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ORIGINAL ARTICLE

Prescribing Pattern of Vitamins in Dermatologic Disorders at Tertiary Care Teaching Hospital in Western India

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Abstract

Skin ailments are a major burden in society. It is thought that Vitamins may help in improving skin health and appearance, but their deficiency may cause disease. The data regarding vitamin usage patterns in dermatologic practice in India is lacking. Therefore, the present study has been planned to analyze the prescribing pattern of vitamins. A cross-sectional, observational study was carried out at the outpatient department of dermatology at GCSMCH and RC, Ahmedabad, for 12 months from October 2019 to September 2020. Prescriptions of 500 patients were analyzed for common skin conditions and prescribing patterns. All the data were compiled into Microsoft Office Excel, and a descriptive statistical analysis was conducted. Out of 500 patients, males and females were 226(45%) and 274 (55%), respectively. Most of them had skin appendage-related diseases (28%). Out of the total of 1935 prescribed drugs, 619(31.98%) vitamins were prescribed in 500 patients with an average of 1.23 per prescription, in which the majority of drugs were as fixed-dose combination (FDC). Of 1211 prescribed vitamins, vitamin A was the most commonly prescribed vitamin 197 (39.4%). There is no association between prescribed vitamins and the prevalence of diseases. ($p>0.05$). However, the P-value is highly significant, suggesting an association between prescribed vitamins and different age groups. ($p<0.05$). Skin appendage-related diseases are commonest skin ailments. The use of vitamins in skin conditions is very common, particularly in oral formulations, among which the majority were prescribed as FDCs.

Keywords: Vitamins, Dermatology, Prescribing Pattern

Introduction

Skin is the outermost layer and the body's largest organ that performs various important functions like protecting against pathological organisms, various chemical agents (corrosive, irritating), and physical factors (sunlight, radiation, and mechanical).[1] Because of the body's outermost layer exposes it to injury by various extrinsic factors such as infectious agents, environmental, chemical, and some intrinsic factors such as genetic, metabolic, and immunological reactions.[2] The prevalence of skin disorders is approximately 2% of total Out Patient Department (OPD) consultations worldwide.[3] The Common Dermatological Diseases in India are acne vulgaris, dermatitis, eczema, vitiligo, melasma, psoriasis, urticaria, and infectious diseases.[4]

Nutrition is one of many factors required to maintain skin functions and overall skin

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health.[5, 6] Vitamins play a significant role in skin health by acting as antioxidants, sebum, and keratinization regulator, regulators of collagen synthesis, providing extra-cellular matrix homeostasis and acting as photoprotective, slowing skin aging and protection against the cellular events involved in the development of skin cancer.[6] There are various vitamin-related studies, but using vitamins in dermatology is infrequent, as these are more frequently prescribed in various dermatologic conditions. Therefore, this study aimed to analyze the prescription pattern of vitamins and other related aspects in dermatologic practice.

Methods

This was a single-center, observational, cross-sectional study conducted at the outpatient department (OPD) of Dermatology at GCS Medical College, Hospital and Research center, Ahmadabad, a tertiary care teaching hospital. Prescriptions of patients attending dermatology OPD of a tertiary care teaching hospital, Ahmedabad, were collected randomly by the twice-weekly survey for 12 months from October 2019 to September 2020. Data from 500 patients were collected and analyzed. Patients of all ages and gender that were prescribed vitamins and were willing to give written informed consent were included.

The Institutional Ethics Committee's permission was taken before the initiation of the study. The data obtained from the prescription were sorted and analyzed for demographic characteristics, drug use patterns, and percentage of drugs prescribed as vitamins. All the data were compiled into Microsoft Office Excel 2010 version, and a descriptive statistical analysis was carried out using Statistical Package for the Social Sciences (IBM® SPSS) trial Version 25. Mean, and standard deviation (SD) were used to describe numerical variables, and frequency (%) was used for categorical variables. The Chi-square test was used for the measurement of association. P-value <0.05 was considered statistically significant.

Results and Discussion

In this study, we categorized the patients according to age group, the prevalence of disease according to age group, and gender-wise (as per ICD 10). Frequencies of vitamins were evaluated in different disease classes and different age groups. This type of study entitled prescribing pattern of vitamins in dermatologic diseases is one of the rare studies conducted per our literature search.

The mean age of the patients was 34.07±16.39 years. Nearly half of the patients were aged 21 to 40 years (46.40%). The maximum age of the patients was 95 years, while the minimum was three years for the study population. Out of 500 patients, males and females were 226 (45%) and 274 (55%), respectively. (Table 1)

Diseases were categorized as per ICD–10 criteria. The highest percentage was patients with skin appendage disease (group G, 28%), where 47.85% of them suffered from acne. Moreover, about 26.6% were classified in Group H, where 67.66% of them suffered from pigmentation disorder. The result of our study is in contrast with Sarkar et al.[10] The most common dermatological disorder was Infectious disease (40%), followed by eczema and dermatitis (31%). In classes B, E, and F, approximately 2% of patients were found. (Table 1)

In the present study, acne hair and fall disorders were found in 14% and 12.4 % of the total study population, respectively, as compared to other studies conducted by Pathak et.al 2016[11] where it was 17.95% and 4.12%.

Table 1. Demographic Details of the Study Population

Demographic characteristic	Result N (%)
Gender	
Male	226(45.20)
Female	274(54.80)
Age (Years)	
0-20	113(22.60)
21-40	232(46.40)
41-60	120(24.00)
>60	35(7.00)
Disease distribution	
A-Infectious disease (Pyoderma, candidiasis, scabies, herpes zoster)	58(11.60)
B-Bullous disorder (pemphigus)	22(4.40)
C-Dermatitis and eczema (prurigo, pityriasis alba)	54(10.80)
D-Papulosquamous disease (Psoriasis and lichen planus)	71(14.20)
E-Urticaria and erythema	11(2.20)
F-Radiation related disorder (PMLE)	11(2.20)
G-Skin appendages disease (Acne, hair loss, alopecia areata, keloid)	140(28.00)
H-Other (pigmentation disorder, SLE, insect bite, nutritional deficiency)	133(26.60)

Vitamins use was increased due to the growing cases of dermatological illnesses and rise in research and development activities, shifting consumer preferences, rising health awareness, growing geriatric population, and cosmetic purpose.[9] Out of the total prescribed 1935 drugs, 31.98% was vitamin (619) (Table 2), which was much more as compared with the study of Mate VH et al.2019[13] and Gambre R et al[2] where it was 9% and 6.73%, respectively.

This increased frequency of prescribing vitamins is because we only enrolled patients with at least one vitamin. The majority of vitamins were prescribed as FDCs. (77.1%)

Out of 1935 drugs, only 13.02% were prescribed from the WHO essential medicine list, while 27.18% from the national list of essential medicine and the vitamins were 2.42%, and 8.11%, respectively. (Table 2) The mean value for all drugs per prescription was 3.87±1.46, which was almost similar to the findings of a study by Gambre R et al.[2] This result contrasts with the study of Narwane SPet al.2011[12] where the mean number of drugs prescribed was less (2.70±0.93).

Table 2. Prescription Pattern according to WHO Prescribing Core Indicators

Sr no	Drug use Indicators	Result
1.	The total number of prescriptions analyzed	500
2.	% of drugs prescribed as per WHO EML (2021)	13.02%
3.	% of drugs prescribed as per NLEM (2015)	27.18%
4.	% of drugs prescribed as FDCs	40.41%
5.	% of drugs prescribed with the generic name	9.76%
6.	% of drugs prescribed in injectable form	0.25%
7.	% of anti–microbial prescribed	9.81%
8.	% of vitamins prescribed	31.98%
9	% of vitamins prescribed as per WHO EML	2.42%
10.	% of vitamins prescribed as per NLEM	8.11%

Vitamin A was the most commonly prescribed (n= 197; 39.4%) followed by folic acid (n=176; 35.2%). Our findings compared to another study conducted by H.R. Lieberman et al. 2015 in which vitamin C was prescribed in 18%, followed by vitamin D (7%) and vitamin E (6%), respectively, in the study population. Vitamin B5 and K were the least prescribed.

Overall, oral route was the most commonly prescribed route. Among them, tablets were the most common dosage form, followed by the topical route in which the most common dosage form was creams. Moreover, the parenteral route prescribed certain vitamins like B3, B12, and D. Most vitamins were prescribed as FDCs. Still, specific vitamins were also prescribed as a single drug, like vitamins A, C, and folic acid, higher in number than others. Vitamin B1, B2, B5, B7 K, and E were only prescribed as FDCs. (Table 3)

Drugs other than vitamins were divided into thirteen groups according to their functions. Of all 1935 drugs prescribed, about 10.3% was the moisturizer, followed by the steroid. (10.2%). (Table 4) In our study total of nine different corticosteroids were prescribed in 169 (33.80%) patients, as compared with other studies conducted by Gupta R et al. 2019 and Gambre R et al.[2,21] where it was 41.7%,11.91% respectively.

On the other hand, we did in cost analysis and considered direct per-day cost only. The average cost of prescribed vitamins was INR 15.61±14.35, and for other concomitant drugs was INR 34.88 ± 27.30. (Table 5).

In disease class H (378), higher numbers of vitamins were prescribed, followed by class G (n= 246), while in F, the least numbers were prescribed. (Figure 1) Vitamin A was the most commonly prescribed vitamin in disease class G (commonly for acne) and H (commonly for pigmentary disease). It may be due to vitamin A having the function of reducing acne form eruption and has an antioxidant action so it has a role in pigmentary disease.[14,15] Vitamin D was most commonly prescribed in class D (psoriasis) because it has a function of an immunomodulator.[18,19]

Table 3. Analysis of Different Vitamins Prescribed (1)

Name of Vitamins	Present in No. (%) of prescription [n=500]	Prescribed as a Single drug No. (%)	Prescribed as FDCs No. (%)	Route with a Dosage form	No. (%)
Vitamin A	197 (39.4)	68(34.51)	129(65.48)	**Oral**	152 (77)
				Capsule	92 (60)
				Tablets	51(34)
				Syrup	9(6)
				Topical	45(23)
				Cream	40(89)
				Gel	5(11)
Vitamin B1	58(11.6)	0	58(100)	**Oral**	58 (100)
				Capsule	6 (10.3)
				Tablets	43(74.1)
				Syrup	9 (15.5)
Vitamin B2	58(11.6)	0	58(100)	**Oral**	58 (100)
				Capsule	6 (10.3)
				Tablets	43(74.1)
				Syrup	9 (15.5)
Vitamin B3	79 (15.8)	4(5.06)	75(94.93)	**Oral**	62 (78.4)
				Capsule	6 (9.6)
				Tablets	47(75.8)
				Syrup	9(14.5)
				Topical	13(16.4)
				Cream	11(84.6)
				Gel	2(15.8)
				Parenteral	4(5)
				IM injection	4(100)

Table 3. Analysis of Different Vitamins Prescribed (2)

Name of Vitamins	Present in No. (%) of prescription [n=500]	Prescribed as a Single drug No. (%)	Prescribed as FDCs No. (%)	Route with a Dosage form	No. (%)
Vitamin B5	44(8.8)	0	44(100)	**Oral**	33 (75)
				Tablets	24(74.1)
				Syrup	9 (15.5)
				Topical	11(25)
				Face wash	11(100)
Vitamin B6	59(11.8)	1(1.69)	58(98.3)	**Oral**	59 (100)
				Capsule	6 (10.1)
				Tablets	44(74.5)
				Syrup	9 (15.2)
Vitamin B7	111(22.20)	0	111(100)	**Oral**	111 (100)
				Capsule	6 (5.4)
				Tablets	105(94.5)
Vitamin B12	86 (17.2)	7(8.13)	79(91.8)	**Oral**	82 (95.3)
				Capsule	6 (7.3)
				Tablets	67(81.7)
				Syrup	9(10.9)
				Parenteral	4(4.6)
				IM injection	4(100)
Folic acid	176 (35.2)	48(27.27)	128(72.3)	**Oral**	172 (97.7)
				Capsule	6 (3.4)
				Tablets	166(96.5)
				Parenteral	4(2.2)
				IM injection	4(100)

Table 3. Analysis of Different Vitamins Prescribed (3)

Name of Vitamins	Present in No. (%) of prescription [n=500]	Prescribed as a Single drug No. (%)	Prescribed as FDCs No. (%)	Route with a Dosage form	No. (%)
Vitamin C	83 (16.6)	23(27.71)	56(72.2)	**Oral**	82 (99)
				Capsule	6 (7.3)
				Tablets	76(92.6)
				Parenteral	1(1)
				IM injection	1(100)
Vitamin D	103(20.6)	2(1.94)	101(98.09)	**Oral**	94 (91.2)
				Capsule	2 (2.12)
				Tablets	83(88.29)
				Syrup	9(9.5)
				Topical	8(7.7)
				Ointment	6(75)
				Gel	2(25)
				Parenteral	1(0.9)
				Intralesional	1(100)
Vitamin K	9 (1.80)	0	9(100)	**Topical**	9 (100)
				Cream	1 (11)
				Tincture	8(88.8)
Vitamin E	137 (27.4)	0	137(100)	**Oral**	62 (45.2)
				Tablets	53(85.4)
				Syrup	9(14.5)
				Topical	75(54.7)
				Cream	44(58.6)
				Gel	20(26.6)
				Face wash	11(14.6)

Vitamins C and E were commonly prescribed in disease class H because of their antioxidant action.[16,17]Among all prescribed vitamin B complex, B7 was most commonly prescribed in disease class G (hair related disorder) because it causes hair growth and reduces hair fall.[15] (Figure 1). Statistically, there is no association between prescribed vitamins and the prevalence of diseases. ($p>0.05$)

In the present study, a higher number of vitamins was prescribed in the age group of 0-20 and 21-40 years compared to others. (Figure 2). Vitamin D was most commonly prescribed in the age group 41-60 years because psoriasis is the most prevalent skin disorder in this group.[20] Among vitamin B complex, B7 was most commonly prescribed in age groups 0-20 and 21-40 years because in this group hair related disorders are much more and B7 has a role in hair growth and reducing hair fall. The p-value is highly significant, suggesting an association between prescribed vitamins (other than B-complex) and different age groups. ($p<0.05$)

This study is important in various aspects It is important to frame our results in terms of limitations. First, although the number of patients enrolled was relatively sufficient, a larger study population is needed for a better idea of disease epidemiology and prescription pattern. Second, it is a single-center study in a tertiary care teaching hospital which may not reflect the scenario at other healthcare facilities. Third, as this was a cross-sectional study, we did not follow up with patients, so long-term adverse effects and toxicity due to the overdose of supplements might have been missed. Fourth, as very few children and adolescents attended dermatologic OPD during our study period, fewer data were available in this age group we could not be generalized our findings. In the future, the study should be conducted at various dermatologic centers, including many children and adolescents.

