$$

Where C_{max}: Maximum concentration (mcg/mL);
C_{min}: trough level (mcg/mL);
Vd: Volume of Distribution = 0.17(age) + 0.22(body weight in kg) +15;
k_e: elimination rate constant ($hour^{-1}$);
T: Dosing interval (hour);
$t_{1/2}$: half-life (hour).

The first measured C_{trough} of vancomycin was 13.6 mcg/mL (CrCl: 96.3 mL/min). The pharmacist recommended increasing the intravenous (IV) vancomycin dose from 1g twice daily (b.i.d.) to 1.25 g twice daily (b.i.d) and repeating the trough level (C_{trough}) after two days.

The second vancomycin trough level (C_{trough}) was 4.4 mcg/mL, with a concurrent creatinine clearance (CrCl) of 129 mL/min. Despite the increased dose, the C_{trough} remained subtherapeutic. As a result, Therapeutic Drug Monitoring (TDM) recommended increasing the dosing frequency from 1.25 g twice daily (b.i.d.) to 1 g four times daily (q.i.d.).

The third vancomycin trough level (C_{trough}) was 9.5 mcg/mL, with an estimated creatinine clearance (CrCl) of 175 mL/min. Although an increase in concentration was observed, the level remained subtherapeutic. Therapeutic Drug Monitoring (TDM) recommended adjusting the intravenous (IV) vancomycin regimen from 1 g four times daily (q.i.d.) to 750 mg every four hours (total daily dose: 4.5 g), with each dose to be infused over a period of two hours.

The fourth trough level of vancomycin was measured at 16.6 mcg/mL (CrCl: 165 mL/min), which was within the target therapeutic range. As a result, the current dosage regimen and infusion time were maintained until the completion of the 1-week IV vancomycin course. A repeat blood culture showed no growth, and the patient was subsequently discharged in stable condition.

DISCUSSION

Augmented renal clearance (ARC) was first described by Udy AA et al. as a process that involves altered glomerular filtration and tubular function, resulting in elevated renal elimination of solutes compared to baseline [5]. Many subsequent studies used creatinine clearance (CrCl) ≥130 mL/min as the diagnostic criteria for ARC [6]. Risk factors for augmented renal clearance (ARC) involved in this case include young age, aggressive fluid therapy, mechanical ventilation, male sex, use of vasopressor drugs, and less frequent use of furosemide [6].

In severe infections, ARC is common. It can be due to the disease itself, the inflammatory state, or therapeutic interventions [6]. Recent studies suggest that ARC may lead to enhanced vancomycin clearance, resulting in sub-therapeutic serum concentrations, thus increasing the risk of treatment failure and bacterial drug resistance [6]. This poses a great challenge for healthcare professionals to maintain the therapeutic level of vancomycin in this patient and to prevent toxicity from aggressive dosing at the same time.

Individualized therapeutic plans for adult patients with ARC by Therapeutic Drug Monitoring (TDM) are essential to ensure adequate therapeutic exposure to vancomycin. A higher therapeutic range (trough level of 15-20 mcg/ml) instead of the standard 10-15 mcg/mL was set for this patient due to his critical condition, which required respiratory support, close monitoring in view of bicytopenia induced by sepsis, and the treating as meningoencephalitis due to a drop in the GCS score [7,8].

The area under the concentration curve over 24 hours to MIC (AUC_{24}/MIC) ratio is not used in this case because this facility only performs monitoring of vancomycin by AUC_{24}/MIC for uncomplicated Methicillin-resistant *Staphylococcus aureus*

Table I. Summary of respective serum creatinine, estimated creatinine clearance (CrCl), estimated elimination rate constant (ke) and estimated half-life of IV vancomycin on the day when TDM was performed.

Trough level, C_{trough} (mcg/mL)	Serum Creatinine (µmol/L)	Estimated CrCl (mL/min)	Elimination constant, k_e ($hour^{-1}$)	Estimated half-life (hours)
First: 13.6	96.4	96.3	0.09448	7.33
Second: 4.4	71.5	130	0.1844	3.76
Third: 9.5	53	175	0.2318	2.99
Fourth: 16.6	56.1	165	-	-

(MRSA) infection with MIC less than 1mg/L in patients with stable renal function, as recommended by the revised consensus guideline by the Infectious Diseases Society of America [9]. ncreased clearance and shortened half-life of vancomycin by ARC had been proven to occur in this patient by TDM calculation, and the trough level of vancomycin remained subtherapeutic despite an increment in frequency or dose (Table I). The estimated half-life was inversely proportional to the estimated CrCl. However, CrCl estimated using the Cockcroft-Gault (CG) formula tends to be less reliable in ICU patients, as other factors associated with low serum creatinine levels, such as malnutrition or muscle wasting, had not been ruled out, which was a downside of this case report [10]. A multicenter prospective study concluded that measured CrCl (by 8-hour urine collection) has a higher value compared with estimated CrCl (by CG formula), suggesting estimated CrCl is a poorer indicator for reaching the target values of pharmacokinetics/ pharmacodynamics indices [11]. Nevertheless, estimated CrCl is essential for healthcare professionals to identify ARC. An 8-hour urine collection can be carried out to measure CrCl for confirmation of ARC.

In this case, TDM suggested increasing the dosing frequency of IV vancomycin to align the dosing interval as closely as possible to the estimated half-life based on the calculated elimination constant (k_e) while keeping the total daily dose at 4.5g/day. Apart from that, TDM also suggested prolonging the infusion time of IV vancomycin in the recommendation because Li J et al. showed that prolonged infusion of IV vancomycin can help to achieve higher trough concentrations and target concentration attainment [12]. This had also been proven to be an effective strategy in this case, as the fourth trough level (C_{trough}) measured was within the therapeutic range. The possibility of accumulation of vancomycin contributing to the fourth therapeutic C_{trough} was minimal, as the patient did not experience any signs of nephrotoxicity [13]. Continuous infusion of IV vancomycin was not implemented in this patient to avoid line complications or incompatibilities with other concomitant intravenous medications, and it is not a common practice for this facility. Further studies are required to investigate the importance of half-life as a parameter in managing the dosing regimen of vancomycin in adult patients with ARC.

CONCLUSION

This case has shown that Therapeutic Drug Monitoring (TDM) is crucial to provide guided individualized dosing for intravenous (IV) vancomycin in adult patients with augmented renal clearance (ARC). ARC has greatly affected the pharmacokinetics/ pharmacodynamics (PK/PD) of vancomycin in this case, where half-life could be an important parameter to be considered in optimizing the dosing regimen. Currently, the guidelines for dosing vancomycin in adult patients with ARC have yet to be established dosing strategies such as prolonged infusion time and higher dosing frequency can be implemented in adult patients with ARC, under the close monitoring of levels with TDM in order to prevent toxicity and ensure sufficient therapeutic exposure.

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CONFLICT OF INTEREST

The author affirms that this case report is original, has not been previously published elsewhere and is not under consideration by another journal or book (print or electronic). The author has no conflicts of interest to disclose.

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Original Research Article

The Effect of Medication Adherence on the Improvement of Psychotic Symptoms among Patients with Schizophrenia under Assertive Community Care in Hospital Kuala Lumpur

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ABSTRACT

Objectives: To determine the relationship between medication adherence and psychotic symptoms before and after introducing a pill box. **Methods:** A pre- and post- interventional, prospective cohort study involving 96 patients diagnosed with schizophrenia was conducted over a duration of 2 months. Improvement in psychotic symptoms was assessed using the BPRS scale, while medication adherence was measured based on the percentage of doses taken. A pill box was provided to each subject with a percentage of doses that was taken less than 80%. The percentage of doses taken was reassessed by a trained pharmacist on a monthly basis for 2 months, and the mental state of participants was assessed by a visiting doctor using the BPRS scale. **Results:** The mean medication adherence during the first visit was 31.27 ± 28.77, while post-intervention adherence averaged 66.48 ± 43.52 (p-value <0.001). In terms of severity of psychotic symptoms, 26 subjects (43.3%) with a median score of 20.50 showed improvement. A total of 36 subjects adhered to antipsychotic medications, and among these, 20 (55.6%) showed improvement in psychotic symptoms (p=0.019). Among the 24 non-adherent subjects, only 25% (n=6) showed improvement in psychotic symptoms. **Conclusion:** The introduction of a pill box positively affects medication adherence and reduces the severity of psychotic symptoms. This study suggests that healthcare personnel can implement this method to promote better adherence to medication in the future.

INTRODUCTION

Schizophrenia is a serious mental disorder with a relatively high prevalence, affecting about 7 per 1000 adults worldwide. It is a persistent, long-term condition.[1]. People with chronic illness, regardless of whether they are medical or psychiatric, need to be on regular medications for life in order to manage symptoms effectively and reduce the risk of relapse. The use of antipsychotics is crucial in treating schizophrenia as well as the symptoms of the illness.

Therefore, medication adherence is essential for patients to achieve remission. However, non-adherence to these medications has been recognized as a significant problem [2]. The majority of clinicians encounter adherence issues with patients regarding prescribed medications, and this issue is more pronounced in patients with psychiatric illness. The adherence rate among patients who are diagnosed with schizophrenia falls between 50% and 60% [3,4]. One study stated that poor psychiatric reasoning skills and lack of insight are the reasons for poor adherence among psychiatric patients [4].

Medication adherence refers to a patient's behaviour in taking medications and specifically denotes the extent to which a patient follows the mutually agreed-upon treatment plan established by their healthcare providers [5]. Research has shown that non-adherence to antipsychotics among schizophrenia patients leads to a higher risk of relapse and readmission, increased risk of violence towards society, suicidal risk and attempts, as well as elevated costs and resource use for healthcare systems [1,5]. Patients with schizophrenia are considered adherent to therapy if they achieve a compliance rate of 80% with their prescribed medications, while partial adherence is defined as compliance of 50%. Non-adherence is defined as being off medications for 1 week or longer [6,7]. A recent study conducted in Sweden showed that 861 patients experienced early rehospitalisation

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shortly after discharge due to non-adherence to their prescribed antipsychotic medications [8]. This, in turn, leads to an increased disease burden on healthcare systems [9]. Efforts to improve medication adherence among individuals with schizophrenia are crucial, as they contribute to better symptom management, reduced psychiatric complications, lower healthcare expenses, and an overall improvement in the patient's welfare and quality of life [10].

Various interventions have been implemented to improve adherence to medication regimens among patients with psychiatric illnesses. At Hospital Kuala Lumpur (HKL), psychiatry patients with severe mental illness are referred to Assertive Community Treatment (ACT) if they are found to be non-adherent to treatment, have limited social support, and have experienced multiple relapses. In ACT, a team consisting of a psychiatrist, a medical officer, a pharmacist, case managers (medical assistants or staff nurses), occupational therapists and social work officers helps patients manage their illness by ensuring adherence, mobilizing support, monitoring symptoms, and providing continuous psycho-education regarding their illness, symptoms and treatment to improve patients' quality of life. The pill box is one of the interventions used in ACT to increase patients' adherence to their medications. Pill counting is more reliable than self-reporting or informant reporting, which may be influenced by opinion, recall bias, and a tendency to obscure the truth. In contrast, a pill box is more organized and may help patients improve their adherence to medications.

However, there are no specific studies on this intervention conducted for patients with mental illness, especially schizophrenia, in Malaysia. Therefore, this study aimed to explore the effect of medication adherence with the use of a pill box on the improvement of psychotic symptoms among patients with schizophrenia under assertive community care in Hospital Kuala Lumpur (HKL).

MATERIAL AND METHOD

Study design and patient selection

A pre- and post- interventional, prospective cohort study was conducted with approved registration ID by National Medical Research Register: NMMR-19-4019-51115. Study samples were collected among psychiatric patients referred for ACT in the Psychiatry Department of HKL using convenience sampling. Patients enrolled had to fulfil the following inclusion and exclusion criteria. All subjects were assessed for their mental status using Brief Psychiatric Rating Scale (BPRS and BPRS-M), and non-adherence to medications was defined as patients taking less than 80% of prescribed doses. Subjects who were chosen into this study could be of those who had not or had used a pill box prior to the study. Those subjects who were within the range of 18 to 65 years old, with clinically diagnosed schizophrenia only, on a single oral antipsychotic that was maintained for the past three months, and who had provided consent. Exclusion criteria included subjects who were actively abusing substances during the study period, who had never tried using a pill box prior to the study, had other medical diagnoses (based on self-report and clinician report), and patients with a BPRS total score above 53, indicating they were markedly ill and not fit to give consent. The formula used for calculating the percentage of dose taken (% adherence) was as follows:

$$\text{Percentages of dose taken} = \frac{\text{Quantity dispensed} - \text{Quantity remaining}}{\text{Prescribed number of tablets per day} \times \text{No. of days between dispensing date and interview}} \times 100\%$$

All subjects were introduced to a pill box by a pharmacist to monitor medication adherence throughout the study period. The pill box was filled with subjects' dose regimen on a monthly basis. The pharmacist in charge will provide information to the subject and his/her caretaker on how to use the pill box in a correct manner. Assertive community care was then continuously maintained for these subjects. During this study, all subjects were assessed using the pill count adherence method for existing medications and the BPRS.

Medication refills for subjects and pill counts were done by a pharmacist, while mental status was assessed by the visiting doctor. The percentage of doses taken and mental status were reassessed during the second and third month of the ACT, respectively. The study data collection period lasted 12 months.

Assessment

Psychiatric symptoms were evaluated using either the BPRS or BPRS-M based on the preferences of the visiting doctor and patient [11]. Each item of the BPRS was assessed during each ACT session to determine the severity of psychotic symptoms among subjects. The BPRS scale had a minimum score of 18 and a maximum of 126. Scores within the range of 31 to 40 corresponded to mild psychotic symptoms; 41-52 indicated moderate psychotic symptoms, while a score above 53 indicated markedly ill subjects. Each item in the BPRS was rated from 0-7 based on symptom severity, where the highest score indicated the highest severity.

Data analysis

The collected data were analysed using descriptive statistics, paired t-test, Wilcoxon signed-rank test, and Pearson's chi-square test. Descriptive analysis was used for the demographic analysis. Paired t-test was used to assess the difference in medication adherence before and after the introduction of the pill box whereas Wilcoxon Signed rank test was used to

determine the median of the BPRS score among these subjects. The association between medication adherence and improvement in psychotic symptoms was assessed using Pearson chi square test. All statistical analyses were analysed using Statistical Package for Social Sciences (SPSS version 20.0) for Windows. Statistical significance was set at a p-value of < 0.001.

RESULT

The total number of patients with mental illness referred to the Community Psychiatry Unit of the Psychiatry Department of Hospital Kuala Lumpur (HKL) was approximately 539 patients, including 350 patients diagnosed with schizophrenia along with other psychiatric diagnoses or medical comorbidities, while 100 patients had a diagnosis of schizophrenia only. Out of the 100 eligible patients, only sixty subjects agreed to be recruited into the study over 2 years, from July 2019 to May 2021. The demographic data of these subjects are presented in Table I. The majority of the subjects fell within the age group of 40 to 49 years old (38.3%), with male subjects comprising 61.7% of the sample size. Among the 60 subjects, 46 (76.7%) were of Malay descent. The employment status of the subjects was predominantly unemployed (85%).

All subjects recruited for the study had a medication adherence score of less than 80% and were given a pill box. The mean medication adherence during the first visit was 31.27 ± 28.77, while the post-intervention mean was 66.48 ± 43.52 (p <0.001). The psychotic symptoms experienced by the subjects were assessed using the BPRS on the first day of the study. The subjects were then reassessed during the second and third visits. Out of the 60 subjects, 26 (43.3%) showed improvement in psychotic symptoms, with a median score of 20.50 (19-21.5). These subjects showed a 20% improvement in the BPRS scores throughout the study. Tables II and III show the impact of the pill box introduction on medication adherence and the improvement of psychotic symptoms among these 60 subjects, respectively.

The relationship between medication adherence and psychotic symptoms was assessed. A total of 36 subjects adhered to their anti-psychotic medications, and out of these, 20 showed improvement in psychotic symptoms, comprising 55.6% (n=20) of the subjects (p=0.019). Among the 24 non-adherent subjects, only 25% (n=6) showed improvement in psychotic symptoms (Figure I). A Pearson chi-square statistical test was used to examine the relationship between these two variables after the introduction of the pill box.

Table I. Baseline sociodemographic (n=60).

Characteristics	Frequency (n, %)
Age (years old)	
20-29	5 (8.3)
30-39	13 (21.7)
40-49	23 (38.3)
50-59	13 (21.7)
More than 60	6 (10.0)
Gender	
Male	37 (61.7)
Female	23 (38.3)
Race	
Malay	46 (76.7)
Chinese	8 (13.3)
Indian	6 (10.0)
Employment status	
Unemployed	51 (85.0)
Employed	9 (15.0)

Table II. Effect of pill box introduction to subjects' medication adherence.

Variable	Mean ± SD (Pre)	Mean ± SD (Post)	p-value
Improvement in medication adherence	31.27 ± 28.77	66.48 ± 43.52	< 0.001

Table III. Effect of pill box introduction on BPRS score.