Conclusion

We conclude from the present study that, acne, hair related, infectious, and pigmentary disorders were the commonest dermatologic ailment in which vitamins are used. Vitamins were most frequently prescribed drugs by various routes, majorities by fixed-dose combinations, while moisturizers and steroids were the most commonly used concomitant drugs. Prescriptions encountered with injections, by their generic name and present in the essential list of medicines, were fewer, which may not be an encouraging sign. In our study, though polypharmacy was found in the majority of prescriptions, in most of the cases, it was unavoidable and justifiable, as per our knowledge, but the risk of adverse reactions and drug-drug interactions couldn't be ignored.

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None

Conflict of Interest

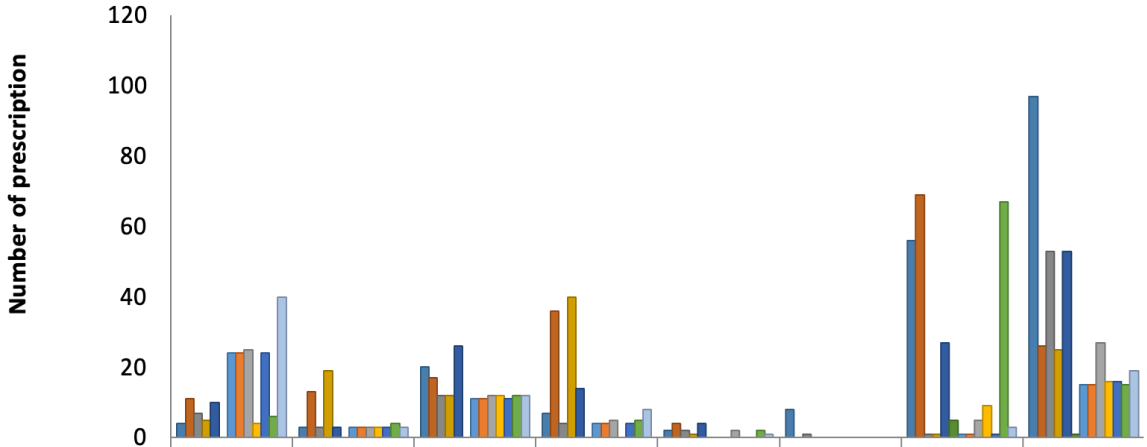
None

Table 4. Frequency of Drugs Prescribed other than Vitamins

Class of drug	Number of prescriptions have this class (500)	% of prescriptions contain this class	Total number of drugs prescribed in the class	% of total prescribed drugs)
Moisturizer	188	37.60	201	10.38
Corticosteroids	169	33.80	198	10.23
Antihistamines	186	37.20	196	10.12
Immunomodulators	106	21.20	120	6.20
Antibiotics	83	16.60	110	5.68
Miscellaneous	112	22.4	112	5.78
Anti-acne	89	17.8	89	4.59
Anti-fungal	50	10	67	3.46
Antacid	63	12.6	63	3.25
Anti-hypertensive	56	11.2	56	2.89
Analgesic	44	8.8	44	2.27
Depigmentation	26	5.20	26	1.30
Anti-viral	13	2.60	13	0.67

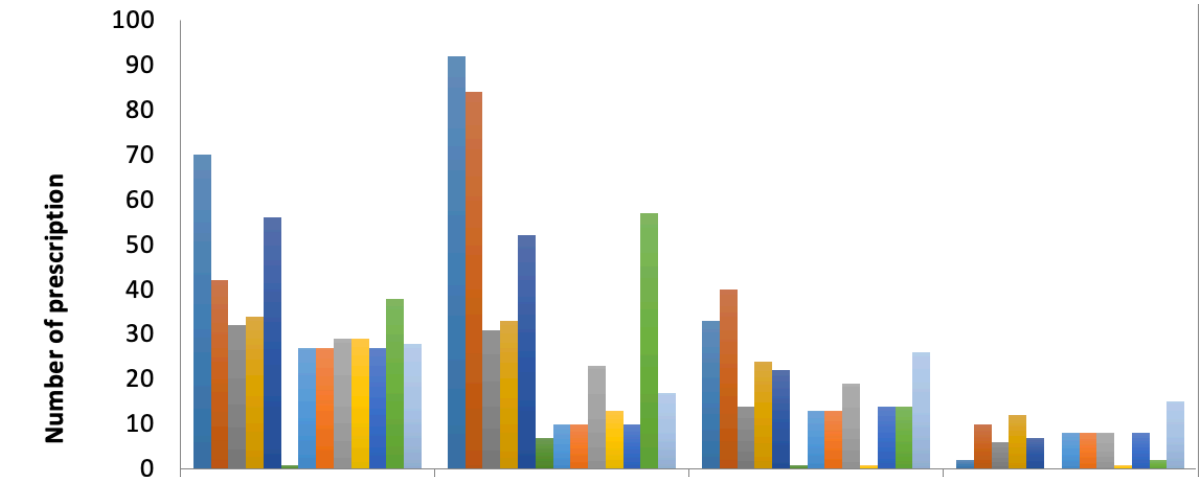
Table 5. Cost Analysis of the Prescription among the Study Participants

Cost of Variable	Result (INR)
1. Total cost/prescription (Mean ± SD)	50.66±29.66
2. Vitamins/prescription (Mean ± SD)	15.61±14.35
3. Concomitant medicine cost/prescription (Mean ± SD)	34.88 ± 27.30



	A	B	C	D	E	F	G	H
Vitamin A	4	3	20	7	2	8	56	97
Folic acid	11	13	17	36	4	0	69	26
Vitamin C	7	3	12	4	2	1	1	53
Vitamin D	5	19	12	40	1	0	1	25
Vitamin E	10	3	26	14	4	0	27	53
Vitamin K	0	0	0	0	0	0	5	1
Vitamin B1	24	3	11	4	0	0	1	15
Vitamin B2	24	3	11	4	0	0	1	15
Vitamin B3	25	3	12	5	2	0	5	27
Vitamin B5	4	3	12	0	0	0	9	16
Vitamin B6	24	3	11	4	0	0	1	16
Vitamin B7	6	4	12	5	2	0	67	15
Vitamin B12	40	3	12	8	1	0	3	19

Figure 1. Frequency of Vitamins Prescribed in Different Disease Classes



	0-20	21-40	41-60	>60
Vitamin A	70	92	33	2
Folic acid	42	84	40	10
Vitamin C	32	31	14	6
Vitamin D	34	33	24	12
Vitamin E	56	52	22	7
Vitamin K	1	7	1	0
Vitamin B1	27	10	13	8
Vitamin B2	27	10	13	8
Vitamin B3	29	23	19	8
Vitamin B5	29	13	1	1
Vitamin B6	27	10	14	8
Vitamin B7	38	57	14	2
Vitamin B12	28	17	26	15

Figure 2. Age-wise Distribution of Prescribed Different Vitamins

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Effects of *Centella Asiatica* (L) Urb. on Cognitive Function in Hypothyroid Mice Offspring

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Abstract

Centella asiatica (*C. asiatica*) is widely used in traditional medicine due to its numerous health benefits. Among its reputed advantages are improved memory, intelligence, and neural protection. Impairment of cognitive function as a center for memory processing occurs due to perinatal hypothyroidism. Although several studies have shown that *C. asiatica* extract may improve memory function, the effectiveness of its extract as a memory enhancer for patients with perinatal hypothyroid is less unknown. Therefore, this study aimed to determine the effects of ethanol extract of *C. asiatica* (EEC) leaf as a memory enhancer in perinatal hypothyroid mice model. *C. asiatica* leaves were extracted by the decoction method, and the ethanol extract was administered to mice. The hypothyroid mouse model was developed by administering antithyroid agents to pregnant mice from gestational day (GD) 18 to postnatal day (PND) 21. The hypothyroid mice were administered either donepezil 5 mg/kg BW/mL (positive control) or treatment group (EEC 2 mg/kg BW/mL) from PND 21 to PND 35 (14 days). The light-dark test (LDT) and memory tests of offspring were conducted on PND 36. We found that EEC improved the cognition and memory of perinatal hypothyroidism mice. This study contributes to the foundational research for developing memory-enhancing supplement preparations, mainly targeting children with perinatal hypothyroidism

Keywords: *Centella asiatica*, ethanol extract, memory enhancer, perinatal hypothyroid

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Introduction

Centella asiatica (*C. asiatica*) is an herbal plant that thrives in tropical climates and is renowned for its medicinal properties. It has been traditionally used to treat various ailments affecting the brain, endocrine system, skin, respiratory system, and gynecological issues.[1,2] *C. asiatica* has also been to improve memory which is attributed to the neuroprotective and neurotrophic factors found in it. The phytochemical analysis of *C. asiatica* has identified several bioactive compounds, including isoprenoids (sesquiterpenes, sterols, pentacyclic triterpenoids, and saponins) and phenylpropanoid derivatives (eugenol derivatives, caffeoylquinic acid, and flavonoids).[3]

Thyroid hormones (TH) play an important role in the development and functional maintenance of the central nervous system. During the development stage, these hormones regulate the growth and morphogenesis of brain and nerve cells by influencing the dendritic growth of cerebellar Purkinje cells, proliferation, and migration of granules. Consequently, thyroid hormone deficiency during development leads to impaired motor coordination in adulthood.[4,5] Moreover, hypothyroidism negatively affects the hippocampus, leading to impaired granule cell migration and dendritic growth of pyramidal cells. This disruption in synaptic function contributes to decreased memory and cognitive processes.[6,7]

Therefore, this study aimed to assess the efficacy of *C. asiatica* leaf extract as a memory enhancer in perinatal hypothyroid mice. Through careful observation of behavioral changes in mice with perinatal hypothyroidism following the administration of EEC, we aimed to evaluate the impact of the extract on memory function. The results of this study would be the primary basis for further research to develop the preparation of EEC as a dietary supplement to improve memory in children, especially in children with a history of perinatal hypothyroidism.

Methods

Extraction and Phytochemicals Screening

C. asiatica leaves were macerated using 70% ethanol. A total of 200 grams of C. asiatica leaves were dissolved in 2L of solvent and soaked for 24 hours, followed by filtration. The resulting filtrate was immersed three times, with each cycle lasting 24 hours and involving the replacement of the solvent. The collected filtrate was combined and concentrated with a rotary evaporator at a temperature of 45°C. The evaporation time was ± 3 hours. After evaporation, the extract was weighed to determine the yield of the extract, then stored in a refrigerator (± 4°C) in a light-tight bottle until it was used. After obtaining the C. asiatica extract, a phytochemical screening process was carried out to determine the content of secondary metabolite compounds such as alkaloids, flavonoids, saponins, steroidal tannins, and terpenoids in the extract.[8,9]

In vivo Analysis

The experimental animal protocol in this study followed directions from the Program Study of Pharmacy, Faculty of Mathematics and Natural Sciences, Bandung Islamic University, Bandung-Indonesia and Departement of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung-Indonesia.

Treatment

A schematic of the animal study schedule is shown in Figure 1. The hypothyroid mouse model (Dam, n= 8) was conducted by administering 100 ppm propylthiouracil (PTU) in drinking water.[6] The hypothyroid mice then were administered either donepezil 5 mg/kg BW/mL (positive control) or treatment group (EEC 2 mg/kg BW/mL) from PND 21 to PND

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35 (14 days). The light-dark test (LDT) and memory tests of offspring were conducted on PND 36.