Variable	Median (Pre)	Median (Post)	p-value
Improvement in psychotic symptoms (BPRS score)	25.00 (28-23)	20.50 (22-18.5)	< 0.001

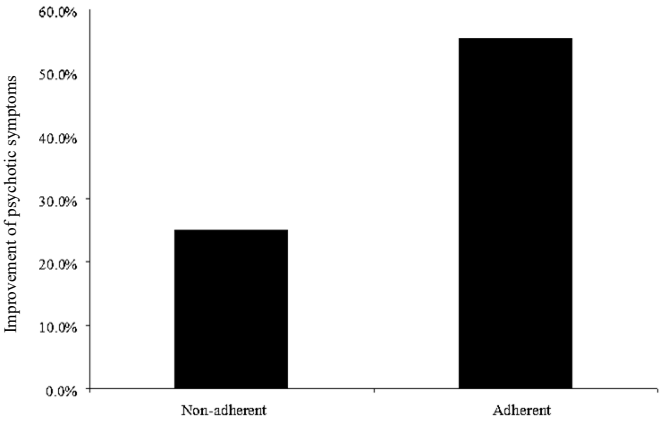

Figure I. The relationship between medication adherence and improvement of psychotic symptoms after pill box introduction.

DISCUSSION

In this prospective cohort study, patients on a single oral antipsychotic that had not been changed for the past three months were selected. Although a modest number of patients were recruited in this study, the introduction of the pill box appeared to lead to improvements in medication adherence and control of psychotic symptoms among schizophrenia patients. More than half the patients showed improvement in medication adherence when the pill box was provided as an aid to increase compliance with their medications. Our findings suggest the benefits of such aids in enhancing medication adherence; however, this still depends on factors such as the severity of psychiatric symptoms and therapeutic response (which were controlled and monitored in this study). Other factors, such as the patient's attitude towards treatment, perceptions or insights regarding the need to take medications, duration of illness, and side effects, were not studied but may also affect medication adherence [6,12]. Patients with better insight into their illness and medications tend to show improvement in medication adherence, which, in turn, supports the achievement of recovery goals and optimizes overall patient wellness [6,13]. Adherence to antipsychotics has shown significant improvement in patients with schizophrenia and can reduce the percentage of relapse in the future [1,2,5,14]. The use of the pill box was also shown to help patients prevent overdosing or underdosing during the treatment course, given the nature of the illness. Studies by Diaa S et al. stated that the pill box can also remind patients about the timing of their prescribed medications [15,16]. This is essential for schizophrenic patients, as the timing of antipsychotic administration is crucial for cognitive function. The pill box also helps prevent medication errors, such as taking the wrong medications, and patients can be educated to organize their medications in the pill box throughout the treatment course [17,18].

About half of the patients showed improvement in psychotic symptoms with the use of the pill box. Patients' compliance has been associated with improvement in psychotic symptoms through adherence to the treatment plan. However, the other half of the patients showed no improvement in psychotic symptoms despite being adherent to treatment. The fact that adherent patients did not achieve significant improvement in psychotic symptoms could be due to non-response to the medications, ongoing and recent stressors, poor family support, high emotional expressiveness within their families, or unsuitable medications. Further treatment interventions should be tailored to patients, such as optimizing oral antipsychotic dosages and durations, considering combination therapy with other oral antipsychotics or mood stabilisers, switching to long-acting injectables, or employing electroconvulsive therapy (ECT). Additionally, optimizing psychosocial interventions involving family members' psychoeducation is vital [19,20,21]. Evidence from some studies also shows that this will eventually lower psychiatric morbidity, reduce the cost of care, and improve overall welfare and quality of life of patients and family members [8,22]. This study was conducted among patients receiving assertive community care; however, these results can be applicable in both outpatient and inpatient settings, as the introduction of the pill box can be implemented in any setting, provided that proper education on its use is given by pharmacists and proper monitoring occurs during clinical follow ups.

Limitations

The study had several limitations. The overall planned sample size was 96 patients diagnosed with schizophrenia. However, only 60 patients agreed to participate in this study, while others faced limitations due to the Covid-19 pandemic, time constraints from the Movement Control Order (MCO) implemented during the study period, and a lack of family support due to stigmatization.

CONCLUSION

In conclusion, this study demonstrated that the introduction of a pill box for patients with schizophrenia has a positive impact on psychotic symptoms, which have improved as a result. Medication adherence also increased when the pill box was introduced to this group of patients. Given the connection between medication adherence and the improvement of psychotic symptoms in schizophrenic patients, this approach may improve quality of life and reduce psychiatric morbidity. In the future, psychiatric departments should implement the use of pill boxes during the continuation of treatment outside the hospital.

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MALAYSIAN Journal of Pharmacy

Original Research Article

Development of an Updated National Protocol for the Use of Disease-Modifying Treatments in Multiple Sclerosis: A MOH-MOE Steering Committee Initiative in Malaysia

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ABSTRACT

Background: There has been an increase in the number of disease-modifying treatments (DMTs) for Multiple Sclerosis (MS). However, treatment accessibility, selection, monitoring, and patient-specific considerations pose constraints in resource-limited settings, such as Malaysia. **Objective:** This protocol aims to develop a consensus statement that will guide MS management in Malaysia, addressing issues related to treatment and monitoring. **Methods:** A working group consisting of clinicians, subject matter experts from the Ministry of Health and the Ministry of Education, private medical centers, senior pharmacy officials, and representatives from patient groups has been established at Kuala Lumpur Hospital. The Delphi method, involving iterative rounds of expert voting on key topics, was applied. A systematic literature review focused on high-quality evidence from clinical trials, systematic reviews, and real-world data. **Results:** The consensus protocol provided comprehensive, evidence-based recommendations for MS management in Malaysia. Key topics addressed include the timing of DMT initiation, selection of treatments for different MS subtypes, strategies for switching treatments due to lack of response, and monitoring protocols. The impact of DMTs on cognition, pregnancy, and breastfeeding was also included. Extra attention was given to overcoming diagnostic and treatment barriers in a middle-income setting, improving access to newer DMTs, and adapting global guidelines to local needs. **Conclusion:** The consensus statement is expected to serve as a crucial guide for healthcare professionals in managing MS, enhancing early diagnosis, optimising treatment strategies, and improving long-term patient outcomes in Malaysia.

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INTRODUCTION

Over the last couple of years, there has been an exponential increase in the number of disease-modifying treatments (DMTs) available for the treatment of Multiple Sclerosis (MS) [1]. Managing MS is challenging due to the varied types of patient disease, differing expectations, treatment responses, and evolving data on its pathogenesis, diagnosis, classification, investigations and management [1,2,3,4,5]. Consequently, a periodic review of the current literature is important to develop guidance on the optimal use of MS DMTs adapted to the local situation [1,2,6]. Recent studies suggest that the early use of DMTs, especially high-efficacy treatments (HET), has improved long-term outcomes in patients with MS (pwMS) regarding relapses and disability progression [4,5,6,7,8].

The Atlas of MS 2020 reports that the prevalence of MS in Malaysia has increased to 6 per 100,000 pwMS [9]. Their caregivers and healthcare professionals (HCPs) face numerous challenges, including barriers to diagnosis, variability in MS management, and access to treatment. These challenges specifically pertain to selecting an initial disease-modifying therapy (DMT), determining the mode of administration, managing the burden of pre-treatment screening and ongoing monitoring, and making decisions about switching therapies in cases of inadequate efficacy or adverse events [2,6].

Resource-limited countries face unique challenges in balancing the ethical imperative to provide treatment with the economic constraints of healthcare delivery. Additional concerns include the absence of reliable efficacy biomarkers, delays in detecting disease progression and cognitive impairment in pwMS, and the need for guidance on managing pwMS in special situations such as pregnancy, breastfeeding, contraceptive use, and vaccination [10-17].

The Malaysian Clinical Practice Guideline Version 1 of 2015 attempted to address this by targeting all HCPs, including MS trained neurologists, general neurologists and pwMS, to improve MS diagnosis and treatment [18]. Although it remains widely used and disseminated as of 2025, ten years would have passed since its original publication. Based on an unpublished survey conducted amongst Ministry of Health (MOH) neurologists in 2020 at Kuala Lumpur Hospital, 100% of respondents concurred with the need for a revised evidence-based guide and consensus statement to make the best risk-benefit treatment decision for pwMS [18,19].

All agreed on the need for education, updated information, and improved access to MS treatments [19]. Currently, there are eight MS drugs registered with the Drug Control Authority (DCA) of Malaysia and are available for use within the country. Of these, only interferons, teriflunomide and fingolimod are included in the MOH's Drug Formulary. These three drugs are commonly listed within the hospital formularies of many state hospitals [20].

Other DMTs, such as subcutaneous ofatumumab, oral cladribine, oral dimethyl fumarate, intravenous alemtuzumab, and intravenous ocrelizumab, are approved for use within the country but are not available in the MOH's Drug Formulary [20]. These drugs are purchased on a named patient basis with special approval from the MOH or self-purchased by patients from private pharmacies or hospitals. The cost of these on-label treatments ranges from RM 3,300 to RM 5,800 per month or RM 3,400 to RM 45,000 per dose, depending on the prescribed dosage and frequency of administration [21].

Off-label rituximab is currently more available locally, either as originators or biosimilars. Many pwMS are still opting for off-label treatments such as IV rituximab (biosimilar), which costs RM 2200 per vial, with most using an induction of 1g (2 vials) followed by 500mg (1 vial) every 6 months. Both originator and off-label rituximab are still subject to a ceiling on the number of units that can be purchased in the MOH hospitals. More recently, in 2023, interferons, teriflunomide, and off-label rituximab were included in the Essential Medicines List (EML) in Malaysia, and in July 2023, rituximab was also included in the WHO EML [22,23]. This inclusion has benefitted many MS and is discussed in a separate upcoming publication.

Thus, with support from the Health Technology Assessment Department (HTA) at the MOH and the Clinical Research Center (CRC) at Kuala Lumpur Hospital (KLH), a steering committee made up of clinical neurologists, neuro-radiologists, ophthalmologists, neuropsychiatrists, pharmacists, patient representatives from the MS society, and health technologists was formed. These members were chosen from MOH Hospitals, Ministry of Education (MOE) Hospitals, private hospitals, and the MS society of Malaysia, considering the unique needs of Malaysian pwMS and the sociocultural and economic challenges, and barriers to treatment locally.

Therefore, the overall aim of this consensus protocol was to establish a consensus with experts and to provide an evidence-based, updated set of recommendations for the Management of MS in Malaysia. This addressed issues related to treatment and monitoring of treatment response, including management of MS in special situations such as pregnancy and breastfeeding. More specifically, it is to review evidence and provide guidance on:

- Establishing the best treatment choices for patients across the clinical spectrum of MS, including Clinically Isolated Syndrome (CIS), relapsing and progressive MS, and Radiologically Isolated Syndrome (RIS).
- Developing a standardized method for monitoring DMT treatment response.

- Switching or discontinuing DMTs.
- Managing pwMS in special situations such as MS dyscognition, pregnancy, and lactation.

METHODS

Study Design

A Delphi survey method was utilized to achieve consensus amongst subject matter experts (SMEs). The entire process is layered into two stages consisting of three rounds of a modified Delphi method [24] from the time of developing questions until the finalization of the recommendations. The first stage involved formulating the clinical questions that would be used to develop the recommendations. The second stage was to develop the recommendations based on the finalized clinical questions. The SMEs met and engaged via email and face-to-face discussions about MS management (Figure I).

Project Governance

A project working group was established after a letter of intent to revise the Clinical Practice Guidelines on the Management of MS was sent to the HTA, MOH of Malaysia in July 2023,

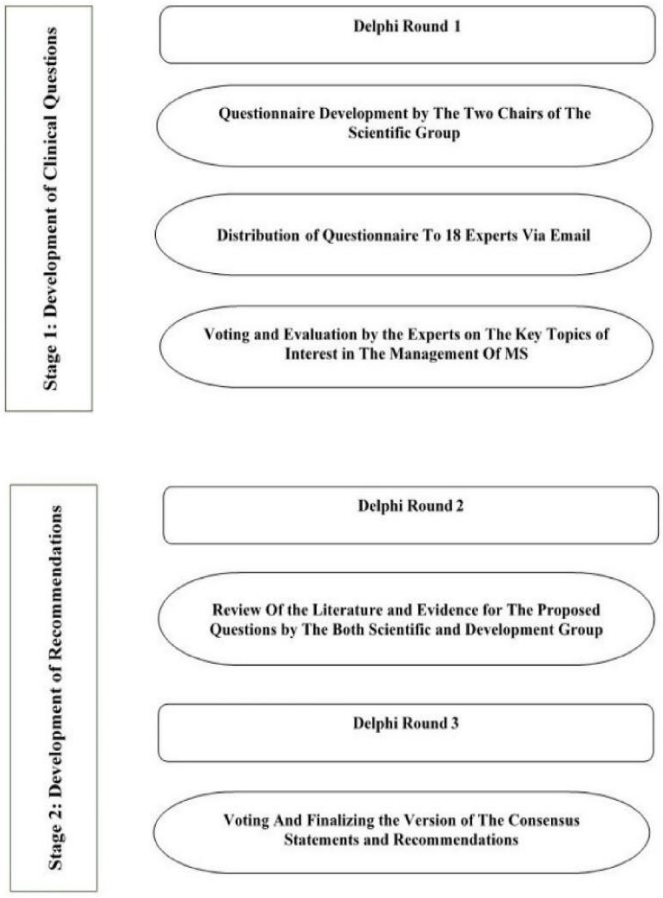

Figure I: Flowchart of Delphi process.

and a reply was obtained in July 2024. Based on the reply, a working group was formed consisting of two steering committees: the Scientific Group and the Development Group. The group comprised clinicians and SMEs from the MOH, the MOE, private medical centers, ophthalmologists, neuroradiologists, neuropsychiatrists, and pharmacy representatives, as well as an invited representative from the Malaysian MS Society.

The Scientific Group consisted of the core members (SA, SV, and LSY) who were responsible for developing the clinical questions to be used in the consensus statement. The Development Group reviewed the evidence for each question in tandem with the Scientific Committee. The Scientific and Development Groups comprised 18 members, including one patient representative.

All clinicians and pharmacists had more than 8 to 10 years of experience in treating and managing pwMS and were recognized as SMEs in their various fields by the MOH of Malaysia and respective universities. They had no conflicts of interest regarding the contents and recommendations to be made in the future after publication of this protocol.

The committee considered the current needs and expectations of pwMS, clinicians at local, state, and national level hospitals, and the ability of the MOH/MOE to provide comprehensive MS care in their deliberations. All members had voting rights in developing the recommendations based on the clinical questions developed by the scientific committee.

Development of the Clinical Questions (Stage 1)

The first stage of developing the clinical questions mainly focused on creating key clinical questions to be included in the questionnaire that would guide the development of recommendations. The key topics discussed were based on evidence for early MS treatments, types of MS to be treated, identifying treatment failure, stopping and switching treatments, monitoring, effects of DMTs on cognition, special situations such as pregnancy and breast-feeding, and counselling on the safety of DMTs. Published literature was used to develop the questionnaire by the two chairs of the Scientific Group. In this process, the first round of the Delphi process was applied.

The questionnaire was later distributed via email to eighteen experts from the Scientific and Development groups using the SurveyMonkey platform, along with one MS patient representative. The experts evaluated key topics of interest in the management of MS with the option of answers: Yes or No. A score of between 0 to 10 on a continuous scale was used for each question, with 0 indicating complete disagreement and 10 indicating complete agreement. A threshold of 85% was set as a requirement before a question was accepted. The final list of

clinical questions was developed from the anonymous voting results (Table I).

Development of the Recommendation Process (Stage 2)

The second stage involved developing the recommendations based on the finalized clinical questions. The Scientific and Development Groups then divided the selected questions amongst the focused panel members and performed a review, looking for evidence and literature for each question. Studies needed to clearly describe the therapeutic regimen used and report quantifiable clinical outcomes, such as relapse rates, neuroimaging endpoints, and Expanded Disability Status Scale (EDSS) scores. To select relevant search titles and abstracts for the consensus, the two scientific chairs, together with designated members, independently searched PubMed, EMBASE, MEDLINE, and Cochrane Databases, and examined unpublished local studies. They then assessed the results of the various searches and performed data extraction and categorization. This was presented in an open-format meeting for discussion. In this stage, the second round of the Delphi process was applied.

Two rounds of voting were conducted anonymously to ensure reproducibility and consensus. The experts assessed the literature in the first round and voted on the statements. Disagreements were resolved by consensus and engagement.

In round two, which is the third and final round of the Delphi process, anonymous voting was conducted, and the finalized version of the consensus statements and recommendations was made. A score of between 0 to 10 on a continuous scale was used for each question, with 0 indicating complete disagreement and 10 indicating complete agreement. A threshold of 85% was set as a requirement before a statement and recommendation could be accepted.

The findings were presented in an open-format meeting for discussion. The steering committee members discussed and reviewed the literature available for the identified clinical questions and anonymously voted on the final statements and

Table I: List of questions to be addressed in the consensus.

1.	Should MS patients be treated as early as possible?
2.	Should patients with RIS be treated with DMTs?
3.	Should patients with CIS be treated with DMTs?
4.	Which DMTs should be started in active RRMS
5.	Which DMTs should be started in highly active RRMS?
6.	Which DMTs should be started in fulminant/aggressive MS?
7.	Which DMTs should be started in progressive MS?
8.	What is the definition of treatment failure?
9.	How should treatment failure/breakthrough disease be managed?
10.	When should DMTs be stopped in patients with MS?
11.	How should patients on DMTs be monitored?
12.	What is the effect of DMTs on cognition in MS?
13.	How and when should MS patients on DMTs be counselled about pregnancy and breastfeeding?
14.	Which DMTs are considered safe during pregnancy and breastfeeding?

Delphi Method	Description	Timeline				
		2024 Jul-Oct	2024 Nov-Dec	2025 Jan-Mar	2025 Apr-Jun	2025 Jul-Dec
Delphi Round 1	Stage 1					
	Development of Clinical Questions	X				
	Anonymous Voting	X				
Dissemination (Protocol on Consensus Statement)						
Presentation					X	
Publication					X	
Delphi Round 2	Stage 2 Systematic Review	X	X	X		
	Anonymous Voting			X		
Delphi Round 3	Final Voting on the Recommendations			X		
Dissemination (Recommendations)						
Presentation						X
Publication						X

Figure II: Gantt chart of study timeline and milestone.

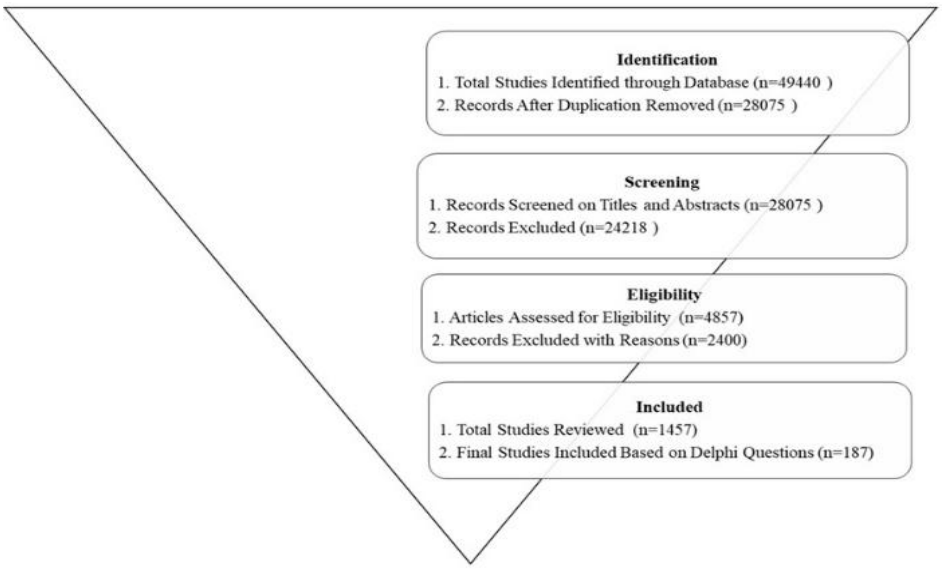

Figure III: PRISMA flow diagram of studies' screening and selection.

recommendations. The detailed timeline and milestones of the study are presented in the Gantt Chart (Figure II).

Data Source

Relevant literature was identified through a search of databases, including PubMed, Cochrane, EMBASE, drug regulatory repositories and MEDLINE. Conference abstracts were excluded. Only peer reviewed studies, RCT, systematic reviews, meta-analysis, consensus statements /guidelines, and real-world data of good quality were considered for this consensus. For RCTs with crossover trials, only data from the pre-crossover period were reviewed, and RCTs with long-term data were included. For RCTs with several arms using the same DMT, variable doses, and modes of administration, the committee decided to include only those with the approved doses and modes of administration.

For real-world data, the committee included only studies with good quality evidence, classified as Level II-III. Some relevant unpublished local data would also be considered for the review to obtain local context. The entire process was reviewed manually.

Search strategy

Inclusion & exclusion criteria for the consensus

The inclusion criteria incorporated studies published from 2006 to March 2025, focusing on adults (≥18 years) with MS. The exclusion criteria included any conference abstracts and studies with limited information.

The process of study selection and characteristics of the excluded studies were documented in a flow chart according to the PRISMA guidelines (Figure III). The PICO (Population, Intervention, Comparison, Outcome) framework (Table II) and search terms (Table III) were developed.

The search strategy was performed using relevant keywords related to the questions developed, utilizing specific databases from 2006 to 2025 March. The studies included should contain the details such as design, clinical setting, trial population or subgroup, MS type, demographic details, type of intervention, subgroup details, length and description of participant follow-up, data analysis, outcomes, DMTs used and outcome measures.

To ensure an evidence-based and reproducible process, full texts were screened based on standard inclusion and exclusion criteria by the two authors of the scientific committee.

Other Data Sources

Where necessary, the consensus statement referenced global guidelines from various health systems, utilizing updated data adapted to the local country-wide setting [1, 23,25, 26,27,28]. In the past, local guidelines and neurologists had always referenced other regional publications on MS management such as the AAN, ECTRIMS, EAN, NICE, British Association of Neurologists, MENACTRIMS, and recommendations by the FDA on new MS drugs approvals. In the current revision, the panel also considered updated versions of these guidelines adapted to the current setting [1,23,25, 26,27,28,29].

Table II: PICO framework.

P	Population	Patients with Progressive Multiple
I	Intervention	Disease-Modifying Therapies (DMTs)
C	Comparison	No Treatment
O	Outcome	Good Prognosis, Slow Disease Progression

Table III: MeSH terms.

No	Finalised list of questions to be addressed in the consensus	MeSH Terms
1	Should MS patients be treated as early as possible?	(("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) AND "early"[All Fields])
2	Should patients with RIS be treated with DMTs?	((((("radiological"[All Fields] OR "radiologically"[All Fields] OR "radiology"[MeSH Terms] OR "radiology"[All Fields] OR "radiologic"[All Fields]) AND ("isolate"[All Fields] OR "isolate s"[All Fields] OR "isolated"[All Fields] OR "isolates"[All Fields] OR "isolating"[All Fields] OR "isolation and purification"[MeSH Subheading] OR ("isolation"[All Fields] AND "purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]) AND ("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "syndrome"[MeSH Terms] OR "syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields])) OR ("rev int stud"[Journal] OR "ris"[All Fields])) AND "multiple sclerosis/therapy"[MeSH Terms])
3	Should patients with CIS be treated with DMTs?	(((("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields]) AND "clinicllly"[All Fields] AND ("isolate"[All Fields] OR "isolate s"[All Fields] OR "isolated"[All Fields] OR "isolates"[All Fields] OR "isolating"[All Fields] OR "isolation and purification"[MeSH Subheading] OR ("isolation"[All Fields] AND "purification"[All Fields]) OR "isolation and purification"[All Fields] OR "isolation"[All Fields] OR "isolations"[All Fields]) AND ("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "syndrome"[MeSH Terms] OR "syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields])) OR "DMT"[All Fields])
4	Which DMTs should be started in active RRMS?	(("multiple sclerosis, relapsing remitting"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields] AND "relapsing remitting"[All Fields]) OR "relapsing-remitting multiple sclerosis"[All Fields] OR ("relapsing"[All Fields] AND "remitting"[All Fields] AND "multiple"[All Fields] AND "sclerosis"[All Fields]) OR "relapsing remitting multiple sclerosis"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]))
5	Which DMTs should be started in highly active RRMS?	(("Highly Active Relapsing-Remitting Multiple Sclerosis"[All Fields] OR "Highly Active RRMS"[All Fields]) AND ("multiple sclerosis/drug therapy"[MeSH Terms] OR "Immunotherapy"[MeSH Terms] AND ("Disease Progression"[MeSH Terms] OR "Treatment Outcome"[MeSH Terms]))
6	Which DMTs should be started in fulminant/aggressive MS?	(("Fulminant Multiple Sclerosis"[All Fields] OR "Aggressive Multiple Sclerosis"[All Fields]) AND ("multiple sclerosis/drug therapy"[MeSH Terms] OR "Immunotherapy"[MeSH Terms] OR "Immunosuppressive Agents"[MeSH Terms]) AND ("Disease Progression"[MeSH Terms] OR "Treatment Outcome"[MeSH Terms]))
7	Which DMTs should be started in progressive MS?	(("Progressive Multiple Sclerosis"[All Fields] OR "Primary Progressive Multiple Sclerosis"[All Fields] OR "Secondary Progressive Multiple Sclerosis"[All Fields]) AND ("multiple sclerosis/drug therapy"[MeSH Terms] OR "Immunotherapy"[MeSH Terms] OR "Immunosuppressive Agents"[MeSH Terms]) AND ("Disease Progression"[MeSH Terms] OR "Treatment Outcome"[MeSH Terms]))

Continued Table III*: MeSH terms.

No	Finalised list of questions to be addressed in the consensus	MeSH Terms
8	What is the definition of treatment failure?	(("Treatment Failure"[MeSH Terms] OR "Therapeutic Failure"[All Fields]) AND ("Multiple Sclerosis"[MeSH Terms] OR "Disease Progression"[MeSH Terms]) AND ("Treatment Outcome"[MeSH Terms] OR "Drug Resistance"[MeSH Terms]))
9	How should treatment failure/breakthrough disease be managed?	(("Treatment Failure"[MeSH Terms] OR "Breakthrough Disease"[All Fields]) AND "Multiple Sclerosis"[MeSH Terms] AND ("Disease Management"[MeSH Terms] OR "Drug Therapy"[MeSH Terms] OR "Immunotherapy"[MeSH Terms] OR "Treatment Outcome"[MeSH Terms]))
10	When should DMTs be stopped in patients with MS?	("Multiple Sclerosis"[MeSH Terms] AND ("Disease-Modifying Therapies"[All Fields] OR "DMT discontinuation"[All Fields] OR "Treatment Withdrawal"[All Fields]) AND ("Treatment Outcome"[MeSH Terms] OR "Disease Progression"[MeSH Terms] OR "Risk Assessment"[MeSH Terms]))
11	How should patients on DMTs be monitored?	(("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) AND "DMT"[All Fields] AND ("monitor"[All Fields] OR "monitor s"[All Fields] OR "monitorable"[All Fields] OR "monitored"[All Fields] OR "monitoring"[All Fields] OR "monitoring s"[All Fields] OR "monitorings"[All Fields] OR "monitorization"[All Fields] OR "monitorize"[All Fields] OR "monitorized"[All Fields] OR "monitors"[All Fields]))
12	What is the effect of DMTs on cognition in MS?	(("Multiple Sclerosis"[MeSH] AND ("Disease-Modifying Therapies"[MeSH] AND ("Cognitive Dysfunction"[MeSH] OR "Cognition Disorders"[MeSH] AND ((y_10[Filter]) AND (ffrft[Filter]) AND (fha[Filter]) AND (clinicaltrial[Filter] OR meta-analysis [Filter] OR randomizedcontrolledtrial[Filter] OR review [Filter] OR systematicreview[Filter]) AND (fft[Filter]))))
13	How/when should MS patients on DMTs be counselled for pregnancy and breastfeeding?	(("Multiple Sclerosis"[MeSH] AND ("Disease-Modifying Therapies"[MeSH] AND ("Pregnancy"[MeSH] OR "Pregnancy Counseling"[MeSH] OR "Breast Feeding"[MeSH] AND ("Risk Assessment"[MeSH] OR "Treatment Outcome"[MeSH])
14	Which DMTs are considered safe in pregnancy and breastfeeding?	((((((("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])) OR ("breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields])) AND "DMT"[All Fields]) OR ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields])) AND "loattrfree full text"[Filter] AND "hasabstract"[All Fields] AND ("clinical trial"[Publication Type] OR "meta-analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Filter]) AND "loattrfull text"[Filter]) AND "loattrfree full text"[Filter] AND "hasabstract"[All Fields] AND ("clinical trial"[Publication Type] OR "meta-analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Filter]) AND "loattrfull text"[Filter]) AND "SAFE"[All Fields])

*All search strategies were limited to published articles within the last 10 years, involving human participants, including clinical trial, randomized controlled trials, meta-analyses, systematic reviews or narrative reviews.

RESULTS AND DISCUSSION

Through this iterative process, the first stage—finalizing the key clinical questions—has been completed. The second stage, which involves developing the recommendation statements, is currently in progress.

A preliminary draft of the publication is expected to be available for internal review by April 2025, with the final version anticipated between May and June 2025. This final document will be subject to evaluation by an independent external review panel comprising both local and international experts in multiple sclerosis.

The finalized protocol will be published in a peer-reviewed journal and submitted to the Ministry of Health's Health Technology Assessment (HTA) unit for publication and nationwide dissemination, accompanied by ECHO training sessions across Malaysia.

The findings will also be presented at the Malaysian Society of Neurosciences conference in July 2025. A nationwide one-year post-publication audit will be conducted to monitor the implementation and adoption of the consensus. This audit will examine the use of the consensus in secondary, tertiary, and quaternary care centers.

CONCLUSION

It is anticipated that this comprehensive process will result in a final document that not only supports and guides clinicians in the management of multiple sclerosis, but also serves as a valuable resource for students, patients, and allied healthcare professionals.

ETHICAL CONSIDERATIONS

Not applicable. This study did not involve human subjects, patient data, or clinical interventions.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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MALAYSIAN Journal of Pharmacy

Original Research Article

Retrospective Study on the Tinea Imbricata Treatment Among the Bateq Subtribe in Peninsular Malaysia

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ABSTRACT

Background: Tinea imbricata (TI) is a chronic and recurrent superficial fungal infection primarily affecting indigenous populations in tropical rainforest regions. Its high prevalence in these communities is attributed to geographical isolation, poor socioeconomic conditions, and limited access to healthcare. The persistent nature of TI and the challenges in effective antifungal treatment contribute to a significant health burden, necessitating a comprehensive review of current therapeutic strategies. **Objective:** This study primarily aimed to evaluate the treatment outcomes of TI in the Bateq subtribe. Specifically, it sought to investigate the clinico-demographic characteristics, compare clinical outcomes between topical antifungal monotherapy and combined oral/topical antifungal therapy, and identify factors influencing antifungal treatment success. **Methods:** This retrospective study utilized universal sampling due to the limited number of patients. All indigenous individuals diagnosed with TI between July and December 2023 were included. Data were extracted from medical records, reviewed, and recorded in a clinical research form. Clinical examinations, including infected body surface area (BSA) and lesion diameter measurements, were conducted before and after treatment. Treatment modalities were evaluated for their effectiveness in reducing disease burden. **Results:** Both terbinafine gel alone and combination therapy (terbinafine gel + oral griseofulvin) significantly reduced lesion size ($p < 0.05$). However, no statistically significant difference was observed between the two treatment groups in terms of lesion diameter reduction ($p = 0.627$) and BSA reduction ($p = 0.392$), indicating comparable efficacy. Additionally, neither gender ($p = 0.479$) nor the presence of side effects ($p = 0.196$) significantly influenced treatment outcomes. **Conclusion:** This study demonstrates the effectiveness of terbinafine gel, both alone and in combination with oral griseofulvin, in reducing lesion size in TI patients from the Bateq subtribe. No significant difference was found between the two treatment approaches, suggesting that terbinafine gel alone is a viable and equally effective alternative. Given its comparable efficacy and better patient compliance, terbinafine gel monotherapy may serve as a more practical and accessible treatment option for this population.

INTRODUCTION

Indigenous people in Malaysia make up only 0.6 percent of the total Malaysian population which is 209, 575. These indigenous communities face a higher risk of exposure to various skin diseases due to their traditional practices, extreme living conditions and poverty. In fact a study found that 9.1% of 550 aborigines had Tinea imbricata (TI) [10]. This research focuses on patients diagnosed with TI, a subtribe of the Bateq community, residing in Jerantut and Kuala Lipis, Pahang. This disease only happens among Bateq subtribe. The most recent case study showed that this disease still persists among indigenous communities, particularly among isolated subtribes, such as the Bateq subtribe in Peninsular Malaysia [1].

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Tinea Imbricata (TI)

TI is a chronic superficial mycosis primarily caused by *Trichophyton Concentricum (T. Concentricum)*, and it results from close contact with the spores and filaments. It primarily affects individuals living in primitive and isolated areas in developing countries and is rarely seen in developed countries, particularly in tropical regions such as Southeast Asia, Oceania, and parts of Central and South America. [1]. The disease is rarely seen in developed countries due to better hygiene, access to healthcare, and living conditions. Its geographic restriction is closely linked to factors like high humidity, poverty, and limited access to medical treatment. This skin disease is frequently found in rural areas with poor hygiene, high atmospheric temperatures and high humidity. Malnutrition, genetic, immunological factors, and both autosomal recessive and dominant inheritance have been suggested as contributing to increased susceptibility rates [10].