Behavior Test

The light/dark test

This test was carried out to see the anxiety-like behavior in mice. All sessions were recorded on video, and exploration time was measured manually with a stopwatch. The parameters calculated are the time of animal exploration in the light compartment and the number of transitions between each compartment.[10] (Figure 2)

Rotarod Test

The accelerating rotarod test assessed motor coordination and motor learning.[11] Mice were placed on a cylinder drum of a rotarod apparatus. The surface of the drum was covered with hard chloroethylene, which does not permit gripping on the surface. Prior to the test, the mice were habituated to remaining on the stationary drum for 1 min. The apparatus was started at an initial speed of 4 to 40 rpm over 2 mins. Mice performed five trials per day, and the test was repeated for three consecutive days to assess motor learning.[12] (Figure 3)

Object Recognition Test (ORT and Object-in-Location Recognition Test (OLT)

This test was carried out to see the memory function in mice. ORT/OLT was done by storing two identical objects. All sessions were recorded on video and exploration time was measured manually with a stopwatch. (Fig. 4) The discrimination ratio is determined by dividing the time spent exploring new objects by the total time exploring both objects during the test session.[6,7,13]

Statistical Analysis

Statistical comparisons were performed by one- or two-way ANOVA followed by the Bonferroni post hoc test using SPSS Software version 22.0 (IBM SPSS, Armonk, New York). Differences were considered significant at $p < 0.05$. All values are presented as the mean ± SEM.

Results and Discussion

Extraction and Phytochemical Screening

The simplicia extraction process was carried out by the maceration method. The maceration method was chosen because it is simple and widely used. Maceration is also the most suitable method to avoid the destruction of thermolabile compounds. The solvent used is

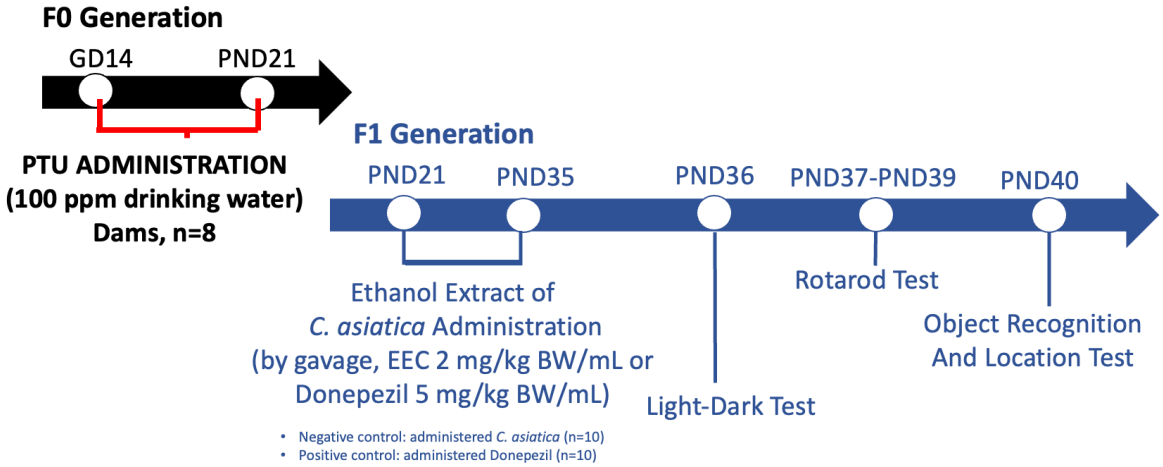

Figure 1. Schematic Drawing of Experimental Procedure

70% ethanol. The extraction process yielded a total of 33.36 grams of thick extract, indicating that approximately 16.68% of the weight of the sample/simplicia was successfully dissolved or obtained during the extraction process. Following the extraction, a phytochemical screening test was conducted to qualitatively determine the chemical classes in the sample/plant material. This screening method predominantly relied on color test reactions with specific color reagents. Detailed results of the phytochemical screening for both the simplicia and the 70% ethanol extract of *C. asiatica* can be found in Table 1.

Animal Model

The hypothyroid mouse model was successfully carried out by giving 100 ppm PTU to the mother mice. The hypothyroid status of the mice was seen from the body weight of hypothyroid mice, which tended to be lower than the control, and the behavioral test results were consistent with the previous study.6 A recent study increased the dosage of PTU to 100 ppm to mimic severe hypothyroidism in clinical cases. PTU was administered to pregnant dams through water bottles from GD 14 to PND 21. On PND 21, dams and female offspring were sacrificed, while the male offspring were continuously administered EEC for 14 days at a dose of 2 mg/kg BW/mL. Gray et al showed that water extract of *C. asiatica*, administrated at the same dose, improved performance in all behavioral tests of aged mice. These findings suggested the potential effects of *C. asiatica* on memory related to the hippocampus and cortex and executive function mediated by the prefrontal cortex.[3]

Behavioral Test Results

We first performed the light-dark offspring. The light/dark test is based on the innate aversion of rodents to brightly illuminated areas and on the spontaneous exploratory behavior of rodents in response to mild stressors, that is, novel environments and light.[14] Activity in the open field was monitored for 10 min. Figure 2a shows that the EEC-treated group stayed longer in the light compartment than the control (control negative= 47.44 ± 12.12 seconds; control positive= 112.17 ± 14.92; EEC= 130.23 ± 8.87. by Bonferroni test, $p<0.001$). Moreover, the EEC-treated group showed less transition between light and dark compartments. (Fig.2b)

Table 1. Results of Simplicia Phytochemical Screening and Pegagan Extract

No.	Compounds	Stain Viewer	Simplisia	Extract
1.	Poliphenolat	FeCl3	+	+
2.	Antraquinone	NaOH	+	+
3.	Flavonoid	Mg Powder and HCl	+	+
4.	Tanin Catechist	Steasny Reagent (formaldehyde, 30% : HCl 2:1	+	+
5.	Tanin Galat	Sodium Acetate + FeCl3	-	-
6.	Triterpenoid and steroid	Liebermann - Burchard	+	+
7.	Alkaloid	Dragendorf	-	-
		Mayer	-	-

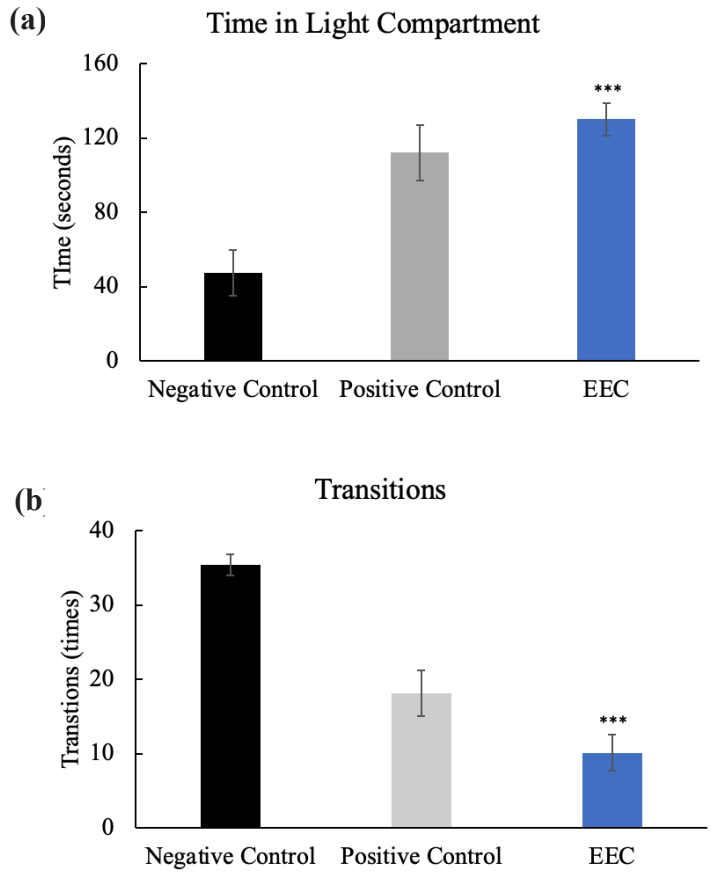

Figure 2. The Effect of EEC Administration in Light-Dark Test.

(a) EEC-treated group stayed longer in the light compartment than the control (by Bonferroni test, $p<0.001$).

(b) The EEC-treated group showed less transition between light and dark compartments. (by Bonferroni test, $p<0.001$).

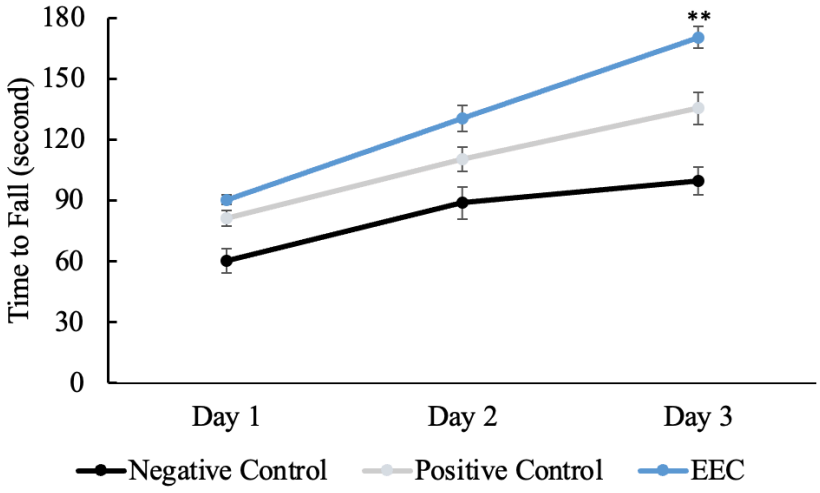

Figure 3. The Effect of EEC Administration in Rotarod Test.

The EEC-treated group showed higher time spent on the rotarod until three consecutive days than the control group (by Bonferroni tes, $p<0.01$)

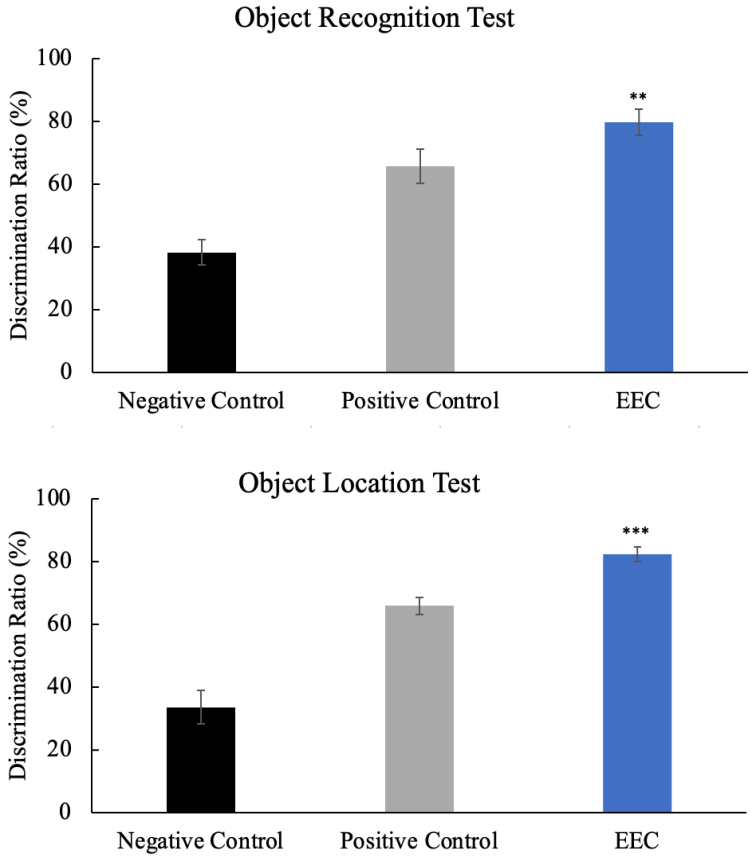

Figure 4. The Effect of EEC Administration in Obejct Recognition Test and Object-in-Location Test.

The EEC-treated group showed a higher discrimination ratio than the control than the control group (ORT, by Bonferroni test p<0.01; OLT, by Bonferroni test p<0.001)

TH plays a critical role in regulating important neurotransmitters, including GABA, serotonin, and norepinephrine. These neurotransmitters are essential for various brain functions and are influenced by TH levels. In hypothyroidism, there is a disruption in the balance of neurotransmitters, which can lead to feelings of depression and anxiety.[15]

Increased anxiety due to hypothyroidism in utero and postnatal and in a thyroid receptor knockout mouse model has been previously reported. A study in mouse adult-onset hypothyroidism in male mice produces a mild anxiogenic effect, possibly due to unliganded receptor actions.[16] The present study confirmed that EEC minimizes the risk of anxiety-like behavior in hypothyroid mice. This result is in line with a study conducted by Wanasuntronwong et al, which showed that the administration of C. asiatica developed an anxiolytic effect in acute and chronically stressed mice.[17] Moreover, human studies have shown that *C. asiatica* supplements can improve mood and arousal in healthy individuals,[18] reduce anxiety-related disorders and stress and depression phenomena significantly.[19] Thus, it can be concluded that *C. asiatica* has good potential in reducing anxiety disorders in hypothyroid mice.