The control and management of TI among indigenous communities can indeed be challenging due to various factors such as their remote locations, certain traditional practices and poor nutritional status [1]. The most recent case study showed that this disease still persists among the indigenous communities [5], particularly among isolated subtribes, such as the Bateq subtribe in Peninsular Malaysia [6]. These communities often reside in isolated areas with limited access to healthcare facilities, which make it difficult to provide timely medical intervention and treatment. Additionally, traditional practices and beliefs may hinder the adoption of modern treatments, leading to the persistence of the disease. Severe malnutrition can also weaken the immune system, making individuals more susceptible to infections like TI. To address these challenges, a comprehensive approach is required. This includes raising awareness about TI, promoting hygiene practices, improving nutrition and overall living conditions and collaborating with community leaders to overcome cultural barriers.

TI is commonly reported among the indigenous population. In Malaysia, there are no established statistics on its prevalence. However, outbreaks have been reported from time to time. Unfortunately, some individuals have claimed to have had the skin disease for many years, going untreated due to poor recognition of the condition by attending healthcare physician and a lack of compliance with medications and follow-up appointments. Therefore, it is essential for healthcare practitioners to be familiar with common skin conditions among the indigenous population to ensure accurate diagnosis and appropriate treatment [4].

According to Yi Xian Er et al, one of the most intriguing tinea infections is TI, which is caused by *Trichophyton Concentricum* [1]. The disease is well-known for its unique circular lesions and flaking of the skin. Common symptoms include pruritus, dry skin, and scaling. The case definition used for TI includes the presence of erythematous pruritic papules or patches that typically appear on the upper extremities first, followed by the trunk, and lower extremities. These lesions then progress into larger and generalised plaques that display lamellar, concentric and annular patterns [2]. The characteristic concentric rings of scaling are formed by desquamating skin with each ring containing a circle of hypopigmented skin surrounded by normally pigmented skin. Importantly, the rings of desquamation do not cross each other. If left untreated, the condition can evolve into larger and more extensive scaling [10].

One of the unique characteristics of this disease is its limited occurence, predominantly observed in indigenous communities residing in three specific geographical regions: Central and South America, Oceania, and Southeast Asia [2]. The prevalence of this disease appears to be significantly higher within isolated and primitive societies, it disproportionately affects indigenous populations with limited access to healthcare and poor living conditions [3]. A contributing factor to this trend is the low awareness regarding treatment and hygiene practices among populations. Transmission of TI primarily occurs through close contact with an infected person. Autoinfection by dermatophytes elsewhere in the body is also possible. [7]. Among these populations, TI presents a significant health burden, leading to discomfort, disfigurement, and social stigma.

Choice of Treatment

The standard practice for treating TI worldwide, including in countries like the Philippines, Thailand, Papua New Guinea and others typically involves the use of griseofulvin [1]. Griseofulvin has been the primary treatment for TI for decades [13].

Data from outcomes studies indicate that several classes of antifungal medications effectively treat TI. The treatment of TI in Malaysia involves the use of griseofulvin or terbinafine tablets, taken for a total of 3–4 weeks. The dosage varies depending on the patient's age. It is important to note that TI does not respond well to standard triazole antifungal drugs, such as itraconazole and ketoconazole [1]. A randomized clinical trial by Wingfield AB et al. involving 59 patients with TI demonstrated the efficacy of both drugs without adverse events. Terbinafine offers longer efficacy and the advantage once daily dosing [9]. Oral Griseofulvin produces a rapid response, with brownish pigmented patches appearing within seven days and negative scraping within ten days. Terbinafine tablets have similar efficacy but are associated with a significantly lower relapse rate compared to itraconazole after thirteen weeks of follow-up [10]. However, terbinafine tablets are not available in our facility. Table I presents the dosage of griseofulvin tablets used in the treatment of TI. The adult dosage is 500 mg twice daily (BD), while the recommended pediatric dosage is 10–20 mg/kg/day, administered as a single dose or in two divided doses [1].

The local standard of care for treating TI typically involves oral griseofulvin or a combination of oral and topical antifungals. The use of additional topical antifungal treatment is dependent on local availability. Although the combination of oral and

Table I Dosage of griseofulvin in the treatment of TI [1].

Drugs	Category	Dosage	Note
Griseofulvin	Adult	0.500 - 1.000g/day	Dosage varies depending on the total area of the lesions
	Paediatrics	0.125 - 0.250g/day	14-23kg
		0.250 - 0.500g/day	>23kg

topical antifungal therapy is commonly used, it is still considered as off-label treatment. The addition of topical keratolytic agents, such as whitfield's ointment, may increase the cure rate [5].

The challenges in managing fungal skin infections are further complicated by the potential side effects of medications. Common side effects of griseofulvin tablets and terbinafine gel include rash, headache, diarrhea, nausea, or vomiting [15]. There are measures that can be taken to help alleviate these effects. In the case of a rash, it is advisable to avoid clothing that irritates the skin and consider taking an antihistamine. If the rash is accompanied by itchiness, gently pat or tap the affected area instead of scratching. Resting and consuming ample fluids can provide relief for headaches and diarrhea [14]. Terbinafine 1% gel is a formulation that contains an alcohol solvent. Upon application to the skin, it quickly evaporates, leaving a smooth, nearly invisible film that delivers terbinafine to the affected area. After a single application, high levels of terbinafine 1% gel penetrate the stratum corneum, where dermatophytes are located. Fungicidal levels of terbinafine remain in the skin for up to 13 days.

Terbinafine is among the most commonly used antifungal agents for treating dermatophyte infections of the skin and nails. It has shown great success due to its excellent penetration at the site of infection and sustained fungicidal activity even after therapy discontinuation [17].

While there have been studies documenting the efficacy of both oral and combined oral topical therapies, there is a lack of local research analyzing the differences in efficacy and compliance. Study reported previously for terbinafine oral not topical. If we do not take action against this disease now, it is not impossible for it to spread throughout the entire indigenous community. This is the main purpose of this study. Research specifically focused on this topic has not yet been conducted. However, the use of terbinafine gel is a standard treatment utilized by the dermatology team in Pahang to treat TI.

To the best of our knowledge, no other nationwide or state-wise analysis has been conducted on the combination treatment of TI using both topical and oral agents.The lack of research emphasizes the need for a more comprehensive approach to treating this disease. Therefore, the aim of this study is to determine the treatment outcomes for TI in the bateq subtribe. The findings of the study will provide valuable insights into how this specific population responds to treatments and tailor interventions accordingly.

Rationale of the study

The significance of this research lies in its potential to enhance the quality of life for indigenous communities. Several factors contribute to their suboptimal health conditions, including limited education, language barriers in understanding Malay, inherited superstitions, and restricted access to health information and medical check-ups [9]. Through this clinical research, we aim to identify the most effective treatment for TI among indigenous populations, ensuring that appropriate and efficient therapy reaches these communities.

MATERIAL AND METHOD

Study setting and sample population

This study was conducted from July to October 2023 within eight villages situated in Jerantut and Kuala Lipis, Pahang, Peninsular Malaysia. These villages, namely Becah Kelubi, Sungai Garam, and Sungai Sekin in Kuala Lipis, and Jeram Dedari, Kampung Ulu Sat, Sungai Tekal, Sungai Tiang and Sungai Keniam in Jerantut are inhabited by 1,091 indigenous individuals. These villages have a climate that is characterized by extreme tropical humidity throughout the year, with a mean annual temperature of 25.2 °C (77.36 °F) and mean annual precipitation of approximately 3999 mm [20]. Findings from this study indicate that all patients with TI resided in hot, humid, riverine areas and were characterized by low socioeconomic status, limited education, and poor personal and environmental hygiene. These factors may contribute to both the development and persistence of the condition. The hot and humid climate creates an optimal environment for fungal proliferation, increasing the risk of exposure to fungal spores. Additionally, proximity to rivers or bodies of water may further elevate the likelihood of fungal exposure. TI is endemic in remote, tropical regions with hot and humid climates [11]. The study was ethically approved with registry NMRR ID-24-03945-6K0 (IIR).

Study type and design

Based on Figure I, patient grouping was conducted retrospectively based on the type of treatment received, as treatment assignment was determined by medication availability during mobile clinic visits rather than through randomization.

This study employs a retrospective study using convenient sampling method. A universal sampling method was used by including all indigenous patients who had been diagnosed with TI among the Bateq subtribe in Jerantut and Kuala Lipis from July 2023 to December 2023. Fifty (50) patients diagnosed with TI were selected from this population.

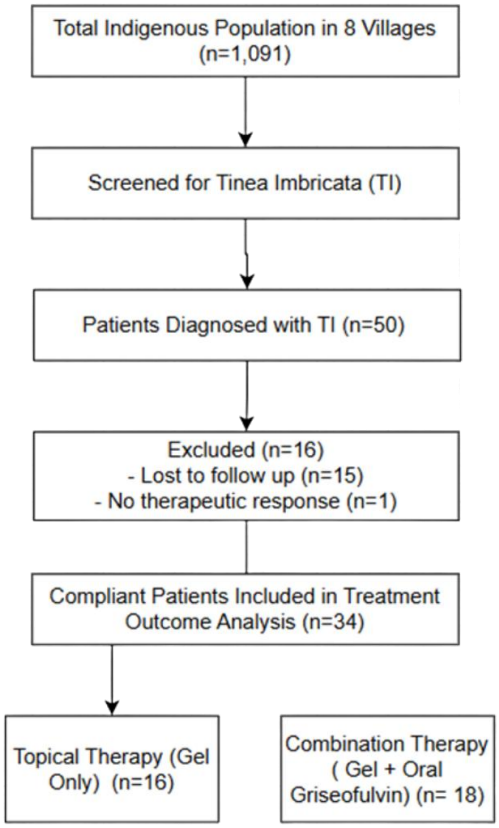

Figure I: Categorization of Treatment Group

Data were extracted from existing medical records available from the records unit. The collected data were reviewed and entered into a clinical research form (CRF) attached to the proposal. Clinical examinations and measurement of the part infected BSA and the diameter of the infected were carried out before and after treatment. Patient case notes entered into a CRF.

This research received approval from the Director General of the Department of Orang Asli Development (JAKOA). Approval to collect the data was provided by the Family Medicine Specialist at the District Health Offices in Jerantut and Kuala Lipis. This research was conducted by the health teams from Hospital Orang Asli Gombak (HOAG), the Dermatologist in Pahang, District Health Offices in Jerantut and Kuala Lipis and the Faculty of Pharmacy at Universiti Teknologi MARA (UiTM). The diagnosis of TI is based on the clinical evaluation and training provided by a consultant dermatologist to local practicing doctors. The dermatologist explained how to differentiate TI from other types of tinea such as tinea corporis and tinea versicolor and provided guidance on the appropriate treatment and techniques for applying terbinafine gel.

The Slovene's Formula was used to estimate the sample size required to determine the prevalence of TI. Based on this calculation, the target sample size is approximately 15 patients (with an additional 5% buffer to account for potential missing information or non-respondents) [32].
The formula used is:

$$Sample\ size\ (n) = \frac{N}{1 + Ne^2}$$

Where N = the target population,
e = the margin of error (5%),
n = the estimated sample size.

In this case, the target population is assumed to be 20 patients, based on previous studies that have reported a similar prevalence of TI among indigenous communities. These studies suggest that the disease remains persistent in these communities [18]. To achieve the maximum power with a minimum of 20 patients, given the limited number of patients diagnosed with TI, we have included all 50 available samples in the study.

Inclusion Criteria and Exclusion Criteria

The inclusion criteria for this study comprised all patients who were clinically diagnosed with Tinea Imbricata (TI), belonged to the Bateq subtribe residing in Jerantut and Kuala Lipis, Pahang, and had not received any prior treatment for their TI. Patients were excluded if they were diagnosed with other superficial cutaneous fungal infections such as tinea corporis or pityriasis versicolor. Additionally, children below two years of age were excluded due to the contraindication of benzyl alcohol, an ingredient in terbinafine gel, in this age group. Pregnant women were also excluded, as griseofulvin is classified as a Category X drug and is contraindicated during pregnancy.

Statistical analysis

All data were analyzed using IBM SPSS Statistics version 28.0. Descriptive statistics were employed to summarize the data, with categorical variables presented as frequency and percentage (%), while continuous variables were expressed as mean ± standard error of the mean (SEM) where appropriate. The socio-demographic characteristics of patients were analyzed using descriptive statistics, including frequency and percentage distributions. Chi-square analysis was performed to assess factors influencing treatment effectiveness and medication adherence. Fisher's exact test was used where applicable to compare categorical variables between the two treatment groups. To evaluate treatment outcomes, an independent samples t-test was conducted to determine differences in mean lesion diameter reduction and affected BSA between the treatment groups. All statistical analyses were performed at a significance level of $p < 0.05$.

Table II: Socio-Demographic Profile and Baseline Distribution of Affected Body Areas Among 34 Compliance Patients Undergoing Terbinafine Gel Monotherapy and Combination Therapy (Terbinafine Gel + Oral Griseofulvin)

Demographic Profile	Combination Treatment [a] n = 18 (%)	Topical Treatment [b] n = 16 (%)	P[c] or P[f]	All n = 34
Gender				
Male	10	7	0.084[c]	17
Female	8	9		17
Age				
Paeds (2-12 years old)	4	5	0.462[f]	9
Adults (above 12 years old)	14	11		25
Village				
Bechah Kalubi	4	3	0.001[f]	7
Jeram Dedari	4	0		4
Sg Tekal	1	1		2
Sg Garam	7	1		8
Sg Keniam	0	0		0
Sg Sekin	1	4		5
Sg Tiang	1	0		1
Ulu Sat/Bukit Gam	0	7		7
Employment Status				
Student	6	4	0.379[f]	10
Farmer	10	5		15
Farmer & Fisherman	2	1		3
Housewife	1	5		6
Bathing frequency				
Once daily	2	6	0.097[f]	8
Twice daily	8	3		11
≥ Three times daily	8	7		15
Family members having the same infection				
Yes	11	8	0.79[c]	19
No	7	8		15
TI disrupting daily life				
Yes	18	16		34
No	0	0		0
Average baseline of affected body diameter (cm^2) (pre-treatment)	1,305.65 ±1,109.71	1,409.04 ± 1,725.17	0.834[d]	
Average baseline of treated body diameter (cm^2) (post treatment)	0.26 ± 1.15	17 ± 39.41	0.072[d]	

[a] Patients received 1% (w/w) terbinafine gel

[b] Patients received combination therapy of 1% (w/w) terbinafine gel and oral griseofulvin.

[c] Chi-squared test used unless stated otherwise

[d] Independent samples t-test used.

[f] Fisher's Exact Test

RESULT

Prevalence of TI

Among the 1,091 individuals of indigenous across eight villages, 50 cases were identified, yielding an overall prevalence of 4.58%. The gender distribution of affected individuals was equal, with 25 males (4.47%) and 25 females (4.70%). The sample was evenly distributed by gender, with equal representation of males and females (50% each), resulting in a male-to-female ratio of 1:1, indicating an equal prevalence of the condition across both genders.

The highest prevalence was observed in Ulu Sat (9.60%), followed by Jeram Dedari (9.30%), indicating a significantly higher burden of TI in these villages. Comparatively, the lowest prevalence rates were recorded in Sungai Tekal (1.11%) and Sungai Tiang (1.03%). Notably, the prevalence in Ulu Sat was significantly higher, approximately twice that of Sungai Keniam (3.38%) and Bechah Kalubi (4.57%). Additionally, Sungai Garam (8.33%) and Sungai Sekin (7.30%) ranked as the third and fourth highest, respectively. These findings highlight substantial geographical variation in TI prevalence, suggesting potential environmental or socio-behavioral factors influencing disease distribution (Table II).

Clinical Findings for TI Diagnosis

The distribution of affected body regions varied among patients. The torso was the most frequently affected site (36 cases; 41.86%), followed by both upper and lower limbs (24 cases; 27.91%). The lower limb (13 cases; 14.65%) and upper limb (12 cases; 13.95%) were also commonly involved. In contrast, widespread lesions involving the entire body (5 cases; 5.81%) and facial involvement (5 cases; 5.81%) were less prevalent. These findings suggest that the torso is the most commonly affected area, which may indicate a possible pattern of disease spread or exposure in the studied population. The lesions, often pruritic, primarily occur on the torso and limbs but can develop on any part of the body [30]. This distribution pattern suggests a tendency for the infection to localize primarily on the central body and extremities, with less frequent spread to the face or full body, which may reflect patterns of exposure, clothing habits, or scratching behavior in the studied population.
All patients (100%) exhibited skin involvement, with varying clinical features as shown in Figure II, including concentric, lamellar, lichenified, plaque-like, annular, as well as hypopigmentation and hyperpigmentation.

Treatment Modalities of TI

Following the classification of patients into two treatment modalities, the first group (n=25) received terbinafine gel alone, while the second group (n=25) underwent combination therapy involving terbinafine gel and oral griseofulvin for approximately one month. In terms of adherence to treatment, the majority of respondents (34 patients;68%) complied with the prescribed regimen and were included in the efficacy analysis, whereas 15 (30%) were lost to follow-up, primarily due to their nomadic lifestyle. A single patient (1; 2%) exhibited compliance but did not demonstrate a therapeutic skin response. This could be attributed to possible antifungal resistance or reinfection due to environmental or household exposure. Further investigation, such as laboratory confirmation (e.g., skin scraping or culture) and evaluation of adherence technique may help clarify the cause in future studies.

Participants were categorized into paediatric (2–12 years old) and adult (above 12 years old) groups, with the majority of respondents (35 patients; 70%) identified as adults and 15 (30%) as paediatric. Based on the Health Management Information System (HMIS) of the Ministry of Health Malaysia (MOH), adults are aged above 12 years, while children are aged 1-12 years [23]. In this study, children aged 2–12 years were selected based on the product leaflet recommendation, which states that terbinafine gel contains benzyl alcohol and should be avoided in children under two years of age. Another distinct challenge encountered with this population is the estimation of chronological age. While individuals were generally aware of their relative age (e.g., older than one person but younger than another), they were unable to provide an exact numerical age.
A comparative analysis of the two treatment groups among the 34 compliant patients revealed no significant differences ($p > 0.05$) in most socio-demographic characteristics, indicating that the baseline patient profiles were well-balanced, thereby minimizing potential confounding factors in treatment outcomes. However, one significant difference ($p < 0.05$) was

Figure II: Clinical features of TI patients: - (A) Hyperpigmented, plaque-like lesions with lichenification. (B) Hypopigmented lesion with scaling and plaque formation. (C) Concentric lamellar scaling (D-F) Prominent lamellar scaling affecting the back, auricular region, and lower limbs, consistent with chronic dermatophyte infection.

observed in the distribution of patients across villages. All patients from Kampung Ulu Sat (n = 7) received terbinafine gel monotherapy, whereas those from Sungai Garam (n = 8), Bechah Kalubi (n = 7), Sungai Sekin (n = 5), Jeram Dedari (n = 4), Sungai Tekal (n = 2), and Sungai Tiang (n = 1) received combination therapy with terbinafine gel and oral griseofulvin. Notably, no compliant patients were recorded in Sungai Keniam (Table II). The choice of treatment by the medical officer depended on the availability of medications during the mobile clinic visits and was not based on the severity of the disease.

In terms of occupational distribution, farming emerged as the predominant occupation, with 21 (42%) respondents engaged in agricultural activities. Students constituted 16 (32%) of the sample, while housewives (8; 16%), farmers and fishermen (4; 8%), and a single toddler (2%) represented the remaining occupations. The majority of patients in both groups reported bathing more than three times daily. The similar bathing habits in both groups further support the notion that hygiene-related factors were not a major source of bias in treatment outcomes. Most affected individuals bathe in rivers without the use of soap and change into new clothes multiple times daily. However, their clothing is washed without detergent and retains a slight odor. Insufficient personal hygiene and inadequate sanitation within living environments may further increase susceptibility to fungal infections and facilitate the spread of fungi.

Despite differences in treatment approaches, no significant disparity ($p > 0.05$) was observed in the average baseline affected body surface area between the single therapy group (1,409.04 ± 1,725.17 cm²) and the combination therapy group (1,305.65 ± 1,109.71 cm²). There is no strong evidence to suggest that combination therapy (terbinafine gel + oral antifungal) is significantly better than terbinafine gel alone in reducing post-treatment lesion diameter. From these findings, we can conclude that both treatment groups were comparable in terms of their baseline affected body diameter and surface area before treatment initiation. The absence of a statistically significant difference ($p = 0.834$) suggests that any observed treatment outcomes are unlikely to be influenced by initial disease severity, thereby reducing potential confounding factors. Additionally, the high standard deviations, particularly in the gel-only group, indicate substantial variability in disease presentation among patients.

Effectiveness of Different Treatment Modalities in Managing TI Lesions

The analysis of treatment outcomes was conducted exclusively on the 34 patients who demonstrated compliance, rather than the total of 50 patients, to ensure an accurate assessment of the true therapeutic efficacy. All data were systematically categorized into groups to facilitate a more structured and comprehensive analysis, ensuring clarity in interpretation and statistical evaluation. Among the 34 patients who adhered to the treatment protocol, the first group (n=18) received a combination therapy consisting of topical terbinafine gel and oral griseofulvin, while the second group (n=16) was treated with topical terbinafine gel alone for approximately one month. A total of 15 patients were excluded from the study due to loss to follow-up or relocation during subsequent visits, whereas one patient exhibited no response to terbinafine gel.

Figure III. Baseline presentation of TI, characterized by a pigmented lamellar pattern with large, coarse scales. The patient achieved complete resolution following a four-week combination treatment of oral griseofulvin (500 mg twice daily) and topical terbinafine gel. Adherence to both oral and topical antifungal therapies resulted in full recovery of the skin. (A–B) Abdominal region, (C–D) Lower limbs, (E–F) Upper limbs. This case represented the most severe presentation, and although the scaly lesions have completely resolved, residual post-inflammatory hyperpigmentation remains.

A statistically significant difference ($p < 0.05$) was observed between the two treatment groups, indicating that both terbinafine gel alone and its combination with oral griseofulvin had a substantial impact on the treatment outcome of TI.

The significance of differences between pre-treatment and post-treatment lesion diameters

The Wilcoxon Signed-Rank Test was performed to evaluate the median differences in lesion diameters before and after treatment among the 34 compliant patients. The results demonstrated a statistically significant reduction in lesion size ($p < 0.001$), leading to the rejection of the null hypothesis. This finding indicates a significant difference between pre-treatment and post-treatment lesion diameters, suggesting that treatment for TI with either terbinafine gel alone or in combination with oral griseofulvin had a substantial impact on lesion size reduction. The analysis combines both treatment groups (combination therapy and topical therapy alone) to determine the overall effectiveness of the prescribed treatments in achieving a cure for TI. The statistical significance of these

findings is further illustrated in Figure III (combination therapy) and Figure IV (topical therapy alone).

Improvement of TI (Reduction of Diameter) among 34 Compliant Patients

The therapeutic efficacy of two treatment modalities—combination therapy (gel and oral medication) and gel-only therapy—was compared in terms of lesion size reduction. The reduction in lesion diameter following treatment for TI was evaluated across three predefined size categories: small (0–500 cm^2), medium (501–1500 cm^2), and large (>1501 cm^2). Among patients who received combination therapy, 26.3% exhibited a small reduction (0–500 cm^2), 42.1% demonstrated a medium reduction (501–1500 cm^2), and 31.6% experienced a large reduction (>1501 cm^2). Conversely, in the gel-only therapy group, 40.0% achieved a small reduction, 26.7% demonstrated a medium reduction, and 33.3% exhibited a large reduction. Statistical analysis using Fisher's exact test yielded a p-value of 0.627, indicating no statistically significant association between treatment type and the extent of lesion diameter reduction. This finding suggests that both treatment modalities, gel-only therapy and combination therapy (gel and oral medication) demonstrate comparable efficacy in reducing lesion size, with no significant difference in treatment outcomes. This suggests that neither treatment is superior to the other in terms of lesion reduction. Given the reluctance of many indigenous patients to take oral medication, topical terbinafine gel alone may be a more acceptable and equally effective alternative for managing TI in this population.

Improvement of TI (Reduction of BSA) among 34 Compliant Patients

The improvement in BSA is categorized into three groups: small (0–25%), medium (26–50%), and large (>51%). Among patients receiving combination therapy, 42.1% experienced a small reduction (0–25%), 31.6% showed a medium reduction (26–50%), and 26.3% achieved a large reduction (>51%). In contrast, patients treated with gel-only therapy demonstrated a higher proportion of small (53.3%) and medium (40.0%) reductions, while only 6.7% exhibited a large reduction (>51%). Statistical analysis using Fisher's exact test ($p = 0.392$) revealed no significant association between treatment type and the extent of BSA reduction. This indicates that both treatment modalities yield comparable outcomes in reducing the affected BSA. Fisher's exact test was utilized due to the fact that 33.3% of expected counts were less than 5, which may violate the assumptions of the chi-square test. Overall, these findings suggest that gel-only therapy may be as effective as combination therapy, particularly in achieving small to moderate BSA reductions.

To determine the contributing factors affecting the outcome of antifungal treatment.

The results indicate that the presence of side effects does not significantly influence lesion diameter reduction (Fisher's Exact Test, $p = 0.196$). Similarly, gender does not show a statistically significant association with lesion diameter reduction (Fisher's Exact Test, $p = 0.479$). These findings suggest that neither side effects nor gender play a crucial role in determining the extent of lesion size reduction following treatment.

Figure IV. The clinical progression of patients with TI following four weeks of treatment with topical terbinafine gel alone. The images depict the before-and-after effects of treatment on different anatomical regions including the upper limb (A-C), lower limbs (D-F) and abdominal region (G-I). Despite patient non-compliance with oral griseofulvin, a significant clinical improvement was observed with terbinafine gel alone.

DISCUSSION

The findings of this study underscore the multifaceted influence of environmental, socio-economic, and cultural factors on the prevalence and persistence of TI within the studied population. With an overall prevalence of 4.58%, the results indicate that TI poses a significant health burden on the affected community. The disease exhibits a notably higher prevalence among isolated and traditional societies [3], a trend largely attributed to limited awareness of treatment options and inadequate hygiene practices within these populations.

The Malaysian government, through the Department of Aboriginal Affairs (Jabatan Kebajikan Hal Ehwal Orang Asli, JAKOA), has implemented initiatives to encourage the Bateq community to transition from a nomadic lifestyle to a more settled existence. These settlement programs provide tools, seeds, rations, and technical support to facilitate agricultural activities, as JAKOA perceives this transition as a beneficial advancement for the community. However, the Bateq often engage in these programs only until the provided rations are depleted or insufficient, typically before the planting cycle is

completed, after which they revert to their nomadic foraging lifestyle. This transient way of life poses challenges for healthcare teams in monitoring the progress of treatment for TI, as consistent follow-up and medical supervision become difficult [24]. Limited access to healthcare services, driven by geographic isolation and low socioeconomic status, may lead to delayed diagnosis and treatment of TI, further exacerbating the disease burden [26].

Terbinafine 1% gel is an alcohol- and water-based formulation that inhibits fungal squalene epoxidase, leading to the accumulation of the squalene, which may exert fungicidal effects through its toxicity at high concentrations. The use of terbinafine gel is approved for the treatment of tinea pedis and tinea corporis [21]. Additionally, terbinafine gel is indicated for the management of skin infections caused by dermatophytes, molds, and Candida species [22]. While terbinafine gel is commonly used in the treatment of TI in Pahang, there is currently no available data or formal study documenting its efficacy and outcomes in this specific population.

Griseofulvin is a fungistatic antifungal agent indicated for the treatment of fungal infections caused by *Epidermophyton*, *Microsporum*, and *Trichophyton* species. It inhibits fungal cell mitosis by interfering with the function of microtubules. Griseofulvin is rapidly excreted from the body, necessitating a prolonged course of treatment for weeks to months to achieve therapeutic efficacy. In Malaysia, there are currently six (6) griseofulvin-containing tablet products registered with the Drug Control Authority (DCA) [25]. Griseofulvin is generally well-tolerated, with adverse effects primarily limited to gastrointestinal disturbances such as nausea, vomiting, and diarrhea, along with headaches and allergic reactions [15]. In contrast, no significant adverse effects were reported during terbinafine gel treatment. However, one patient experienced nausea and gastrointestinal discomfort after taking oral griseofulvin and subsequently discontinued its use, opting to continue treatment with terbinafine gel alone.

The significant reduction in affected body surface area ($p < 0.001$) in both treatment groups highlights the efficacy of terbinafine gel, both as a monotherapy and in combination with oral griseofulvin, in the management of TI. A statistically significant difference ($p < 0.05$) was observed between pre-treatment and post-treatment lesion diameters, indicating a substantial therapeutic impact of both treatment modalities. However, statistical analysis using Fisher's exact test ($p = 0.627$) revealed no significant association between treatment type and the extent of lesion diameter reduction, suggesting that terbinafine gel alone and its combination with oral griseofulvin demonstrate comparable efficacy. Similarly, Fisher's exact test ($p = 0.392$) indicated no significant association between treatment type and affected BSA reduction, further supporting the comparable effectiveness of both therapies. Given the reluctance of many indigenous patients to take oral medications due to concerns about side effects and difficulty swallowing, topical terbinafine gel emerges as a more acceptable and equally effective alternative for treating TI. These findings suggest that terbinafine gel monotherapy may serve as the preferred treatment option, particularly for patients who are apprehensive about systemic antifungal therapy.

After one month, no post-treatment results were obtained in Sungai Keniam and another 15 patients due to patient relocation to another village or non-compliance, primarily influenced by parental refusal of modern medicine. Despite the Malaysian government's financial support for the indigenous in areas such as healthcare, education, and employment, many tribes prioritize preserving their culture and traditional beliefs. This cultural adherence directly influences their health, perceptions of disease, and adherence to medical treatment [31]. Poor adherence to long-term therapies remains a significant barrier to effective healthcare delivery. Aboriginal populations are often perceived as having low adherence rates, with global evidence indicating lower medication compliance among marginalized groups. However, medication non-adherence is not exclusive to this population. Studies suggest that approximately half of the general population with chronic diseases do not take their medications as prescribed. The reasons for medication non-adherence are multifactorial, influenced by various social, cultural, and psychological factors. Notably, beliefs about medicines have been identified as stronger determinants of adherence than socio-demographic or clinical factors [8].

From a pharmacoeconomic perspective, the cost of treatment is comparable between the two modalities. A one-month course of oral griseofulvin for an adult is equivalent in cost to three tubes of terbinafine gel. The total quantity of terbinafine gel required depends on the severity and extent of skin involvement. Consequently, the overall treatment expense for terbinafine gel monotherapy aligns with that of combination therapy.

In the evolving landscape of modern medicine, the rise of resistant superficial dermatophytic infections has become a critical global health concern, particularly affecting antifungal agents such as terbinafine [27] and the azole class of drugs [28]. Notably, certain dermatophyte strains exhibit reduced responsiveness to triazole antifungals, including ketoconazole and itraconazole [29]. A study by Bagra et al. (2024) further demonstrated that terbinafine possesses potent anti-dermatophytic activity, whereas fluconazole exhibited the lowest efficacy [6].

Our findings further substantiate these observations, revealing that clinical isolates of T. concentricum exhibit significant susceptibility to terbinafine ($p<0.001$) with a minimum inhibitory concentration (MIC) of 0.125 µg/ml and a minimum fungicidal concentration (MFC) of 0.250 µg/ml. However, reduced efficacy was observed with griseofulvin (MIC = 8 µg/ml; MFC = 32 µg/ml) and fluconazole (MIC = 32 µg/ml; MFC = 128 µg/ml). Miconazole demonstrated the lowest potency, with a MIC of 64 µg/ml and no observable fungicidal or fungistatic activity even at concentrations up to 128 µg/ml, suggesting potential drug resistance. All patients with TI reported a lack of improvement with miconazole cream and requested not to receive it as part of their treatment. These

findings hold significant implications amid the increasing prevalence of antifungal resistance worldwide. Therefore, the implementation of in vitro susceptibility testing in clinical laboratories is essential for the early detection of resistant strains, enabling informed therapeutic decision-making and more effective antifungal intervention strategies.

CONCLUSION

This study highlights the effectiveness of terbinafine gel, both as a monotherapy and in combination with oral griseofulvin, in managing TI among the Bateq subtribe. The findings suggest that both treatment modalities exhibit comparable efficacy, with no significant difference in lesion size reduction or affected BSA improvement. Given the high adherence challenges associated with oral medication, terbinafine gel monotherapy may serve as a more practical and acceptable treatment option for this population. Additionally, the study underscores the multifaceted factors contributing to the persistence of TI, including environmental conditions, low socioeconomic status, inadequate hygiene, and cultural beliefs. Poor adherence to treatment, influenced by traditional practices and limited healthcare access, remains a significant barrier to disease eradication. Therefore, a holistic approach integrating medical treatment with health education, improved hygiene practices, and culturally sensitive community engagement is essential for long-term disease control. Future research should explore the long-term outcomes of terbinafine gel monotherapy, relapse rates, and potential antifungal resistance. Addressing these gaps will contribute to more effective treatment strategies and better health outcomes for indigenous communities affected by TI.