We conducted the rotarod test to examine motor coordination and motor learning. The EEC-treated group showed higher time spent

on the rotarod until three consecutive days than the control group. (Day 1 to Day 3. Negative control: 60.3 ± 6.06 seconds, 88.95 ± 7.95 seconds, 99.55 ± 6.96 seconds; Positive control: 81.2 ± 4.04 seconds, 110. 37 ± 6.00 seconds, 135.31 ± 7.91 seconds; EEC: 90.32 ± 2.45 seconds, 130.21 ± 6.44 seconds, 170.3 ± 5.32 seconds. By Bonferroni test $p<0.01$).

Several brain regions are involved in motor coordination, but the cerebellum plays a major role. TH regulates cerebellum function. Perinatal hypothyroidism reduced the growth and branching of Purkinje cell dendrites and the number of synapses between Purkinje cell dendrites and granule cell axons.[13] The recent study found that the EEC-treated group showed higher time spent on rotarod and developed better motor learning in three consecutive days. The specific mechanisms by which *C. asiatica* enhances motor coordination and learning require further investigation. However, a study conducted by Lee et al.[20] using multiple stroke models in rats suggested that asiatic acid caused a significant reduction in infarct volume and improved neurological outcomes. Further studies are necessary to examine the effect of *C. asiatica* on motor coordination and learning.

We evaluated memory function in mice by performing ORT and OLT. The EEC-treated group showed a higher discrimination ratio than the control (ORT: Negative control= 38.30 ± 4.07%; Positive control= 65.77 ± 5.44%; EEC= 79.75 ± 4.12%. OLT: Negative control= 33.53 ± 5.25%; Positive control= 65.91 ± 2.75%; EEC= 82.30 ± 2.30%).

Previous studies have reported that developmental thyroid hormone insufficiency impairs spatial learning memory in rodent models[7,21,22] This study showed that the administration of EEC improved memory function. The beneficial effects of *C. asiatica* on neuronal health and cognitive function have been well-known both in vitro and in vitro.[2,3,23,24] The previous study declared that the improvement in the object-in-location test might cause by asiatic acid, a major triterpene component of *C. asiatica*,[25] which improves performance in the same task in healthy and impaired rodents. Moreover, improved memory can be associated with increased ARE gene expression, particularly in the hippocampus, suggesting a possible reduction in oxidative stress in addition to the natural cellular response to pathology.[26] This study clearly described that *C. asiatica* improves cognitive function in hypothyroid mouse models.

Conclusion

In conclusion, the findings of this study provide evidence for the effectiveness of *C. asiatica* in reducing anxiety levels and improving cognitive function in a hypothyroid mouse model. In contrast, the donepezil-treated group exhibited slightly better outcomes than the EEC-treated group. Furthermore, our study suggests that *C. asiatica* has the potential for further development as a memory enhancement supplement for individuals with hypothyroidism. Further research is warranted to explore the underlying mechanisms and optimize its formulation for therapeutic use in hypothyroid cases.

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Nil

Conflict of Interest

None declared

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Kratom *(Mitragyna speciosa)* Leaf Ethanol Extract Showed In Vivo Analgesic Activity

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Abstract

Analgesic drugs like morphine and other opioids exhibit several harmful effects. Thus, the exploration of a new and safer analgesic drug is necessary. Utilizing Indonesia's biodiversity richness, medicinal plants can serve as an alternative source of novel analgesic drugs. Here, we show the analgesic activity of Kratom (*Mitragyna speciosa*) leaf ethanol extract (KE) in formaldehyde-induced rat (*Rattus norvegicus*) models. The effect of KE was examined by observing the duration of spontaneous nociceptive behavior such as paw licking or limp leg. The result showed that rats treated with 70 mg/kg KE demonstrated significantly ($p<0.01$) decreased nociceptive behavior compared to those receiving vehicles. However, a higher KE dose (210 mg/kg) failed to increase the analgesic effect and showed a slight reduction (not significant) compared to the control group. These findings proved that kratom leaf ethanol extract has the potential to alleviate painful conditions.

Keywords: *Mitragyna speciosa*, kratom leaves, ethanol extract, opioid analgesic

Introduction

Pain is a distressing sensory and emotional experience related to actual or potential tissue damage or mimicking that experience. Pain is a multidimensional sensory experience and can be distinguished in intensity (mild, moderate, severe), quality (blunt, burning, sharp), duration (transient, intermittent, persistent), and spread (superficial or deep, localized or diffuse).[1]

Based on the 2013 Baseline Health Research (Riskesdas) data, the citizen of East Java Province, Indonesia, was the most users of analgesic drugs in all provinces in Indonesia. This shows the high prevalence of pain in Indonesia, especially in East Java.[2] Regarding the treatment of mild pain, non-steroidal anti-inflammatory drugs (NSAIDs) are still effective in blocking pain sensations. However, for moderate to severe pain due to cancer or post-surgery, more potent opioid analgesics are needed, such as codeine, tramadol, oxycodone, morphine, or fentanyl. This class of drugs has proven effective in treating severe pain by blocking opioid receptors in the central nervous system (CNS).

On the other hand, these opioid analgesics also possess concerning side effects, such as constipation, respiratory depression, addiction, and the potential for drug abuse.[3] Therefore, it necessitates developing a new and safer opioid analgesic drug. Utilizing

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Indonesia's biodiversity richness, medicinal plants are a viable option since they contain various chemicals from which new analgesic medications might be developed.

Mitragyna speciosa, known as kratom, has several properties such as analgesic, antinociceptive, sedative, antiobesity, anticancer, anti-inflammatory, antioxidant, and antibacterial.[4–8] Specifically for its analgesic activity, several studies have reported that the content of kratom leaves can bind to opioid receptors in the CNS, resulting in severe pain cessation.[4,9] This effect is mediated by two major constituents, mitragynine and 7-hydromitragynine, which are isolated from the methanol extract of kratom. Whereas withdrawal symptoms and addiction were evident in both animal models and regular kratom users, indicating that mitragynine possesses the risk which closely mimics those of morphine.[10,11] Therefore, the present study aimed to explore antinociceptive activity of kratom leaf ethanol extract in rats (*Rattus norvegicus*).

Methods

Collection and preparation of plant extract

Fresh leaves of Kratom (*Mitragyna speciosa*) were bought from a supplier in West Kalimantan, Indonesia, and authenticated by Tri Puji Lestari Sudarwati (Pharmacy Academy of Surabaya, Indonesia). Leaves (around 30 g) were then washed, shade dried, and crushed into powder. Subsequently, dry leaves powder (20 g) was macerated with 150 mL of 96% ethanol for 24 hours at ambient temperature. The mixture was stirred occasionally to maintain homogeneity and then filtered.[5] The crude extract (3.38 g) was then concentrated using a rotary evaporator and coded as KE (Kratom Extract). The yield of the extract was found to be 16.9% w/w.

Animals

The preclinical study protocol was approved by the Institutional Ethical Committee of the University of Surabaya, decree number: 97A/KE/VII/2022. Male Wistar rats used in this study were purchased from the animal house of Drh Rachmad Priyadi farm weighing 80–150 g. The animals were placed in plastic cages in a room maintained at a room temperature (21°C) and 12 h light: dark cycle, with unlimited access to standard chow and water, then acclimatized for seven days before the study started.

All feasible measures were taken to minimize animal suffering and limit the number of animals utilized in research. On day one, they were randomly placed in a group of three. Later on day eight, each group was assigned to receive different treatments as follows: Group I was the negative control (vehicle-treated), Group II was the positive control tramadol 0.9 mg/kg p.o, Group III received KE 70 mg/kg p.o., and Group IV received KE 210 mg/kg p.o. All animals were sacrificed after the treatment and measurement to avoid further pain.

Formaldehyde-induced pain model

The test substances and controls were administered to the subject animals according to the previously outlined protocol. After administering the treatments for one hour, 50 µL of a solution containing 2% formaldehyde was injected subcutaneously into the left/right hind paw of the Wistar rats and immediately transferred to a transparent plastic cage for better observation. The spontaneous nociceptive behavior was determined instantaneously by looking at the animal behavior and measuring the duration every time they were licking paws and limping injected-leg.

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The paw licking and limping injected-leg duration was examined from 0 to 5 minutes (first phase, neurogenic) to 15 to 30 minutes (second-phase, inflammatory).[12] The inhibition percentage (%) of nociceptive behavior was also calculated following this formula:

$$\text{Inhibition}(\%) = \frac{\text{Duration of nociceptive behavior (control)} - \text{Duration of nociceptive behavior (test)}}{\text{Duration of nociceptive behavior (control)}} x\ 100\% \quad (1)$$

Statistical Analysis

The results were reported as mean ± standard error of the mean (SEM). The statistical analysis was determined by One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests and performed using GraphPad Prism version 8.0.1 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com; $P<0.05$ was considered as significant.

Results and Discussion

In the past decade, kratom's popularity has soared in Western nations; recent estimates suggest that about five million Americans regularly take kratom. This is supported by the easy use of kratom leaves such as chewing, brewing like tea, smoking as cigarettes, and swallowing directly as compressed tablets or capsules.[13] In Indonesia, kratom obtained from the West Kalimantan region has not been widely studied for antinociceptive activity. Only two articles have been published, the first examines the effect of the dichloromethane fraction in mice, and the second examines the water fraction in male mice.[14,15] In the present study, we opted to determine the antinociception properties of kratom leaves ethanol extract in Wistar albino rats.

Following the oral administration of test substances, animals were induced with formaldehyde to examine the analgesic activity of kratom leaves ethanol extract and compare it with positive (tramadol) and negative (vehicle) control. Figure 1 depicted the duration of paw licking or limping leg after formaldehyde induction, while Table 1 showed the inhibition percentage of rats' nociceptive behaviors. Compared to the control group, KE

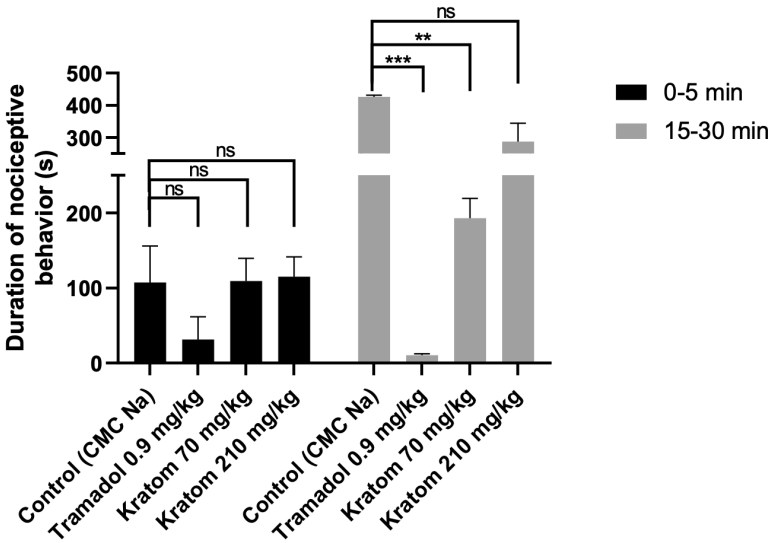

Figure 1. Effect of KE at all the tested doses in both early neurogenic (0-5 min) and late inflammatory phases (15-30 min) estimated by formalin-induced pain models. The duration of nociceptive behavior is presented as mean ± SEM (n = 3). *** P < 0.001, ** P < 0.01 versus negative control using one-way ANOVA followed by Tukey's post hoc multiple-comparison test

Table 1. Average Percentage Inhibition of Nociceptive Behavior

Groups	Neurogenic phase (0-5 min)	Inflammatory phase (15-30 min)
Control (CMC Na)	Ref	Ref
Tramadol 0.9 mg/kg	70.1%	97.5%
Kratom 70 mg/kg	-1.6%	54.7%
Kratom 210 mg/kg	-7.1%	32.5%

with the oral dose of 70 mg/kg significantly ($P<0.01$) reduced rats' nociceptive behavior in the late phase (54.7% reduction). Although, the higher dose did not show a significant reduction, and tramadol (0.9 mg/kg) had more significant ($P<0.001$) reductions than tested extracts. Furthermore, in the first neurogenic phase, kratom leaf ethanol extract did not exhibit blockage to formaldehyde-induced pain stimulation. This model is a biphasic pain reaction.

The induced pain is mediated by glutamate during the neurogenic phase of pain transmission. While the second phase (15 to 30 minutes) of the inflammatory pain response is characterized by releasing inflammatory mediators such as prostaglandins, excitatory amino acids, and histamine. Bradykinin has the unusual ability to influence both stages simultaneously.[16]

Interestingly, another study reported that methanol extract of kratom leaves with a dose of 200 mg/kg could show significant reductions in both phases of the formalin test, indicating that extract active compounds can act in central and peripheral pain.[8] In contrast, our findings suggest that active compounds from 70 mg/kg ethanol extract tend to act as antiinflammatory pain, which inhibits peripheral pain pathway. Meanwhile, a study by Goh et al. (2021) revealed that 200 mg/kg of kratom leaf ethanol extract possessed a similar antinociceptive effect as morphine (5 mg/kg) in the tail-flick test. This means ethanol extract of kratom leaves also possesses central pain blockage. Yet, Goh and co-workers used an accelerated solvent extraction technique that increases the interfacial interaction with the analyte by driving the solvent into the sample matrix's pores, resulting in enhanced analyte recovery and dry yield of extract (29.1% w/w).[17] Taken together, kratom leaves ethanol extract might show antinociceptive and anti-inflammatory properties.

Its antinociceptive activity is influenced by the alkaloid content of mitragynine and the active metabolite of 7-hidroxymitragynine (7-HMG), which can bind to brain opioid receptors.[9,18] Within ethanol-dried extract of kratom, it contains approximately 6.5% of mitragynine, slightly lower than methanol extract, which has more than 7%.[17] Regarding the pharmacokinetics profile, mitragynine is a lipophilic, weak base that passively crosses the intestinal and blood-brain barrier; thus, it quickly permeates and is dispersed in the brain.

The bioavailability was calculated to be 21%, and 85-95% of the drug is bound to plasma proteins.[19] Therefore, kratom and its mitragynine demonstrate potential utility for managing severe pain; however, abuse potential and addiction risk hurdle their clinical usage. According to Hemby et al. (2018), 7-HMG possesses more abuse potential and induces withdrawal than mitragynine,[20] whereas 7-HMG is the product of phase I metabolism

of mitragynine.[21] Structural modification to avoid the formation of 7-HMG during metabolism might ease further development of mitragynine as an opioid analgesic.

This study has limitations, such as the number of animals and a single parameter for antinociceptive activity measurement. Furthermore, the formaldehyde-induced pain model measurement relies on rats' behavior might result in observation bias. However, the chosen method was beneficial in exploring the possibility of both antinociceptive and antiinflammatory activity of a certain compound.

Conclusion

To conclude, we reported the analgesic activity of kratom leaves ethanol extract based on Wistar rats' behavior following formaldehyde induction. Prior to a human clinical study, future researchers should pave the way to examine the exact mechanism of kratom alleviating pain and its safety profile.

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Conflict of Interest

The authors declared no conflict of interest in the manuscript.

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Pharm-Care Tadulako: Web-based Design Application to Improve Pharmaceutical Care Services

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Abstract

Pharmaceutical services recently require new ideas and innovation to provide maximum benefit concerning the pharmacological treatments of patients and take responsibility for monitoring their therapy. One of the proposed efforts by pharmacists is the pharmaceutical care program designed to ensure pharmacists can monitor safe and effective medication use and provide timely access to medicines for the population. Moreover, eHealth application in terms of technology is expected to be effective, networked, patient-centered, and accessible for patients. Therefore, Pharm-Care Tadulako, a personalized eHealth application designed with key features of pharmaceutical care to enhance communication between pharmacists and patients, is presented in this study. Some of the services intended to be provided by this application include electronic medical records (EMR), drug reminders, pharmaceutical messenger, clinical data monitoring, and medication analysis. The application was developed using Software Development Life Cycle (SDLC) Waterfall. A pilot study was conducted at four pharmacies in Palu City, Centre of Sulawesi, Indonesia, using 30 patients who volunteered willingly to participate in the experiment. It was discovered that 65% of the 30 patients were 26-45 years old, out of which 36% suffered from hypertension. The Pharm-Care Tadulako application positively impacted pharmacists when providing pharmaceutical care services to patients. At the same time, they could monitor their treatment through the five main features of the application

Keywords: pharmaceutical care, pharm-care tadulako, SDLC, applications

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Introduction

A continuous increase in scientific and technological knowledge is associated with clinical pharmacy and pharmaceutical care. This is observed from the contribution of pharmaceutical care to the evolution of the pharmaceutical profession, which is discovered to have started expanding to other sectors, specifically the community pharmacy.[1] Moreover, improving the effectiveness of treatment and disease management requires innovations in telemedicine through electronic or website-based applications.[2,3]

It is important to note that pharmacists act as intermediaries between doctors and patients by providing both medicines and free medical advice.[4] They are also crucial to the health systems because they can offer health services by dispensing medicinal products, advising patients on drug assumption regimens, and offering pharmacovigilance services.[5]

Patients need more opportunities to increase their attention towards their health and disease management in recent times.[2,6] They can optimize therapeutic outcomes through the development of tools and applications that can provide information on the treatment of diseases with a focus on compliance and adherence, Adverse Drug Reactions (ADRs), and Drug-Drug Interactions (DDIs).[7,8] Moreover, more applications have been developed for pharmacists to utilize their expertise, knowledge, skills, and commitment to providing all the information needed to increase the quality of life of individuals.[4,9]

Pharmacists perform specific clinical roles, including providing information to increase patient compliance in taking drugs required to improve their safety, efficacy, and positions in drug dispensing.[10,11] Previous studies showed several cases of drug contraindications, excessive doses, side effects, and drug interactions due to the lack of health services, specifically from pharmacists.[12,13] This indicates the need to ensure faster and more flexible access to pharmacists. Therefore, Europe was reported to have developed a web-based application to be used by patients through QR codes to connect with pharmacists to evaluate drug use.[14]

There is minimal monitoring of drug use by pharmacists, as indicated by the results of a previous study that 56% of patients are not familiar with pharmacists. In comparison, 86.6% are expected to consult on drug-related problems.[15,16] Therefore, this study aims to facilitate the activities of pharmacists in drug administration and evaluation and to increase patient knowledge of their treatments.

Materials and Method

System Development Life Cycle (SDLC) creates and modifies systems, models, and methodologies to develop software.[17] At the same time, the waterfall method is generally used for systematic development from one stage to another.[18] It is important to note that the SDLC method was applied to develop software to solve obstacles related to the development of health information technology. The process was initiated with the need identification stage, followed by prototypes, functional validation, and evaluation.[19]

Meanwhile, the waterfall method follows a linear sequential flow, with the progress observed to be flowing down as it was in the developing phase. This approach does not allow a return to the previous step but will enable changes. Moreover, the SDLC model used a step-by-step approach to complete the software development process. It is essential to note that a robust process usually leads to a solid final product and a successful project.[20]

The seven stages involved in the development of the Pharm-Care Tadulako application using this method are explained as follows:

1. Planning: This stage involves searching for information related to the reasons for developing the Pharm-Care Tadulako applications and the needs of pharmacists towards improving pharmaceutical services and care services as the foundation for the development of the application.
2. Needs Analysis: This involves analyzing the features to be added to the design of the proposed application about the main problems.
3. System Design: This stage involves developing the preliminary system design related to the proposed application as indicated by the algorithms in the form of flowcharts/flow diagrams, details of the features to be added, and the inclusion of cases from the perspectives of admins and users.
4. Development: This stage focuses on searching and finding the needs to be completed before creating the application. Some of the things considered include the software, hardware, and brainware required to ensure the successful development of the application.
5. Implementation: The developers combine the system design and development stages to execute the application using the previously highlighted software, hardware, and brainware requirements. It is important to note that the sublime text code editor was used for coding, which serves as the application's core.
6. Evaluation: This stage involves analyzing the shortcomings and weaknesses of the application. A black box method which is usually used to assess an application from the outside without critical observation was applied in this study.
7. Maintenance: This stage involves determining the shortcomings and weaknesses of the application and how they can be resolved. Maintenance is usually conducted after evaluation for a specific time.

Data Collection

This study invited four pharmacies in different sub-districts to use the Pharm-Care Tadulako application developed. The clinical study was approved by the Faculty of Medicine, Tadulako University, number 5480/UN.21.8.30/KL/2021. All pharmacists in each store were provided with detailed information concerning the application and the data collected between October 19th to 23rd, 2021, in Palu City, Centre of Sulawesi, Indonesia. It is important to note that pharmacists and patients were asked to fill out an informed consent form.

Data Analysis

The Pharm-Care Tadulako application was used for pharmaceutical services at several pharmacies in Palu in October 2021. The users who also served as the respondents include four pharmacists between 23-37 years old and 30 patients of all ages. The data analyzed include the patient disease patterns, age, gender, medications, and the most often used features of the Pharm-Care Tadulako application.

Results and Discussion

In developing The Pharm-Care Tadulako, seven processes were run to a successful application. Based on observation of the pharmacy condition in Tadulako, we have planned and designed the features for Pharm-Care Tadulako. (Fig. 1). The web domain was purchased from Hostinger (http://hostinger.co.id). The web-based application was created using HTML, CSS, PHP, and Javascript.

The system internally saved all data inside the website. The website was well-developed to make it easier for users to access it. The

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steps for using the web started with the login, registration, EMR drug reminders, and clinical data monitoring, the pharm messenger and medication analysis (Fig.2) were also accessible on the website. To start the application testing, we submitted an ethical clearance. This study was approved by the Research Ethics Committee of the Faculty of Medicine and Health, Faculty of Medicine, the University of Tadulako, with the number 5480/UN/28.1.30/KL/2021. All efforts were made to protect participants' data on the website.

A total of 4 pharmacists, including three males and one female between the age range of 29-35 years, willingly participated. This showed that young pharmacists better understand application usage than older ones. Meanwhile, patients who used the application were between 6-74 years, most in the adult category (65%), while the least were the children and the elderly (3%) (Fig. 3).

It is important to note that pediatric patient data was filled in by their parents, who are 35 years old and categorized as adults. In contrast, elderly patients were assisted by their children, who are 25 years old and included in the adult category. This can be concluded that adult patients have a better understanding of the usage of the application technology and are also considered more susceptible to disease.

It was observed that the technological gap among internet users is associated with the age factor, which has profound implications. Several studies explained that the inability of the elderly group to adopt digital media in their daily lives has a significant effect on their personal and broader lives. On a personal level, they are excluded from modern development, leading to wider negative consequences such as reducing their participation in the work environment, ultimately creating financial problems for them.[21]