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Original Research Article

Selective Gas Chromatography Analysis of 5-Fluorouracil from Serum of Cancer Patients after Chemotherapy by Derivatization

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ABSTRACT

Background: 5-Fluorouracil (5-FU) is correlated as a structural derivative of the nucleobase uracil; it is widely used as an anti-cancer drug in chemotherapy treatments. The reliability and accuracy of the quantification of 5-FU in biological fluids is essential for therapeutic monitoring. **Objective:** This study focuses on the development of a simple and selective analytical method for determining drug content in the serum of patients. **Method:** A procedure based on gas chromatography (GC) has been developed for the analysis of 5-FU from deproteinised serum of cancer patients using isobutyl chloroformate (IBCF) as a reagent. GC was performed using a DB-5 column (30 m x 0.32 mm id) connected to flame ionisation detector (FID). GC elution was carried out at a column oven temperature of 130°C for 2 min, followed by a heating rate of 15 °C/min up to 220 ^{0}C, with a flow rate of nitrogen at 2 mL/min., with a 10:1 split ratio. **Results:** At the optimised conditions of derivatization and elution, the nucleobases (uracil, adenine, cytosine, thymine and guanine) were completely separated from 5-FU. The calibration curve for 5-FU was obtained with concentrations ranging from 2-50 µg/mL, with 0.06 µg/mL as the limit of detection (LOD). **Conclusion:** The method was repeatable with a relative standard deviation (RSD) of 2.7% (n=4). The method was used for the estimation of 5-FU from cancer patients' serum after infusion of 250 mg of 5-FU, and the amounts found were 4.6-21.2 µg/mL with an RSD 2.5%.

INTRODUCTION

5-Fluorouracil (5-FU) is a pyrimidine with a fluorine atom attached at position 5 in the ring of uracil (Figure I). It is widely used as an anti-cancer agent against a number of solid tumors, since for more than the last 40 years [1]. It is used as a chemotherapeutic agent in a single dose or multiple doses in combination with other drugs. It imparts anti-neoplastic effects against tumors like breast, head, neck, and gastrointestinal tract with a response rate of 10-30% [2]. After the administration of the drug 5-FU, the injected dose (80%) is degraded rapidly under the action of dihydropyrimidine dehydrogenase (DPD) to 5-fluorouracil-5,6-dihydro (5,6-FUH_2), which is an inactive metabolite [3]. The administration of 5-FU has numerous side effects along with severe hematologic, mucosal and digestive effects, which may be observed even at moderate doses [4]. It is therefore considered important to monitor the concentrations of 5-FU in the blood serum of patients on chemotherapy with 5-FU. Santos et al. [5] reviewed methodologies for the determination of 5-FU in samples of biological and pharmaceutical nature. Pandey et al. [6] reviewed the separation procedures for the selective determination of uracil and 5-fluorouracil. Breda and Baratte [7] reviewed analytical procedures for the assay of 5-FU in biological samples. A number of different procedures were reported for analysis of 5-FU from biological samples, which include chromatographic and non-chromatographic procedures. However, chromatographic procedures were reported frequently; amongst the methods are high pressure liquid chromatography (HPLC) coupled with UV detector [8], HPLC with photodiode detector (PD) for 5-FU [25], hydrophilic interaction liquid chromatography (HILIC) with PD detector [9], LC-MS/MS methods for the assay of uracil, 5,6-FUH_2, 5-FU, and 5-fluoro-5,6-dihydrouracil [10], and LC-MS/MS of 5-FU, and FUH_2 [11]. Fluorometry [12], capillary electrophoresis [13], electroanalytical methods [14], UV photometry [15], and gas chromatography (GC) methods [16] are also reported for the analysis of fluorouracil. GC is also used for the separation and quantitation of 5-FU, together with other chromatographic

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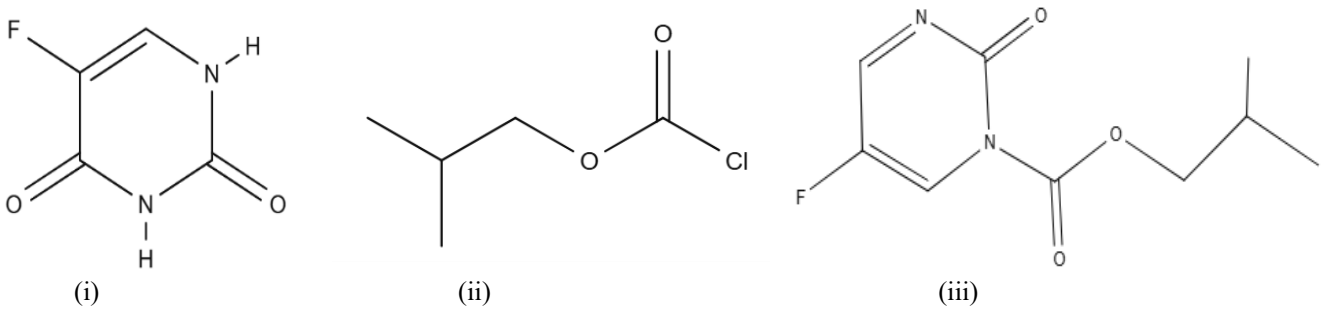

(i) (ii) (iii)

Figure I. Structure of (i) 5-Fluouracil (5-fluoro-1H-pyrimidine-2,4-dione), (ii) isobutyl chloroformate, and (iii) 5-fluoro-1-(isobutoxycarbonyl)-1H-pyrimidine-2,4-dione

techniques, because of its relatively low running cost. However, 5-FU is less volatile and highly soluble in water; therefore, derivatization procedures are generally carried out before its GC determination. The common reagents used for the derivatization are different silanization reagents. Some of the derivatizing reagents are trimethylsilyl (TMS), tert-butyl-trimethylsilyl, N,O-bis(trimethylsilyl)trifluroacetamide [16, 17]; N, N-dimethylacetamide or pentafluorobenzyl bromide [18]. Zonur et al. [19] used hexafluoroacetylacetone as a reagent for the GC assay of 5-FU. Isobutyl chloroformate is used as a derivatizing reagent for the GC assay of primary and secondary amino compounds [20,21]. Brohi et al. [22] reported GC-FID analysis of cytosine, guanine, adenine, and thymine with isobutyl chloroformate (IBCF) as the derivatizing reagent.

The present work examines the application of isobutyl chloroformate (IBCF) as a derivatizing reagent for the quantitative analysis of 5-FU from the serum of patients after chemotherapy with 5-FU from aqueous samples with a shorter derivatizing time. The presence of nucleobases did not affect the analysis of 5-FU.

METHODS

All reagents were used in analytical or standard grade; the solutions were prepared in double-distilled water. Reference standard of nucleobases (uracil, thymine, cytosine, guanine, and adenine) and 5-FU (Sigma-Aldrich, St. Louis, Mo; USA) were used. Chloroform, IBCF, and acetonitrile (Fluka, Busch's, Switzerland), pyridine (E-Merck, Darmstadt, Germany), and methanol were obtained from RDH chemicals (Co Spring Vally, CA; USA).

Standard grade chemicals of sodium bicarbonate, hydrochloric acid, potassium chloride, acetic acid, sodium carbonate, sodium acetate, sodium tetraborate, boric acid, ammonium chloride, and ammonia solution were obtained from E-Merck, Darmstadt, Germany. The buffer solutions were prepared at the unit intervals of 0.2 M within the pH range of 1-11, and were prepared as follows: For buffers at pH 1-2, potassium chloride was adjusted with hydrochloric acid; buffers at pH 3-6 were from acetic acid-sodium acetate, pH 7 was made from ammonium acetate, pH 7.5-8.5 was prepared from sodium tetraborate-boric acid; pH 9 was made from sodium carbonate-sodium bicarbonate; pH 10-11 was prepared from ammonium chloride-ammonia solution. The stock solution (1mg/mL) of 5-FU was prepared in double-distilled water with a methanol-water (1:1 v/v) mixture, and other solutions were prepared by serial dilutions.

Equipment

Gas chromatography (GC) was connected to flame ionization detector (FID) and a split/splitless injection system (GC model 6890, Agilent Technologies, Santa Clara CA, USA). Pure hydrogen gas was from a hydrogen generator (Parker Hannifin, Haverhill, USA, H2 -90), and nitrogen gas was supplied by the British Oxygen Company (BOC), Karachi, Pakistan. The GC was computer-controlled with ChemStation software. The capillary column used was DB -5 (30 m X 0.32 mm id) with a film of 0.25 µm (J & W Scientific, Wilmington, NC, USA). The measurements of pH were made with a pH meter Orion 420 A (Boston, USA) attached to glass and reference internal electrodes.

GC analytical procedure

Solutions (0.2-1 mL) comprising concentrations of (1-25 µg 5-FU) were mixed with 0.5 mL pyridine-methanol-acetonitrile-water (10:10:40:40 v/v) solvent system, 0.5 mL pH 9 buffer, and 0.3 mL IBCF (10% in methanol). The mixed contents were sonicated at room temperature (30 °C) for 20 min. The extracting solvent (chloroform) (0.5 mL) was then combined, and the mixture was mixed well. The organic layer was permitted to separate, and a part of the chloroform was relocated to a screw-capped sample vial. An organic layer (1.0 µL) was introduced onto the GC column at an oven temperature of 130 °C for 2 min, followed by a heating rate of 15 °C/min to 220 °C. The total run time was 9 min. The flow rate of nitrogen was 2.0 mL/min. The injector split ratio was maintained at 10:1. The temperatures for the detector and injection were fixed at 280 °C and 270 °C, respectively. The flow rates of gases were

fixed: for nitrogen 45 mL/min, air 450 mL/min, and hydrogen 40 mL/min.

Analysis of blood serum of patients for 5-FU

Blood samples (n=10) from colon cancer patients (4-5 mL), registered at National Institute of Medicine and Radiology (NIMRA), Jamshoro, Sindh, Pakistan, were collected through intravenous methods and mixed in EDTA-loaded tubes. After 45 min of infusion of 5-FU (Utoral injection 250 mg/5mL), the drug 5-FU is reported to metabolize more rapidly [23,24]. The blood samples were centrifuged for 20 min at 3500 rpm after keeping the samples for 15 min at room temperature (30 °C). Methanol was combined twice in volume for the collection of supernatant layers. The mixed contents were centrifuged again for 20 min at 3500 rpm. The deproteinized serum (1-2 mL) obtained as upper layer was analyzed following GC procedure. The freshly prepared calibration curve, regression equation was used for quantitation. All the patients were briefed on the research work objectives, and they gave verbal/written permission to collect the samples. Ethical approval was obtained from the Institute of Advanced Research Studies in Chemical Science, University of Sindh, Pakistan.

For the standard addition process (n=4), samples were analyzed. The deproteinized serum (1.0 mL) in duplicate was captured, and one sample was spiked with 5-FU (10 µg) standard, and both samples were treated according to the GC procedure. The quantitation was supported by the regression equation of the calibration curve and enhancement in the response with the added standard.

RESULTS AND DISCUSSION

The GC elution of 5-FU was considered without derivatization, but because of its polar nature, it was poorly retained on the column, with a short retention time and tailing. It was, therefore, decided that derivatization with IBCF should be considered. IBCF reacts with secondary amino groups to form carbamate derivatives [20]. 5-FU contains two NH groups (Figure. I) and can react with IBCF to form carbamate derivatives. The elution of 5-FU after derivatization from the GC column was achieved as a single peak and completely separated from the derivatizing reagent (Figure. II). An attempt was therefore made to optimize the experimental conditions for the derivatization, and elution of 5-FU from the

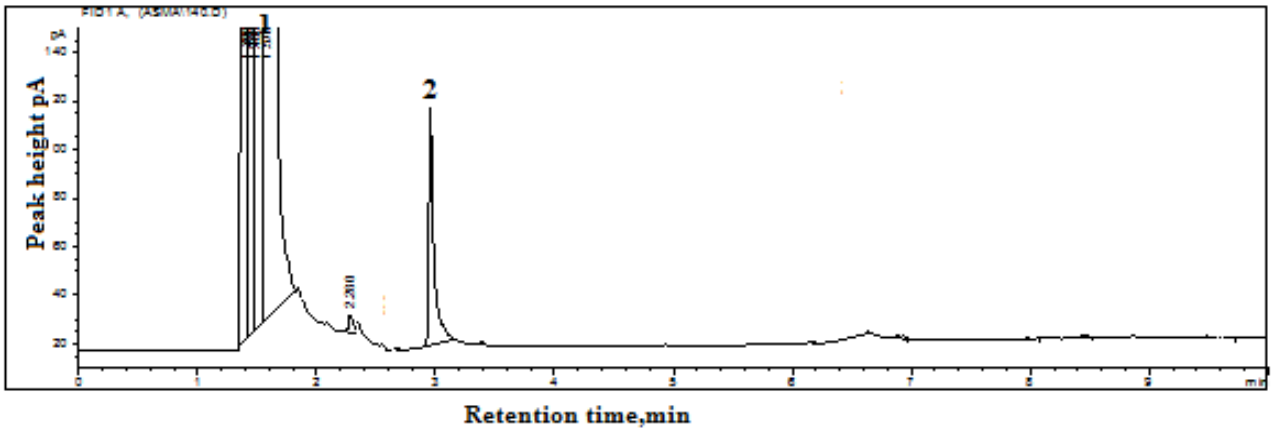

Figure II. GC elution of reagent isobutyl chloroformate (1), 5-FU (2)

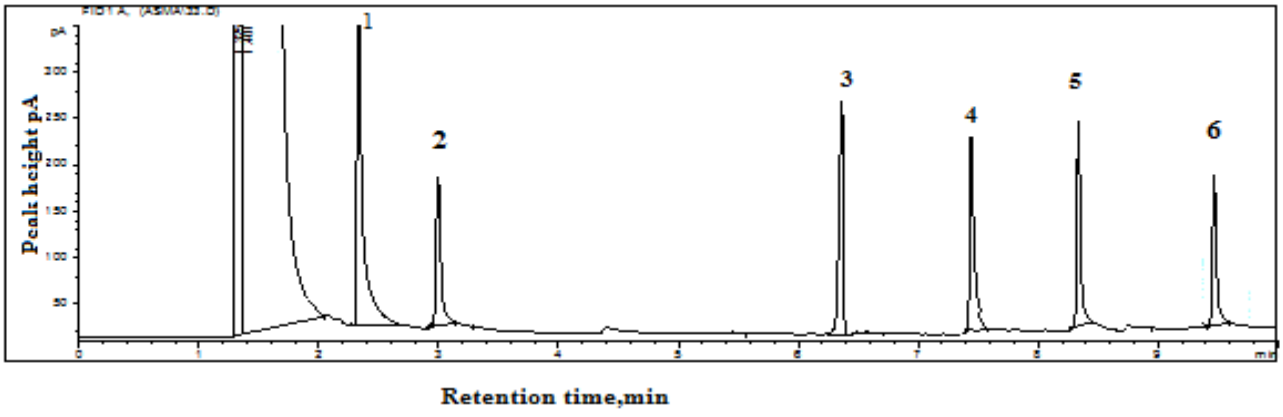

Figure III. Plot of peak height against retention time: GC separation of 1. Adenine, 2. 5-FU, 3. Thymine, 4. Cytosine, 5. Guanine, 6. Uracil

Table II. Comparative summary of reports on 5-Fluorouracil

Method	Calibration range	Limit of detection	Limit of quantitation µg/mL	Biological samples	Reference
HPLC-UV	0.1-100	0.1	-	Human serum	8
GC-FID (hexafluoroacetylacetone)	0.5-40	0.2	-	Human serum	22
LC-MS/MS	0.013-9.75	-	0.013	Human plasma	10
GC-FID (isobutyl chloroformate)	2-50	0.06	0.2	Human serum	Present work

GC column. pH was varied within 2-11 at a distance of 0.5 to 1 pH unit, and a similar response was observed within 8.5-10, and pH 9 was selected [22]. The derivatizing reagent IBCF (10% in methanol) was altered from 0.1-0.5 mL with an interval of 0.1 mL, and the concentration of derivatizing reagent was absolute and comparable for all concentrations (0.1-0.5 mL). The extraction of 5-FU at the concentration of 0.3 mL was selected as the optimized method. Sonication time at 30 °C (room temperature) was varied from 5-25 min at intervals of 5 min; analytical returns were achieved even at 15 min, and thus approximately 20 min was selected (Figure. III). Different extracting solvents were investigated for the extraction of the analyte, including chloroform, 1,2-dichloroethane, carbon tetrachloride, and chlorobenzene. Chloroform provided the optimum analytical results. Different oven temperatures for the column were checked from 120 °C to 140 °C for 1 to 3 min, followed by a heating rate of 10 to 20 °C/min up to 200 to 230 °C. The temperature program gave baseline separation at a column temperature of 130 °C for 2 min with a heating rate of 15 °C/min up to 220 °C with a nitrogen flow rate of 2 mL/min.

5-FU is similar to nucleobase uracil; the possible effect of nucleobases adenine, thymine, cytosine, guanine, and uracil on the separation with quantitation of 5-FU was investigated under the optimized conditions of GC. All the components were taken at similar concentrations. All were separated completely and did not interfere with the quantitation of 5-FU

Table I. 5-Fluorouracil as commercial drug Utoral (50 mg/mL) and patient data.

Gender	Age in years	Human serum in µg/mL (RSD %)
Male	40	21.2 (1.3)
Female	35	9.6 (0.4)
Female	45	15.4 (1.9)
Male	55	6.8 (2.5)
Male	60	4.6 (1.8)
Male	62	10.6 (2.1)
Female	65	11.6 (2.7)
Female	45	6.4 (1.3)
Male	49	16 (0.7)
Male	52	11.6 (2.0)

in terms of retention time and peak height/peak area, with a relative error of 2.9%.

The linearity of the calibration curve was investigated by plotting the average peak area (n=3) versus concentration and was observed within 2-50 µg/mL with $r^2 = 0.998$. The signal-to-noise ratio measured as 3.3:1 and 10:1 for the limit of detection (LOD) and limit of quantitation (LOQ) were calculated as 0.06 µg/mL and 0.20 µg/mL, respectively. Test solutions (n=4) were analyzed using the external calibration, and a relative error was observed within 3.5%. The repeatability and reproducibility of the determination were measured by intra-day and inter-day (n=5) variation, and the relative standard deviations were 1.4% and 2.5%, respectively.

Sample analysis

Ten blood samples from patients who were on therapy with 5-FU were collected from NIMRA hospital, Jamshoro. The deproteinized serum (1-2 mL) was analyzed by the GC analytical procedure. The identification of the peak was achieved by examining retention times with the standard drug 5-FU. The patients were aged 35-65 years. The samples collected from 4 women revealed the occurrence of 5-FU in concentrations of 6.4, 9.6, 11.6, and 15.4 µg/mL, and six male patients indicated the concentrations as 4.6, 6.8, 10.8, 11.6, 16.0, and 21.2 µg/mL with RSD within 0.7-2.7% (Table I). Four samples identified by standard addition indicated results that agreed with direct calibration, with a recovery of 92-96% and RSD of 2.8%. The results obtained agreed with the stated values by Zonur et al. [19]. The method was compared with described chromatographic methods (Table II). The results indicated comparable sensitivity with HPLC-UV and GC-FID methods but were less sensitive than LC-MS/MS and GC-MS/MS procedures.

CONCLUSION

An analytical method has been developed for the analysis of Fluorouracil (5-FU) from blood serum of cancer patients on 5-FU therapy using pre-column derivatization with isobutyl chloroformate. The limit of detection and calibration ranges were observed to be 0.06 µg/mL and 2-50 µg/mL, respectively.

The presence of nucleobases, together with uracil, did not interfere with the separation and quantitative determinations of 5-FU. The method was applied for the estimation of 5-FU in the blood serum of 10 cancer patients after chemotherapy with 5-FU, and the amounts found were within 4.6-21.2 µg/mL, with a relative standard deviation of 0.4-2.7%.

CONFLICT OF INTEREST

Authors states no conflict of interest.

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Original Research Article

Herbal and Dietary Supplement Use among Patients with Type 2 Diabetes Mellitus (T2DM) from a Rural Region in Malaysia: A Cross-Sectional Study

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ABSTRACT

Background: Herbal and dietary supplements (HDS) are commonly used for diabetes management and health maintenance due to their perceived safety and benefits. However, HDS can have potential adverse effects, and data on their use among rural communities in Malaysia are limited. **Objective:** This study explores the prevalence, associated factors, and disclosure rates of HDS use among diabetic patients in a rural region of Malaysia. **Methods:** A multicentre cross-sectional survey of Type-2 Diabetes Mellitus (T2DM) patients was conducted in seven healthcare facilities located in Hulu Selangor, Malaysia. Data were collected from randomly sampled patients using an interviewer-administered questionnaire and from patient medical records. Logistic regression analyses examined the association between HDS use in general and for diabetes management with various patient characteristics. **Results:** A total of 273 patients responded to the survey. 34.8% of patients reported HDS use in the past month, while 13.5% of patients attributed the use of HDS to T2DM management. The most common form of HDS used for diabetes was *Momordica charantia* (14%), followed by functional beverages (12%). 16% of these identified HDS were either unknown to patients or were unregistered products. Indian patients were significantly less likely to consume HDS compared to Malay patients. The odds of HDS consumption increased by 62.7% with each higher income bracket and by 45.2% with higher physical activity levels. Patients with secondary education or higher were more than twice as likely to use HDS for diabetes management. Less than 17% of patients disclosed the use of HDS to healthcare professionals. **Conclusion:** The use of HDS among T2DM patients in the studied rural region is slightly lower but broadly comparable to that reported in more developed settings. Efforts to educate patients on safe HDS use while optimising its disclosure to healthcare providers are crucial to prevent adverse events or compromised therapy.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes globally, afflicting over 463 million people worldwide [1]. It is also one of the most prevalent non-communicable diseases in Malaysia, with relative prevalence rates increasing by 39.3% from 11.2% in 2011 to 15.6 % in 2023 [2]. Current statistics estimate that about 3.6 million Malaysians above the age of 18 are suffering from T2DM.

While many pharmacological treatment options exist for diabetes, some patients use herbal and dietary supplements (HDS) as an adjunct in the management of diabetes. HDS is a type of complementary and alternative medicine (CAM) that includes products with plant-derived materials, dietary ingredients, and traditional herbal medications from various ethnicities in Malaysia, such as Malay, Chinese, Indian, and Indigenous groups, and is widely used due to its accessibility and availability over the counter [3-7].

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HDS is widely accepted for health maintenance and disease management, particularly among patients with diabetes [8, 9]. In the National Health & Morbidity Survey 2015 (NHMS 2015), Malaysian patients with diabetes have been reported using TCM for better disease control and fewer side effects from conventional medication [10]. Local studies revealed that 44.7% of patients with diabetes attributed their very good health status to HDS use, while 80% of respondents in a similar study found HDS somewhat effective, and 35% perceived it as very effective [11, 12].

However, the concurrent use of HDS and conventional medication can lead to possible compliance issues whilst posing risks of supplement-drug interactions that could result in adverse events. CAM users tend to be 6.16 times less compliant with prescribed anti-diabetic medication than non-CAM users [6], and a significant number of patients fail to inform healthcare professionals about their HDS use [5, 13, 14].

Rural areas show higher usage of alternative treatments, including HDS. In both the US and Australia, rural populations exhibit significantly higher rates of HDS use and self-prescribed supplement use compared to their urban counterparts [15, 16].

Given the potential for supplement-drug interactions and the high prevalence of HDS use in rural areas, there is a need to better understand HDS usage patterns among patients with T2DM and their disclosure practices with healthcare professionals. However, published research on HDS use among Malaysia's rural population remains limited. Locally conducted studies tend to focus on general CAM use with limited attention to rural dwellings [3, 11, 17]. Therefore, the primary objective of this study is to determine the prevalence and factors associated with the active use of HDS among Malaysian patients with T2DM living in a rural region, with active use defined as consumption of HDS within the past month. This study also attempts to investigate patients' expenditure to purchase HDS, sources of acquisition, and disclosure rates for its use to attending healthcare professionals as secondary objectives.

METHODS

Study design and setting

A cross-sectional survey of patients with T2DM registered in Kuala Kubu Bharu Hospital, a district public hospital, and six public health clinics, namely Serendah Polyclinic, Selisik Polyclinic, Kalumpang Polyclinic, Ulu Yam Bharu Polyclinic, Soeharto Polyclinic, and Rasa Polyclinic, was conducted from April 2018 to December 2018. All these public health facilities are in the Hulu Selangor district of Selangor, a state located on the west coast of Malaysia. It has the second lowest population density (140 people per km^2) [18] in the state and has a rural population of 64,640 individuals, which represents the largest share (22%) of the total rural population in Selangor, which is predominantly Bumiputera (74.9%), with a significant minority of Indian (13.3%) and Chinese (11.3%) [18]. Most of the polyclinics operate in district subdivisions classified as rural based on population size as stipulated in the Population and Housing Census of Malaysia 2020 [19]. While the hospital and Serendah Polyclinic are in sub-districts that surpass the rural threshold, the population demographics of these two study sites are unlikely to differ much from other clinics, especially since 19 out of the 25 sub-districts (76%) can be classified as rural regions [18, 19], and the hospital remains the sole secondary care facility available in the region [18]. Thus, patients recruited from these sites will also be assumed to be from a rural locality.

Study participants

Registered Malaysian patients with T2DM who are at least 18 years old and currently residing in the Hulu Selangor region were eligible for this study. Patients who were unable to communicate, cannot give consent, or were pregnant were excluded.

Sample size and sampling procedure

Based on the prevalence of HDS use in local studies, which was approximately 77% [4, 5], together with a precision of 5% and a 95% confidence interval, an estimated sample size of 273 participants was required. After accounting for a 10% non-responder rate, we attempted to recruit 304 participants. A list of active patients with T2DM currently receiving treatment in Hulu Selangor was obtained from the Selangor State Health Department, and each patient was assigned a running number from which 304 numbers were randomly selected.

These patients were then approached by trained interviewers whilst waiting to collect their medications at the pharmacy. They were given explanations regarding the nature and methodology of this study and were allowed to pose any questions before deciding to participate. When a language barrier prevented patients from full participation, family members or a suitable language translator were allowed to answer on behalf of the patient.

Informed consent was then obtained from patients who agreed to participate before a 15–20-minute face-to-face interview was conducted. Participants were assigned identification numbers to avoid capturing personal identifiers and to preserve their anonymity.

Data Collection

Patient's data were collected using two questionnaires. The first questionnaire was adapted and modified from three previously developed surveys on CAM/HDS use: a primary care survey developed by Kuo GM et al., which provided a foundational template for multiethnic patient survey design; a Malaysian primary care survey by Ching SM et al., and a tertiary hospital survey at Hospital Pulau Pinang by Saw JT et

Table I: Socio-demographic and lifestyle characteristics of the study population and their association with HDS use

Characteristics	Overall (n=273)	Active HDS users (n=95)	Non-active HDS users (n=178)	p-value	Active HDS user for DM (n=38)	Non active HDS user for DM	p-value
Age (years) (n=273), (mean±SD)	58.92 (± 10.29)	58.76 (±10.35)	59.00(±10.28)	0.8535	56.03 (±9.60)	59.38 (±10.34)	0.0619
Weight (kg) (n=272), median (IQR)	68.5 (60.0 – 78.0)	67.0 (62.0-77.0)	69.0 (60.0-78.0)	0.999	70.0 (65.0 – 78.0)	68.0 (60.0-78.0)	0.433
Gender (n=273), n (%)							
Male	102 (37.36%)	35 (36.84%)	67 (37.64%)	0.897	13 (34.21%)	89 (37.87%)	0.665
Female	171 (62.64%)	60 (63.16%)	111 (62.36%)		25 (65.79%)	146 (62.13%)	
Marital status (n=273), n (%)							
Single	9 (3.30%)	4 (4.21%)	5 (2.81%)	0.553	1 (2.63%)	8 (3.40%)	0.524
Married	233 (85.35%)	83 (87.37%)	150 (84.27%)		32 (84.21%)	201 (85.53%)	
Divorce	2 (0.73)	1 (1.05%)	1 (0.56%)		1 (2.63%)	1 (0.43%)	
Widow	29 (10.62%)	7 (7.37%)	22 (12.36%)		4 (10.53%)	25 (10.64%)	
Ethnicity (n=273), n (%)							
Malay	167 (61.17%)	62 (65.26)	105 (58.99)	0.027	29 (76.32)	138 (58.72%)	0.117
Chinese	43 (15.75%)	19 (20.00)	24 (13.48)		3 (7.89)	40 (17.02))	
Indian	60 (21.98%)	12 (12.63)	48 (26.97)		5 (13.16)	55 (23.40)	
Other	3 (1.10%)	2 (2.11)	1 (0.56)		1 (2.63)	2 (0.85)	
Monthly salary (RM), (n = 245), n (%)							
< 1,500	153 (62.45%)	48 (53.33%)	105 (67.74%)	0.035	20 (54.05%)	133 (63.94%)	0.207
1,500 – 4,000	77 (31.43%)	32 (35.56)	45 (29.03%)		13 (35.14%)	64 (30.77%)	
4,000-9,000	11 (4.49%)	7 (7.78%)	4 (2.58%)		2 (5.41%)	9 (4.33%)	
> 9,000	4 (1.63%)	3 (3.33%)	1 (0.65%)		2(5.41%)	2 (0.96%)	
Education level (n=272), n (%)							
No education	28 (10.29%)	8 (8.42%)	20 (11.30%)	0.419	2 (5.26%)	26 (11.11%)	0.079
Primary	102 (37.5%)	32 (33.68%)	70 (39.55%)		9 (23.68%)	93 (39.74)	
Secondary	121 (44.49%)	45 (47.37%)	76 (42.94%)		24 (63.16%)	97 (41.45%)	
Tertiary	21 (7.72%)	10 (10.53%)	11 (6.21%)		3 (7.89%)	18 (7.69%)	
Length of diagnosis for diabetes (years); Median (IQR) (n = 273)	(5 – 15)	8 (5 – 13)	8 (5 – 15)	0.9038	8 (5 – 13)	8 (5 – 15)	0.5921

Table I: Socio-demographic and lifestyle characteristics of the study population and their association with HDS use (continued)

Characteristics	Overall (n=273)	Active HDS users (n=95)	Non-active HDS users (n=178)	p-value	Active HDS user for DM (n=38)	Non active HDS user for DM	p-value
Diabetic family history (n=273), n (%)							
Yes	167 (61.17%)	62 (65.26%)	105 (58.99%)	0.585	26 (68.42%)	141 (60.00%)	0.613
No	88 (32.23%)	27 (28.42%)	61 (34.27%)		10 (26.32%)	78 (33.19%)	
Not sure	18 (6.59%)	6 (6.32)	12 (6.74%)		2 (5.26%)	16 (6.81%)	
Smoking status (n=273), n (%)							
Yes	29 (10.62%)	10 (10.53%)	19 (10.67%)	0.970	3 (7.89%)	26 (11.06%)	0.556
No	244 (89.38)	85 (89.47%)	159 (89.33%)		35 (92.11%)	209 (88.94)	
Smoking history if currently not smoking (n=243), n (%)							
Yes	22 (9.05%)	6 (7.06%)	16 (10.13%)	0.713	3 (8.57)	19 (9.13%)	0.914
No	221 (90.95%)	79 (92.94%)	142 (89.87%)		32 (91.43%)	189 (90.87%)	
Alcohol consumption status (n=273), n (%)							
Yes	19 (6.96%)	7 (7.37%)	12 (6.74%)	0.846	1 (2.63%)	18 (7.66%)	0.258
No	254 (93.04%)	88 (92.63%)	166 (93.26%)		37 (97.37%)	217 (92.34%)	
Alcohol consumption history if currently not drinking (n=254), n (%)							
Yes	18 (7.09%)	6 (6.82%)	12 (7.23%)	0.903	2 (5.41%)	16 (7.37%)	0.666
No	236 (92.91%)	82 (93.18%)	154 (92.77%)		35 (94.59%)	201 (92.63%)	
Physical activity (n=273), n (%)							
Low	70 (25.64%)	19 (20.00%)	51 (28.65%)	0.048	9 (23.68%)	61 (25.96%)	0.517
Moderate	67 (24.54%)	19 (20.00%)	48 (26.97%)		7 (18.42%)	60 (25.53%)	
High	136 (49.82%)	57 (60.00%)	79 (44.38%)		22 (57.89%)	114 (48.51%)	
Insulin therapy (n=273), n (%)							
Yes	114 (41.76%)	36 (37.89%)	78 (43.82%)	0.344	17 (44.74%)	97 (41.28%)	0.688
No	159 (58.24%)	59 (62.11%)	100 (56.18%)		21 (55.26%)	138 (58.72%)	

DM, Diabetes Mellitus; HDS, Herbal and dietary supplement; IQR, Interquartile range; RM, Ringgit Malaysia; SD, Standard deviation.
p-value is based on Chi Square, t-test, or Mann-Whitney test to measure association between active and nonactive users of HDS in general and for DM management. The p-value is considered significant at $p < 0.05$

al., both of which comprehensively informed locally relevant attitudes and reasons for use among Malaysian diabetics, expenditure patterns, and predictors of use, thereby ensuring the questionnaire's applicability to local disease and cultural patterns [3, 13, 20]. The questionnaire was then translated into the Malay language for use in our Malay majority constituency and was validated by three subject experts to ensure that the questionnaire was suitable for local use. The questionnaire was pilot tested with 35 individuals. Pilot test data were not included in the final data analysis.

The final version of the questionnaire is divided into four domains: socio-demographic characteristics, disease and family medical history, lifestyle (smoking habits and alcohol consumption), and HDS use.

The second questionnaire is a self-administered Malay language version of the International Physical Activity Questionnaire (IPAQ-Short form), which was used to assess the physical activity of recruited subjects [21].

Documented diabetes-specific information, such as duration of DM, insulin usage, and the number of drugs and anti-diabetic medications prescribed, were extracted from patient's medical records.

Statistical Analysis

Descriptive and inferential analyses were performed using Stata version 16, with a significance level set at 0.05. Chi-square tests and multivariate logistic regression analyses were used to examine the association between HDS use and socio-demographic characteristics as well as physical activity.

Ethics Statement

This study (NMRR-18-513-40025) was approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia and the Hulu Selangor District Health Office, Selangor, Malaysia.

RESULTS AND DISCUSSION

A total of 296 patients were approached for this study, out of which 23 patients refused to participate. 273 patients consented and were enrolled in the study. However, certain questions presented, such as the monthly salary and education level, did not achieve a 100% response rate. Socio-demographic characteristics and lifestyle of enrolled patients are presented in Table I.