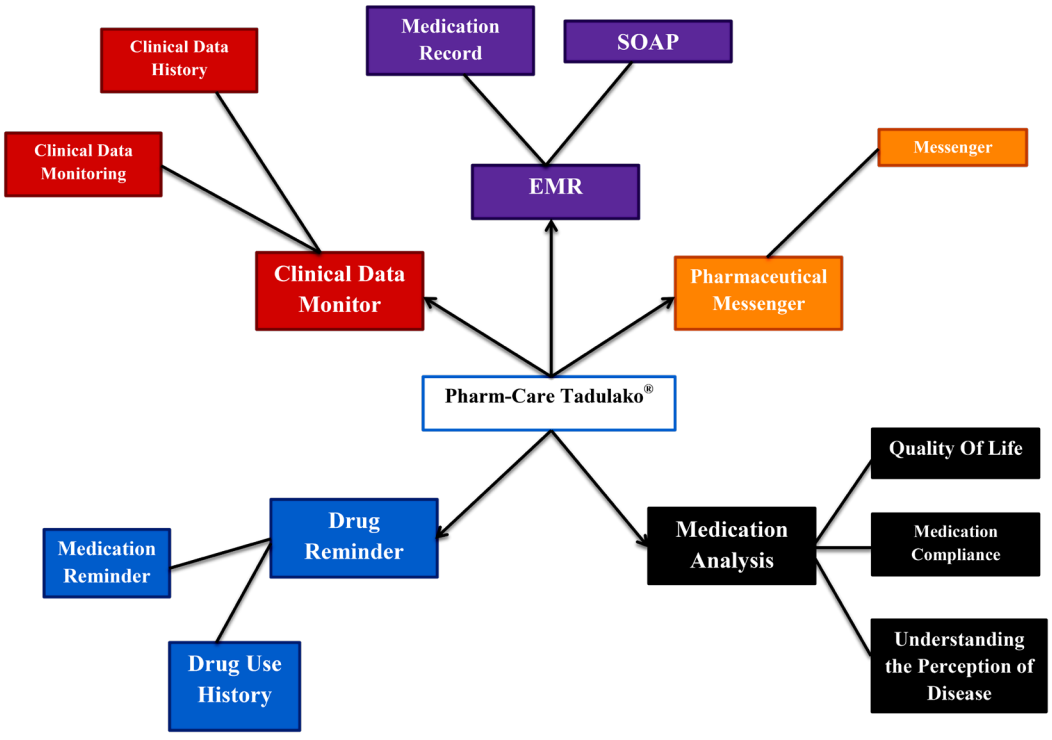

Figure 1. Pharm-Care Tadulako Application Features

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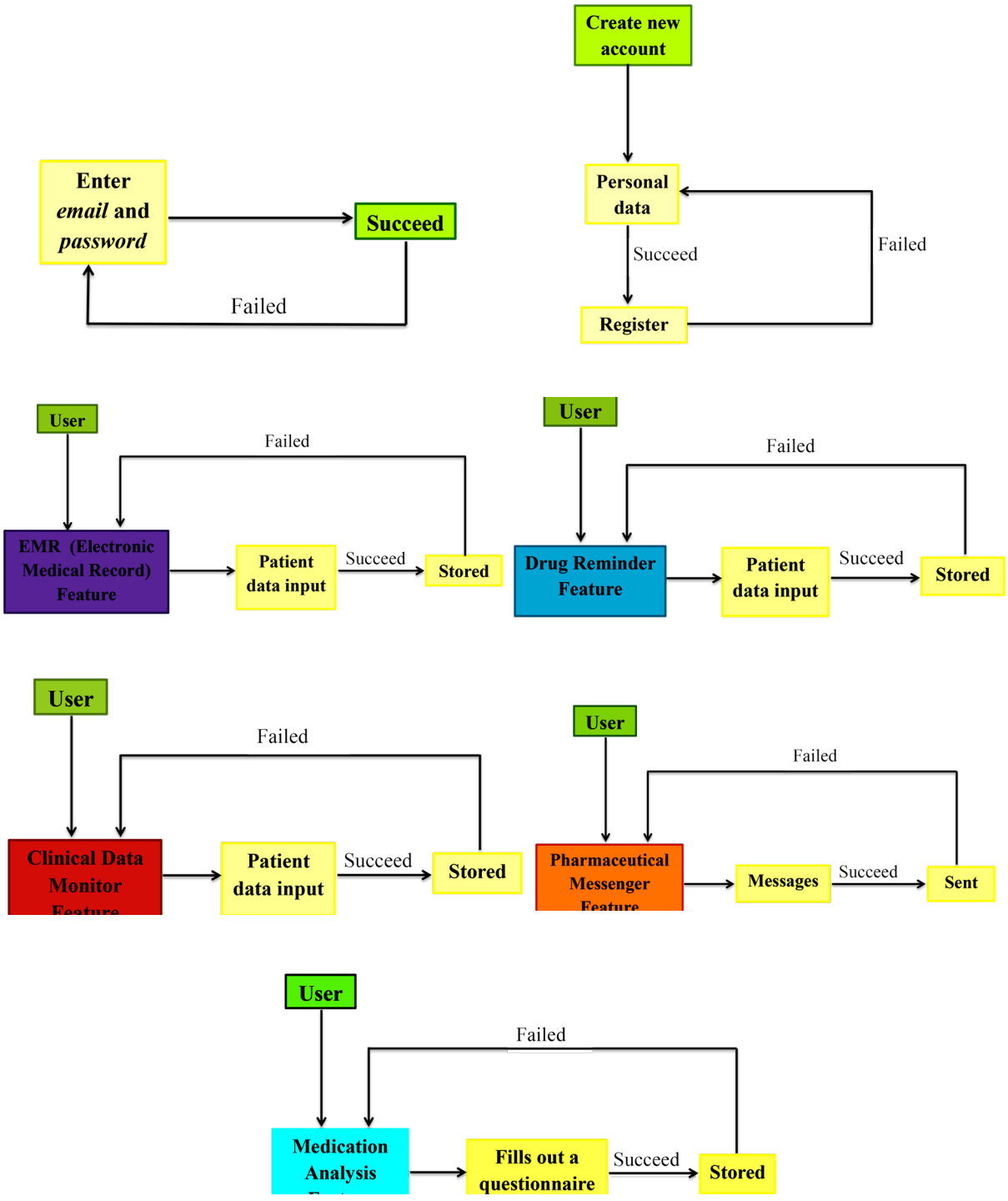

Figure 2. Algorithm Features
(a) Registration. (b) Log in. (c) EMR. (d) Clinical Data Monitoring. (e) Pharmaceutical Messenger. (f) Medication Analysis

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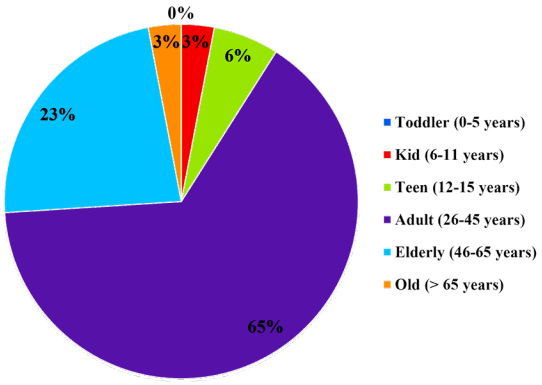

Figure 3. Age Distribution among Pharm-Care Users

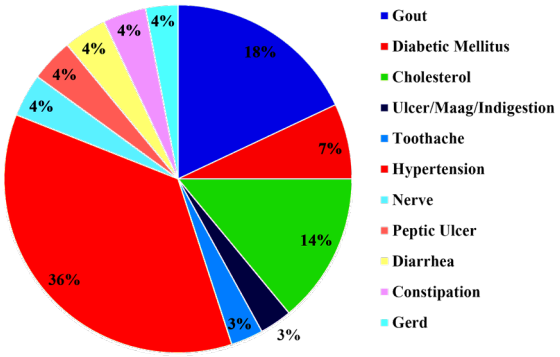

Figure 4. Disease Patterns of Pharm-care Users

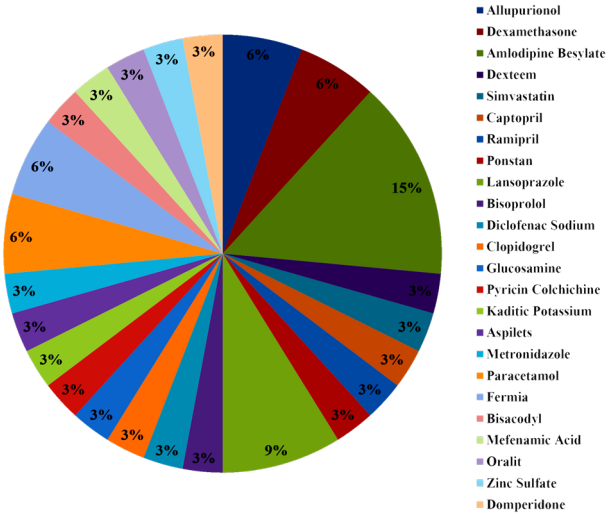

Figure 5. Drug Profiles

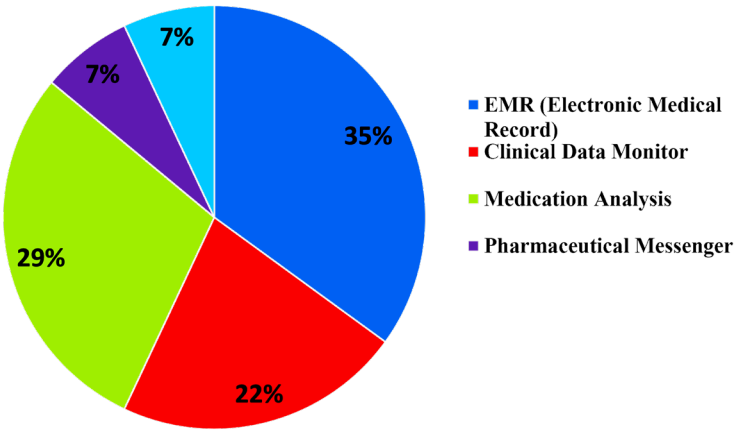

Figure 6. Pharm care Most Used Features

This was proved using the statistical data from the survey conducted by the Association of Indonesian Internet Service Providers (APJII) in 2016, which showed internet usage reached 132.7 million users in the country. The penetration was dominated by those between 25-34 years, which represented 75.4%, while those between 55 years and above were only 2%.[22] The patient profile showed that the most dominant disease out of the 11 used in the application was hypertension, with 36%. (Fig.4) Hypertension or elevated blood pressure (BP) is a severe medical condition that significantly increases the tendency of the other organs in the body to become damaged. It has been estimated that 1.28 billion adults aged 30-79 years worldwide have this disease, with most, approximately two-thirds, living in low- and middle-income countries. Moreover, 46% of adults with hypertension are unaware that they have this disease (WHO, 2021).

Its prevalence has also been reported by Riskesdas (2018) to be relatively high, with 34.1% among those aged 18-24, 20.1% for those aged 25-34, and 31.6% for those aged 25-44. The trend increased compared to the 25.8% recorded for those between 18 years and above in 2013. Hypertension has some modifiable risk factors, such as an unhealthy diet in the form of excessive salt consumption, high saturated fat, and trans-fat diet, low intake of fruits and vegetables, lack of physical activity, tobacco and alcohol consumption, and being overweight or obese. However, the non-modifiable risk factors include family history, over 65 years of age, and comorbidities such as diabetes or kidney disease (WHO, 2021).

The most common drug use profiles included amlodipine at 15%, lansoprazole at 8%, and allopurinol at 8%. (Fig.5) Meanwhile, amlodipine belongs to the CCB dihydropyridine (DHP) class, an L-type calcium channel blocker that reduces Ca^{2+} entry into vascular smooth muscle. It has a slow rate of elimination over 40-60 hours, but it is an excellent first-line drug compared to other hypertensive agents.[28-30] The first-line agent indicated for the uric acid-lowering disease is allopurinol, inhibiting xanthine oxidase. It is usually recommended due to its effectiveness, low cost, and availability. It can also reduce the excretion of uric acid for 24 hours more but has a severe side effect of allopurinol hypersensitivity syndrome when the wrong dosage is administered. Therefore, NSAIDs are initially given for 3-5 days to reduce the gout therapy algorithm.[31-33]

Lansoprazole is a PPI drug that inhibits H+ K+ATPase independently of acidic pH but requires 3 to 5 days to provide the maximum acid-blocking effect. Japan developed a new drug known as lansoprazole in 2015, and it is declared to be better and more effective in the long term than lansoprazole. Vonoprazan inhibits novel potassium-competitive acids that benefit acid disorders.[34,35] According to indications, patients must consult a doctor or pharmacist to use these two drugs. This makes it essential to develop applications for drug information services to ensure patients have better knowledge of the medicines used towards ascertaining their medication adherence.

There are five main features in Pharm-Care Tadulako: EMR, medication analysis, drug reminder, clinical data monitoring, and pharmaceutical messenger. The most frequently used is EMR, as indicated by 35% usage, followed by medication analysis with 29% due to its ability to assess the quality of life, medication adherence, and understanding of disease perception. (Fig. 6) This application provides questionnaires to be filled in by people with or without the disease to assess their quality of life.

Moreover, the clinical data monitor is designed to monitor patient clinical data, specifically for those on clinical examination, and this means it is only for a particular class of patients. A feature rarely used is the drug reminder because some respondents claimed to have forgotten the names of the drugs they are using while others have even stopped taking their medicines. Pharmaceutical messengers also have low usage because patients are not always required to have virtual chats with their pharmacists.

Conclusion

The current Pharm-Care Tadulako application has five main features, including electronic medical records, drug reminders, clinical data monitors, pharmaceutical messengers, and medication analysis, which produced several results based on age, disease patterns, drugs, and users. Age was found to have a significant influence on the usage of the application, as indicated by the fact that those between 26-45 years of age who are classified as adults and other age categories guided by adults mostly used the Pharm-Care Tadulako application. The results also showed that pharmaceutical care applications are widely used for degenerative diseases like hypertension and gout, requiring special attention. This eHealth Pharm-Care Tadulako is expected to assist pharmacists in performing their pharmaceutical care services and monitoring patients' health.

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The Effect of Prebiotic Starch and Pectin from Ambon Banana Peel (*Musa acuminata AAA*) on The Growth of Skin Microbiota Bacteria In Vitro

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Abstract

Propionibacterium acnes is a bacteria which causes acne. This bacteria is hypothesized to be inhibited by *Staphylococcus epidermidis (S. epidermidis)*. Prebiotics have been shown to enhance the number of *S. epidermidis* and decrease the growth of *Propionibacterium acnes (P. acnes)*. The prebiotic action of starch and pectin from diverse plant sources is known in the skin microbiome. The prebiotic activity of Ambon banana peel starch and pectin on skin microbiota has not been researched. This study aims to investigate the prebiotic activity of starch and pectin from Ambon banana peels on skin microbiota, represented by *S. epidermidis* and *P. acnes*. The results showed that starch, and pectin have a prebiotic activity because they promoted the growth of *S. epidermidis* while suppressing the growth of *P. acnes*. *P. acnes* inhibitor percentages were 1.62% for starch and 65.07% for pectin. Negative inhibition values were -184.95% for starch and -5.80% for pectin suggesting an increase in S. *epidermidis* proliferation.