Table II: Prevalence of consuming at least 1 HDS in the past month (n = 273)

HDS Consumption	Overall	DM
Yes	95 (34.80%)	38 (13.92%)
No	178 (65.20%)	235 (86.08%)

The majority of participants were female Malay Muslims who were already married. Patients were predominantly either working or unemployed, with a monthly salary of less than RM1,500 (USD360), with most possessing primary or secondary level school education.

Table II below reports the prevalence of HDS usage. 95 patients (34.80%) were using at least 1 type of HDS within the past month. 38 of these patients reported using HDS for their DM condition, which accounts for a prevalence of 13.92% among recruited patients. Ethnicity, monthly salary, and physical activity were found to be significantly associated with the active use of HDS. However, none of the studied variables were significantly associated with the active use of HDS for diabetic management purposes.

Table III presents patient-reported expenditure incurred monthly towards purchasing HDS. Median (IQR) expenditure on HDS per month totalled at RM 50 (RM10 – RM123). Median expenditure increased with monthly salary until the RM4000 – RM9000 salary bracket. The highest expense was reported to be RM500, and this was for the purchase of a single product for general well-being (Deer Placenta). Patients who reported no expenses obtained their HDS by harvesting raw herbs from their garden or receiving herbs or products from family or friends.

Based on Supplementary Table A, our study reports that the majority of HDS users consumed only 1 type of HDS (62.1%). Similarly, only 1 type of HDS was consumed among most patients who used it for DM management (84.2%). As shown in Supplementary Table B, a total of 147 HDS were reported to be used among the 95 HDS users, most of which were either self-purchased (74.8%) or home-grown (15.6%).

We reviewed the list of 50 HDS that were reported to be used for DM management purposes among active and past users

Table III: Monthly expenditure associated with the use of HDS stratified according to monthly salary category

Monthly salary	n	Median (RM)	IQR (RM)	Min (RM)	Max (RM)
Overall sample	95	50.00	10.00 – 123.00	0	500.00
< RM1500	48	40.00	3.00 – 117.50	0	290.00
RM1500-4000	32	60.00	16.00 – 124.00	0	500.00
RM4000-9000	7	110.00	10.00 – 124.00	0	450.00
> RM9000	3	100.00	0 - 400.00	0	400.00

Table IV: Univariate and multivariate logistic regression analyses of factors associated with HDS use in general and for T2DM management.

	HDS in general		HDS for T2DM management	
	(Univariate) OR (SE)	(Multivariate) OR (SE)	(Univariate) OR (SE)	(Multivariate) OR (SE)
Age	0.998 (0.0123)		0.969*(0.0145)	0.980 (0.0165)
Weight [b]	1.000 (0.00744)		1.009 (0.00941)	
Ethnicity				
Malay [c]	1(.)	1(.)	1(.)	
Chinese	1.341(0.465)	1.166 (0.441)	0.357 (0.226)	
Indian & Others	0.484*(0.166)	0.456*(0.162)	0.501(0.239)	
Monthly salary [a]	1.760**(0.355)	1.627*(0.347)	1.498(0.373)	
Education [b]	1.422(0.366)		2.540*(0.969)	2.220*(0.893)
Length of disease	1.006(0.0173)		0.979(0.0237)	
Family History	0.835(0.179)		0.755(0.236)	
Smoking	0.985(0.407)		0.689(0.439)	
Alcohol	1.100(0.544)		0.326(0.340)	
Insulin	0.782(0.204)		1.152(0.406)	
Physical activity	1.435*(0.232)	1.452*(0.255)	1.188(0.266)	

OR, Odds ratio; SE, Standard error.
+ p < 0.10, * p < 0.05, ** p < 0.01, *** p < 0.001
[a] 245 patients responded to this parameter.
[b] 272 patients responded to this parameter.
[c.] Reference category.

(see Supplementary Table C for the full list). Past users were patients who used HDS within the past year, which numbered 12 patients. Not all these patients listed the type of HDS that was used. *Momordica charantia* (bitter gourd) was the most commonly used herb (14%), followed by functional beverages (12%). 10% of HDS were unknown as patients had no knowledge regarding the ingredients or plant extracts used to make the concoction. Moreover, 6% of HDS consisted of dietary supplements that were either untraceable on the internet or had unknown Malaysian product registration status due to their absence in the National Pharmaceutical Regulatory Agency (NPRA) product search web portal. NPRA is Malaysia's regulatory authority for medicinal, supplements, and cosmetic products.

Table IV presents the univariate and multivariate logistic regression analyses conducted to determine factors associated with the use of HDS in general, and HDS specifically for T2DM management To avoid sparse data issues, several categories were recoded. The 'Others' ethnic group had only three respondents and was therefore combined with the Indian ethnic category to form an 'Indian & Others' group. This decision was supported by similar religious or cultural backgrounds between the two groups (see Supplementary Table D). We also collapsed the education level variable into two categories: below secondary education, and secondary education and above. Multivariate logistic regression was conducted using purposeful selection of variables that were significantly associated with HDS use at the 25% significance level in the univariate analysis. In the final model, Indians & Others had a 54.4% lesser likelihood of consuming HDS compared to Malays (OR = 0.456, 95% CI = 0.228 – 0.915). The odds of a patient consuming HDS were 62.7% higher with each successive rise in studied income brackets (OR = 1.627, 95% CI = 1.072 – 2.470). Similarly, the likelihood of a patient consuming HDS increases by 45.2% with each increase in physical activity level (OR = 1.452, 95% CI = 1.029– 2.048). The odds of a patient consuming HDS for T2DM management more than doubled if they had secondary education and above (OR = 2.220, 95% CI = 1.009 – 4.884).

Table V reports the proportion of patients informing healthcare professionals about their HDS usage. Disclosure rates of HDS use to doctors and pharmacists were found to be 16.8% and 7.4% among HDS users, respectively. Among HDS users for T2DM management, 15.8% and 2.6% of them informed their doctor and pharmacist about it, respectively.

Similar reasons behind non-disclosure to both doctors and pharmacists were expressed by patients consuming HDS, as shown in Supplementary Table E & F The two most cited reasons were healthcare professionals never asked patients about their HDS usage, and the perception that disclosure was unimportant.

Supplementary Tables A–F, discussed in the Results section, are provided in Appendix 1 at the end of this article..

DISCUSSION

Our study found that over one-third of individuals with T2DM reported using HDS, with usage associated with ethnicity, income level, and physical activity. Among those who used HDS, a substantial proportion reported using them specifically to manage their diabetes, with educational level being significantly associated with this decision. Our findings also raised concerns as some participants reported using unregistered or unidentified HDS products. Moreover, most users did not disclose their supplement use to their healthcare providers, suggesting a significant communication gap in diabetes management.

Most studies investigating HDS use among patients with diabetes in Malaysia tend to assess it in urban localities alongside other forms of complementary and alternative medicine (CAM), resulting in higher reported usage rates that exceed 50% due to their broader scope and possibly more affluent or educated participants [3, 7, 11]. In contrast, a more comparable local study was conducted in rural Sarawak, East Malaysia, where the use of traditional health supplement products (HSPs) was examined among patients with chronic illnesses, including T2DM. Compared to the present study, they reported a lower prevalence of supplement use, with only 24% of participants actively taking HSPs [22]. This lower rate may be partly due to the study not accounting for the use of herbs consumed as dietary supplements, unlike our current study. Furthermore, their sample comprised a higher proportion of lower-income participants while observing that supplement use was associated with higher household income. These findings align with our study, which also found income level to be significantly associated with HDS use.

From a regional perspective, Putthapiban et al. (2017) examined HDS use among patients with T2DM at a tertiary hospital in urban Bangkok, Thailand, and reported an active usage rate of 28% [23]. In comparison, although only surveying herbal medicine usage, Prasopthum et al. (2022) reported a higher prevalence of 37.5% among T2DM patients attending semi-rural district hospitals in Thailand [8]. Another similar study conducted both in rural and urban health facilities among patients with chronic disease in Thailand also observed similar rates [24]. Although nuanced, there is potentially a greater uptake of HDS in less urbanised regions of Thailand compared to our rural setting in Malaysia. A possible explanation for this difference is that although our study was conducted in a rural region, the surrounding locality is undergoing rapid development through rural-urban transformation initiatives within the state of Selangor, one of Malaysia's wealthiest and most developed states [25]. Increased exposure to urban infrastructure and heightened cost of living due to ongoing rural-urban developments may have influenced HDS usage patterns to closely resemble those observed in urban contexts like Bangkok.

Several studies have reported a notable increase in HDS use during the COVID-19 pandemic. For instance, a Malaysian survey found that 42% of adults used HDS for COVID-19 prevention [26], while similar trends were observed in Saudi Arabia and Indonesia [27, 28]. While these increases were likely driven by pandemic-specific concerns, they may have influenced longer-term attitudes and behaviors toward HDS use. However, whether these patterns persisted post-pandemic remains uncertain. This underscores the need for updated surveys to assess current usage trends among patients with T2DM to trace evolving health-seeking behaviors.

One alarming finding seen during the HDS identification process lies with the discovery of products or herbs which were either unregistered or unknown to the patient. Unregistered or unregulated HDS products are notorious for causing severe or unwanted adverse effects to consumers [29, 30]. These products may be contaminated, adulterated, or contain ingredients that exceed safety levels or contain toxic properties [31-33]. Unknown herbs or products may pose risks of adverse events for similar reasons [34]. Multiple surveys have found that Malaysians in general are ill-equipped with the skills necessary to identify and use HDS responsibly from a regulatory and safety perspective [35-37]. This highlights the need to bolster efforts directed at improving the health literacy of Malaysians via effective educational campaigns regarding safe and responsible HDS usage.

Malay patients with T2DM were more likely to use HDS in this study, a finding that is equally supported by another Malaysian study that examines CAM usage among patients with T2DM [3]. This observation may be attributed to their Islamic faith, which encourages holistic disease management and the use of traditional remedies like olive and honey, as mentioned in the Quran, Sunnah, and Hadith [10, 38, 39]. The NHMS 2015 also supports this finding, showing that many Islamic medical practitioners attribute their use for therapeutic purposes [10].

Patients with at least a secondary education were more likely to use HDS for managing diabetes. While most studies indicate education level as an insignificant factor for overall HDS use [8, 9, 40-42], our finding suggests that higher health literacy may drive the use of HDS for diabetes management in rural areas, possibly due to greater awareness of alternative

therapies, coupled with increased confidence in evaluating health information and making informed decisions about supplement use.

More physically active patients were found to have a higher likelihood of using HDS. While some studies support this finding, others show contrasting results. For example, a prospective cohort study using US National Health and Nutrition Examination Survey data from 1999 to 2018 found that supplement users were more likely to be physically active than non-users (26.8% vs. 19.8%; $p < 0.001$) [43]. However, cross-sectional surveys of patients with T2DM in Thailand found that those using HDS were more likely to be physically inactive [8, 44]. The results of our study may suggest that physically active patients display a more proactive attitude toward managing their disease [45], and hence were more inclined to use HDS.

The majority of our surveyed patients used HDS for general health, while only a small fraction used them to manage their T2DM. However, this contrasts with a local CAM survey conducted across an entire Malaysian state, whereby 40.6% of surveyed T2DM patients used CAM to help manage their condition [7]. The higher rate observed in that study may reflect a broader definition of CAM use, and the inclusion of participants from more urbanized areas where health-seeking behaviors and access to health information may differ.

The overwhelming majority of HDS users surveyed did not disclose their usage of HDS to both doctors and pharmacists. This mirrors the disclosure rates seen in local [14, 22, 46, 47], regional [23], and international studies [9, 48], which ranged from 16.2% to 58%. While the disclosure rate over time was not explicitly studied in this survey, a Malaysian study conducted 13 years prior to our study reported a strikingly similar non-disclosure rate [46]. This suggests that poor disclosure rates remain a long-standing issue in the country that requires urgent attention from Malaysian healthcare providers.

Low disclosure rates of HDS use may occur because patients often downplay its importance, believing it doesn't affect their disease management. This can lead to HDS-related adverse events going unnoticed and complicating treatment. To improve disclosure rates, healthcare providers should encourage proactive discussions about HDS use, as a lack of inquiry is a major reason for non-disclosure [22, 47, 49] Additionally, healthcare providers should adopt adaptive communication strategies, especially in multicultural settings with diverse socioeconomic backgrounds, as differences in terminology and understanding of HDS can affect communication. For instance, a study by Ben-Arye et al. found that including HDS-related keywords during history-taking more than doubled disclosure rates [50]. Furthermore, integrating CAM education into medical training and offering capacity-building courses could also significantly improve healthcare providers' competency and confidence to prompt and address HDS usage among patients [49].

There are several limitations to our study. The findings might only be applicable to the broader local region due to the rapid urbanization of the Hulu Selangor area. Another limiting factor is that data collection was conducted within healthcare facilities, which might have excluded patients who are exclusively on HDS for the management of T2DM and do not seek conventional medical care..

While significant research has been conducted on the prevalence, type, and factors behind HDS use, and the prevalence of non-disclosure rates and their reasons, studies on the impact of remedial actions taken to improve disclosure remain few and far between. Further research on evaluating and optimising existing strategies could be helpful in improving communication between patients and healthcare providers as well as allowing for more holistic management of diabetes.

CONCLUSION

In summary, the use of HDS among T2DM patients in the studied rural region was slightly lower but broadly comparable to rates reported in more developed settings. This suggests that urbanization and socioeconomic development may influence usage patterns even in rural areas. Given the potential risks of HDS use in compromising diabetes management, particularly when involving unknown or potentially harmful products, there is an urgent need to educate and empower patients while strengthening regulatory surveillance of unregistered products in the market. Lastly, taking a proactive, open, and adaptive approach to communicate on HDS usage will allow both patients and healthcare providers to navigate the complexities of multimodal DM treatment in an informed manner.

CONFLICT OF INTEREST

Authors states no conflict of interest.

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APPENDIX

Supplementary Table A: Number of HDS consumed per patient

Number of HDS	Overall HDS users (n=95)	HDS users for T2DM management (n=38)
1	59 (62.1%)	32 (84.2%)
2	24 (25.3%)	5 (13.2%)
3	9 (9.5%)	
4	2 (2.1%)	1 (2.6%)
5	1 (1.0%)	

Supplementary Table B: Prevalence of reported sources for HDS consumed

Source of HDS	n (%)
Self-purchase	110 (74.8)
Homegrown	23 (15.6)
Hospital or clinic pharmacy	6 (4.1)
From neighbour's or friend's garden	4 (2.7)
Harvested from plants growing naturally outside of home	2 (1.4)
Given or bought by a family member	2 (1.4)

Supplementary Table C: Frequency of HDS use for DM management among active and past users

Herbal or Dietary Supplement	n (%)
Momordica charantia	7 (14)
Functional Beverage	6 (12)
Orthosiphon stamineus	4 (8)
Vitamin B12 / Methylcobalamin	4 (8)
Helminthostachys zeylanica	2 (4)
Punica granatum	2 (4)
Clinacanthus nutans	2 (4)
Piper nigrum + *Trigonella foenum-graecum*	1 (2)
Moringa oleifera Lam.	1 (2)
Oenanthe javanica	1 (2)
Centella asiatica	1 (2)
Stevia rebaudiana	1 (2)
Mariposa christia vespertilionis	1 (2)
Andrographis paniculata	1 (2)
Clitoria ternatea	1 (2)
Artocarpus altilis	1 (2)
Gynura procumbens	1 (2)
Murraya koenigii	1 (2)
Abelmoschus esculentus	1 (2)
Flaxseed	1 (2)
Evening Primrose oil	1 (2)
CoEnzyme Q10	1 (2)
Unknown dietary supplement [a]	3 (6)
Unknown (liquid, leaves, plant extract beverage)	5 (10)

[a] Untraceable on the internet or unknown Malaysian product registration status.

Supplementary Table D: Religion of participants by ethnicity

Religion	Ethnicity			
	Malay	Chinese	Indian	Others
Islam	167	0	0	0
Buddhism	0	41	0	0
Hinduism	0	1	56	0
Christianity	0	0	3	1
Sikhism	0	0	0	1
None	0	0	0	1
Unspecified	0	1	1	0

Supplementary Table E Reasons for nondisclosure to doctor among patients consuming HDS

Reason	Frequency (%)
Was never asked	54 (68.3)
Not important	13 (16.4)
Doctor will not agree to it	4 (5.1)
Unsure	2 (2.5)
Just started	2 (2.5)
Traditional remedy	1 (1.3)
Doctor will not understand	1 (1.3)
Friend informed not to disclose	1 (1.3)
Infrequent consumption	1 (1.3)

Supplementary Table F: Reasons for nondisclosure to pharmacist among patients consuming HDS

Reason	Frequency (%)
Was never asked	63 (71.6)
Not important	16 (18.2)
Unsure	5 (5.7)
Just started	1 (1.1)
Traditional remedy	1 (1.1)
Friend informed not to disclose	1 (1.1)
Pharmacist will not agree to it	1 (1.1)