Keywords: ambon banana; starch; pectin; prebiotic

Introduction

Acne is a common skin disorder that occurs during adolescence. Various factors can trigger the development of acne, including genetics, hormones, diet, and environmental factors (Dipiro, 2020). Four stages characterize the process of acne formation: increased sebum production, colonization by *P. acnes*, inflammation formation due to the release of inflammatory mediators, and follicular keratinization process.[1]

P. acnes produces lipase that hydrolyzes sebum triglycerides into fatty acids. These fatty acids trigger keratinization and the formation of microcomedones (damage to sebaceous glands and follicles). Closed comedones are the first visible acne lesions. *P. acnes* triggers inflammation due to immune response.[1] Recent studies have shown that *S. epidermidis* play a role in the pathophysiology of acne. Acne can be caused by an imbalance of the skin microbiome between *S. epidermidis* and *P. acnes*. Both *S. epidermidis* and *P. acnes* produce short-chain fatty acids (SCFAs) that act as antimicrobials against each other. These two bacteria are found on acne-prone skin. There is no evidence that *S. epidermidis* is the

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cause of acne formation.[2] Wang et al. (2016) states that *S. epidermidis* can ferment glycerol to produce SCFAs that suppress the growth of *P. Acnes*.[3]

Current acne treatments often involve the use of oral and topical antibiotics. However, recent developments have shown increased resistance to macrolide antibiotics such as clindamycin, used for acne treatment. Approximately 50% of *P. acnes* strains have developed resistance, decreasing antibiotic effectiveness.[4] The use of probiotics in acne treatment has shown positive results by controlling the growth of them. The oral use of probiotics as an adjuvant therapy to existing treatments can improve the healing of mild to moderate acne. Probiotics can produce bacteriocin substances, which are antibacterial proteins that inhibit the growth of *P. acnes*. Probiotics also inhibit IL-8 and TNF-alpha cytokines in epithelial cells and keratinocytes, reducing inflammatory reactions.[4]

Prebiotics are substances that can enhance the growth of probiotics. The use of prebiotics in acne treatment shows promising potential due to their ability to increase the growth of probiotics. Banana peel is one prebiotic studied for its role in acne therapy. Ethanol extract of yellow banana peel (*Musa balbisiana*) has been found to inhibit the growth of *P. acnes* at a concentration of 10%.[5] Ethanol extract of Ambon banana peel at concentrations starting from 10% inhibits the growth of *P. acnes*.[6] Traditional use of banana peel by rubbing the inner part of the peel on the acne-prone face in 45 teenage girls can reduce the severity of acne after seven days of application.[7]

Research on the benefits of banana peel prebiotics against bacteria involved in acne formation is still limited. This study demonstrates the benefits of starch and pectin in Ambon banana peel in restoring the balance of *P. acnes* and *S. epidermidis* growth.

Methods

Banana peels were obtained from a banana cake bakery in Bandung, West Java. The banana species from these peels is Musa acuminata (AAA group) 'Ambon' based on the determination by the School of Life Sciences and Technology (SITH), Bandung Institute of Technology (ITB), certificate number: 5214/IT1.C11.2/TA.00/2022.

Pectin Preparation

Pectin was extracted using a procedure developed by Saches Lopes et al. (2016).[8] The banana peels were ground after thorough washing and then washed three times with ethanol (Bratachem, technical grade). At each washing step, the material was filtered using cheesecloth. The washed residue was subsequently dried at room temperature. After drying, the pectin was extracted using a citric acid solution (pH 2.7) (Bratachem, technical grade) with a 1:20 w/v ratio for 190 minutes at 83°C with stirring.

The solution was then centrifuged (1147 g, 30 minutes, 10°C) to separate the supernatant. The supernatant was vacuum-filtered, absolute ethanol (Sigma Aldrich, pro analysis) was added, and the pH was adjusted to 3.5 using KOH (Merck, pro analysis). The mixture was stirred for 30 minutes, allowed to settle for 2 hours at 4°C, and then centrifuged for 15 minutes at 3500 rpm. The resulting pellet was collected, washed with 70% ethanol (Bratachem, technical grade), and centrifuged again (20 minutes, 3500 rpm). The pellet was dried at room temperature. Once dry, the pellet was dispersed in pH 7 water (adjusted with KOH) and dried again.

Starch Preparation

Starch was prepared following the procedure conducted by Uraipan et al. (2014).[9] The banana peels were sliced into small pieces and then dried at 55°C for 7 hours. After drying,

the starch was extracted using a 1:1 ratio of NaOH (Bratchem, technical grade) and water. The slurry was then filtered, and the starch precipitate was rinsed several times with distilled water. The starch was subsequently dried in an oven at 65°C for 15 hours.

Bacterial Preparation

The bacteria used in this study were *S. epidermidis* (ATCC12228) and *P. acnes* (ATCC11827) obtained from the Microbiology Laboratory, Islamic University of Bandung. Both bacteria were cultured in Tryptic Soy Broth (TSB, Oxoid) and incubated overnight at 37°C under aerobic conditions. After incubation, the media from each culture were collected and diluted with their respective media at a dilution ratio 1:10. The diluted samples were ready for antibacterial testing. The pH of *S. epidermidis* cultures were measured at 0, 3, and 24 hours.

Antibacterial Testing

The antibacterial testing method followed the procedure reported by Di Lodovico et al. (2020).[10] The absorbance of the diluted cultures of *S. epidermidis* and *P. acnes* was measured using a UV spectrophotometer (Shimadzu UV-1800, Japan) at a wavelength of 600 nm (optical density, OD600), adjusted to OD600 = 0.12. Then, a solution of media containing 2% w/v starch/pectin was added to the bacterial suspension at a 1:1 ratio, resulting in a final concentration of 1% w/v starch/pectin in the culture solution.

Cultures without adding starch/pectin were used as controls, and TSB media served as blanks. The OD600 of the samples and controls was measured at 0 hours, and then the cultures were incubated at 37°C for 24 hours. OD600 measurements were also taken at 3 and 24 hours. Each treatment and measurement was performed in duplicate.

The percentage of inhibition was calculated using the following formula:

Percentage of inhibition (%) = [(ODcontrol - ODsample) / ODcontrol] × 100. The OD600 value and the percentage of inhibition were statistically analyzed using Kruskall-Walis because the data were not normally distributed.

Results and Discussion

The Prebiotic Effect of Ambon Banana Starch and Pectin

The ability of starch and pectin in Ambon banana peel to selectively enhance the number of beneficial bacteria is called prebiotic effect. In this research, in vitro studies were performed on *P. acnes*, a skin microbiota that causes acne[11] and *S. epidermidis*, which represent beneficial microflora bacteria.[12] This is about earlier study findings showing *S. epidermidis* can prevent the skin against acne.[11] This study selected glucose as a standard carbon source required for bacterial growth[13] and inulin as an established and frequently utilized prebiotic.[14]

The OD600 was used to monitor the development of the test bacteria. The number of bacteria is related to the OD600 value. The OD600 value increases with the number of bacteria. Figure 1 shows starch had an average OD600 value lower than control, glucose, and inulin after 3 hours of incubation. However, after 24 hours of incubation, the OD600 value of starch was not significantly different from inulin and control but remained lower than glucose.

At the 3rd and 24th hours of incubation, the average OD600 value of the *P. acnes* culture treated with Ambon banana peel pectin was lower than the control group or inulin as a standard prebiotic but not statistically significant ($p>0.05$) compared to another group. Based on the OD600 value, the least number of *P.acnes* bacteria were observed in the cultures treated with pectin for 24 hours of incubation.

At the same incubation hour, the number of *P. acnes* exposed to starch was equivalent to that of *P.acnes* exposed to inulin and the control (without additional carbon sources), but fewer than that of *P. acnes* exposed to glucose.

Figure 2 depicts the influence of Ambon banana peel starch and pectin on the growth of *S. epidermidis* bacteria. The graph demonstrates that at 3rd hour of incubation, pectin had the lowest OD600 value when compared to the comparative compound, inulin, and control. Pectin had an OD600 value equivalent to the control and lower than starch and inulin after 24 hours of incubation. At the 3rd and 24th hours of incubation, starch had the highest OD600 value when compared to glucose and inulin and controls. Overall, the number of *S. epidermidis* treated with pectin was the lowest when compared to starch, inulin, and glucose after 3 or 24 hours of incubation. *S. epidermidis* that was treated with starch had the highest number than cultures that were treated with pectin, inulin, and glucose although not statistically significant (p>0,05). The percentage of inhibition was calculated using the OD600 values obtained from the test and control substances. Table 1 shows the percentage inhibition of *P. acnes* and *S. epidermidis*. Starch inhibited *P. acnes* the most at 3 hours compared to pectin, inulin, and glucose, but its inhibition was reduced at 24 hours. Conversely, glucose promotes the development of *P. acnes* at 24 hours. This is most likely due to the fact that *P. acnes* cannot use starch as a carbon source to promote its growth, but can use glucose as one.[15,16]

Pectin inhibits *P. acnes* effectively at the 3rd and 24th hours of incubation. This is consistent with prior research, which found that pectin from tea leaves had antiadhesive effects against *P. acnes* in vitro that lead to suppression of the growth of these bacteria.[17] Although based on the Kruskall-walis test a significant value was obtained > 0.05, so there was no difference in the percentage of inhibition of *S. epidermidis* and *P. acnes* at 24 hours for all groups.

The potential of starch, pectin, and inulin to enhance the development of *S.epidermidis* was demonstrated after 24 hours of incubation with a negative inhibition percentage as a sign. In comparison to glucose, inulin, and

Table 1. Percent Inhibition of the Test Compounds on the Growth of *P. acnes* and *S. epidermidis*

Compound	Percentage of inhibition against *P. acnes* at		Percentage of inhibition against *S. epidermidis* at	
	3 h of incubation	24 h of incubation	3 h of incubation	24 h of incubation
Glucose	13.02 ± 2.16	-24.03 ± 13.39	-5.63 ± 0.88	-120.22 ± 37.09
Inulin	30.07 ± 1,90	-2.13 ± 19.67	18.04 ± 1.47	-54.05 ± 24.20
Ambon banana starch	71.44 ± 0.79	1.62 ± 3.88	61.43 ± 0.81	-184.95 ± 20.76
Ambon banana pectin	58.01 ± 0.76	65.07 ± 0.72	71.53 ± 0.67	-5.80 ± 15.63

The data are presented as mean ± SD (n=2)

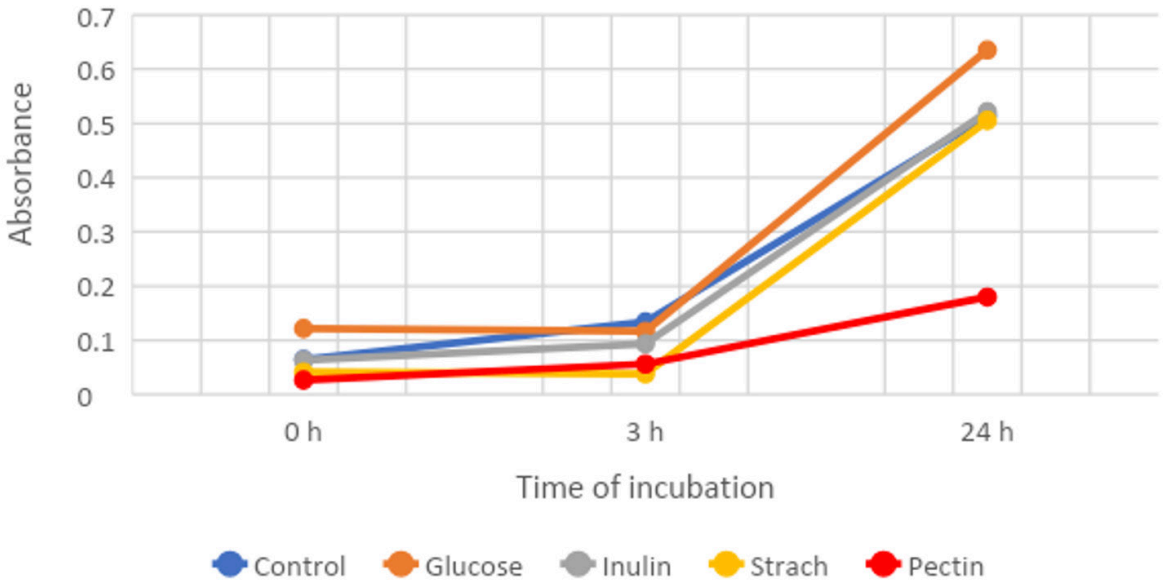

Figure 1. The average OD600 values (n=2) of *P. acnes* Cultures Treated with Starch and Ambon Banana Peel Pectin compared to Glucose, Inulin, and the Control.

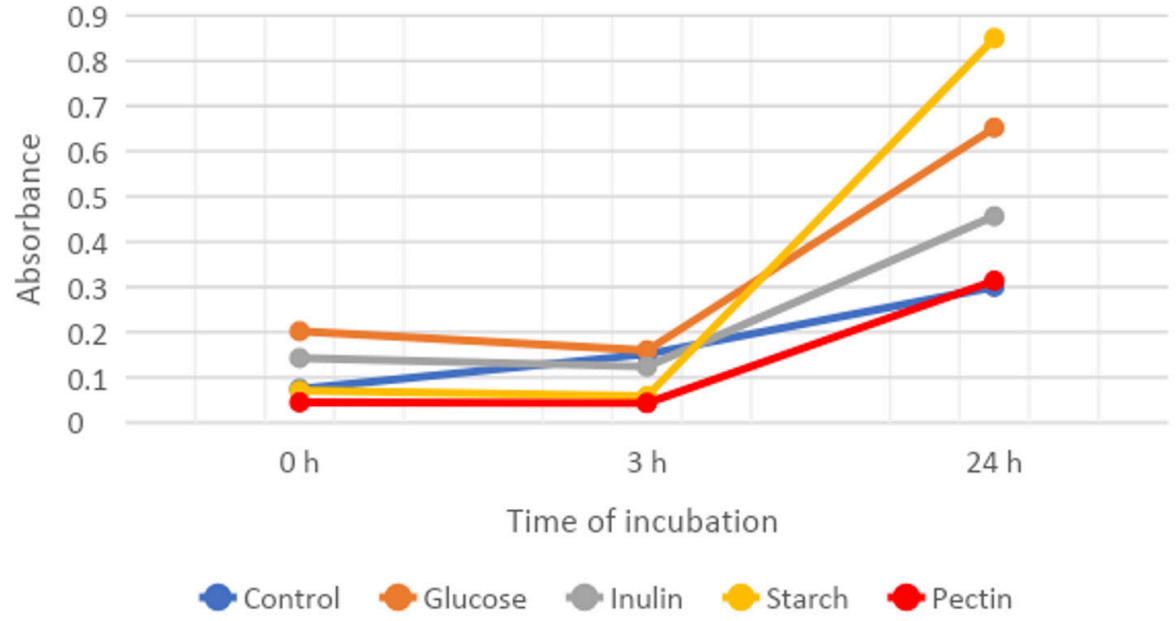

Figure 2. The average OD600 values (n=2) of *S. epidermidis* Cultures Treated with Starch and Ambon Banana Peel Pectin compared to Glucose, Inulin, and the Control.

pectin, starch gives the lowest percentage of inhibition, implying that starch might increase the number of *S. epidermidis* the most. Glucose also demonstrated a negative inhibitory percentage at 24 hours of the incubation period, which was similar to *P. acnes*, implying that glucose can promote the development of both bacteria.

Starch and pectin exhibit a negative inhibition percentage for *S.epidermidis* and a positive inhibition percentage for *P.acnes* indicating that these substances promote *S. epidermidis* development but inhibit *P.acnes* growth. The ability to selectively increase the growth of beneficial bacteria is called prebiotics. The prebiotic activities of Ambon banana peel pectin is comparable to that of tea leaves pectin, which has also been shown to have a selective effect in enhancing *S.epidermidis* and decreasing *P.acnes*.[17] In terms of percentage inhibition, starch, and pectin have a greater potential to enhance the number of *S.epidermidis* while decreasing the number of *P.acnes* than inulin.

Prebiotics can be administered orally or topically to balance the composition of opportunistic microbiota and minimize inflammatory reactions in treating acne vulgaris (acne).[4] Antibiotics, stress, and diet can all affect changes in microbiota makeup in the skin.[18] Alteration in the microbiota composition, such as an increase in the number of *P. acnes*, might increase the likelihood of getting acne.[19]

In acne-prone skin, the increased number of S. epidermidis caused by prebiotic treatment can restrict the development of *P. acnes* through various predicted mechanisms. S. epidermidis can create succinic acid, which inhibits *P. acnes* bacterial growth.[20] *S. epidermidis* is also thought to create a polymorphic toxin that inhibits *P. acnes* growth. Christensen et al. (2016). *S. epidermidis* can also create lipoteichoic acid, which can diminish *P. acnes*-induced inflammation.[21,22]

The anti-inflammatory action of kepok banana peel extract in the treatment of acne has been researched, and the substances considered to be responsible for this effect are ascorbic acid, carotene, cyanidin, trigonelline, isovanillic acid, and ferulic acid.[23] The prebiotic effect of banana peel starch and pectin on skin microbiota has not been extensively studied. Still, starch has been studied as an additive in cosmetic formulas used to treat acne caused by *P. acnes*.[24–26]

Pectin has been researched as an anti-acne excipient and has been shown to boost the anti-acne impact of the active ingredients used in pharmaceutical preparations.[27,28] The prebiotic impact may contribute to the preparation's anti-acne efficacy. Based on the findings of this study's prebiotic effects of starch and pectin from Ambon banana peels, these two compounds have the potential to be developed as excipients that strengthen the effects of active ingredients in acne treatment formulations.

Conclusion

Ambon banana peel starch and pectin have been shown to have prebiotic potential because they inhibited P. acnes growth with a percentage of inhibition of 1.62% and 65.07%, respectively, and increased the growth of S. epidermidis with a percentage of inhibition of -184.95% and -5.80%, respectively.

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Conflict of Interest
None declared

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Evaluation of Rationality in Prescribing Antidiabetic in Outpatient with Type 2 Diabetes Mellitus at PKU Muhammadiyah Yogyakarta Hospital, Special Region of Yogyakarta - Indonesia

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Abstract

In the past few decades, the number of people with diabetes mellitus has steadily increased in various countries. Type 2 Diabetes Mellitus (DM) is the most common type of DM. An increase follows this significant increase in the number of patients in the use of antidiabetic drugs and the risk of irrational drug use, where drug use evaluation is one of the strategies to reduce it. This study aims to evaluate the rational use of antidiabetics in outpatients with type 2 DM at PKU Muhammadiyah Yogyakarta Hospital, Special Region of Yogyakarta - Indonesia. This study is a retrospective analytical observational study. The data used as reference is patient medical records from October 2021 to March 2022. Antidiabetic accuracy based on Indonesian Endocrinology Society guidelines and Drug Information Handbook ed. 22. A total of 155 medical records patients were included in this study. The result showed that patients with complications (50,4%) were higher than patients without complications (49,6%), with the most complication was nephropathy (67,9%) and the most comorbidity was hypertension (21,2%). The rationality of antidiabetics includes the right patient (94%), the right medicine (74%), the right dosage (100%), the right time administration (100%), and the right interval administration (97%). The rational drug use is expected to reduce the risk of drug side effects, reduce patient treatment costs, and improve patient life quality.

Keywords: diabetes mellitus, evaluation, rationality, antidiabetic

Introduction

DM is a chronic metabolic disease characterized by increased blood glucose levels, which, in the long term, might affect the damage to organs such as the heart, blood vessels, eyes, kidneys, and nerves. As the most common type of DM, type 2 DM shows a significant rise in diabetes sufferers in some countries. Indonesia is included in the ten countries with the most DM sufferers in 2019, with 10.7 million sufferers.[1] The increasing prevalence of DM in Indonesia showed 8.5% in 2018 compared to 2013, with only 6.9%.[2]

The use of antidiabetic drugs will follow a high ratio of DM cases. Antidiabetic drugs, which are divided into oral antidiabetic and insulin, have their respective advantages and disadvantages it is necessary to consider pharmacokinetics, pharmacodynamics, and side effects in their administration to optimize blood glucose control and to evaluate the use of antidiabetics.[3]

On the other hand, the use of irrational drugs will increase the risk of hypoglycemia and drug interaction, as well as reduce medication

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adherence, which both have an impact on increasing hospitalization length, mortality, and healthcare cost.[4,5] Rational drug use is a major implication of drug use studies. According to a WHO survey, irrational drug use is the cause of death for one-third of global patients.[6,7] Evaluation of drug use, the right diagnosis, and appropriate medication are important to reduce the risk of DM and improve the patient's quality of life. This study aims to evaluate the rational use of antidiabetics at PKU Muhammadiyah Yogyakarta Hospital, Special Region of Yogyakarta - Indonesia.

Methods

Data collection

This study is an observational analytic with a retrospective design using the total sampling method. We used all medical records of outpatients with type 2 DM from October 2021 to March 2022 in PKU Muhammadiyah Yogyakarta Hospital with a total of 155 medical records of outpatients with type 2 DM.

The data collected include patients' clinical data (allergies, diagnosis, and laboratory examination) and patients' medication (drug name, dosage, directions for use). This study has ethical exemptions from PKU Muhammadiyah Yogyakarta Ethics Committee, number 00059/KT.7.4/III/2022, 9 March 2022.

Data Analysis

This study analyzed complications, comorbid type 2 DM, and rationality evaluation. Rational evaluation is reviewed from the right patients, dosage, medicine, and time and interval drug administration based on the criteria for rational drug use, according to the Ministry of Health of the Republic of Indonesia.

The right patient is the accuracy of the drug given according to the patient's condition, such as allergic conditions and the condition of the patient who is contraindicated for anti-diabetes based on the 22nd edition of the Drug Information Handbook (DIH).

The right medication based on the Guidelines for the Management and Prevention of Type 2 DM from the Indonesian Society of Endocrinology, 2021. In contrast, the right dose, the right time administration, and the right interval of drug administration are the accuracy based on the Indonesian Society of Endocrinology 2021 and DIH 22nd edition.

Results and Discussion

The characteristics of clinical patients including complications and comorbidities are presented in Table 1. Complication is comorbidities related to the diagnosis of the main disease or diseases that occur during the treatment period and require additional treatment. Comorbidities is a coexisting health condition that can be related to the main disease or occur independently.[8] This study showed there were more patients with type 2 DM with complications (50.4%). Another study showed type 2 DM patients with complications at a ratio of 94.[9] The average type 2 DM patient is over 45 years old with uncontrolled blood glucose which tends to cause acute and chronic complications[1,10,11]

The most complications occured in this study were nephropathy (67.9%), followed by neuropathy (16.7%), and peripheral diseases (3.8%). Diabetic nephropathy used to be a chronic complication of type 1 diabetes and type 2 diabetes. Diabetic neuropathy is a multifactorial condition, which includes several risk factors, including elevated HbA1c, hypertension, smoking and obesity.[12] The distribution of outpatient type 2 diabetes comorbidities in this study is shown in Table II.

Table 1. Clinical Characteristics of Type 2 Diabetes Mellitus Patients

Characteristics	The number of patient (%)
Complications of Type 2 DM	
No Complications	77 (49,6)
Complications	78 (50,4)
Type of Complications	
Kidney	53 (67,9)
Neurology	13 (16,7)
Peripheral artery disease	3 (3,8)
Other	9 (11,6)

Table 2. Distribution of Comorbid Diseases in Type 2 Diabetes Mellitus Patients

Comorbid	The number of patient (%)
Hypertension	64 (21.2)
Nephropathy	54 (17.9)
Dyslipidemia	26 (8.6)
Neuropathy	26 (8,6)
Anemia	19 (6.3)
Congestive Heart Failure	18 (6)
Dyspepsia	14 (4.6)
Ulcer	9 (3)
Gout	8 (2.6)
stroke	7 (2.3)
Breast cancer	6 (2)
Erectile dysfunction	6 (2)
Covid	5 (1.6)
Vertigo	5 (1.6)
Depression	4 (1.3)
Heart failure	4 (1.3)
Lung cancer	3 (1)
Peripheral Artery Disease	3 (1)
Asthma	2 (0.7)
Bronchitis	2 (0.7)
Rheumatoid Arthritis	2 (0.7)
*Other	15 (5)
Total	**302 (100)**

Note: 1 patient can have more than one comorbid disease; *others: gastroparesis, hypoglycemia, insomnia, dementia, urinary tract infections, hyperkalemia, osteoarthritis, tuberculosis

Table 3. Rationality of Antidiabetic Use in Type 2 Diabetes Mellitus Patients

Criteria	The number of patient (%) n=155
The right patient	145(94)
The right medicine	115(74)
The right dose	155(100)
The right time administration	155(100)
The right interval administration	151(97)

Complication is comorbidities related to the diagnosis of the main disease or diseases that occur during the treatment period and require additional treatment. Comorbidities is a coexisting health condition that can be related to the main disease or occur independently.[8] This study showed there were more patients with type 2 DM with complications (50.4%). Another study showed type 2 DM patients with complications at a ratio of 94.[9] The average type 2 DM patient was over 45 years old with uncontrolled blood glucose which tends to cause acute and chronic complications.[1,10,11]

The most common comorbidities in type 2 DM patients were hypertension (21.2%), nephropathy (17.9%), dyslipidemia (8.6%) and neuropathy (8.6%). This result of this study supports the previous research which showed the most comorbid disease was hypertension (42.31%).[13]

Research in Japan states that the most comorbidities in DM patients are kidney disorders (35.4%).[14] Many studies show that hypertension and diabetes mellitus often occur together. Hypertension can cause atherosclerosis, which was a high-risk factor for microvascular and macrovascular disease.[15] Hyperglycemia can damage blood vessels and lead to atherosclerosis, and also might increase blood viscosity which will cause hypertension or ischemic stroke.[8]

The second biggest comorbidity is nephropathy (17.9%). Diabetic nephropathy is a clinical symptom in diabetics characterized by albuminuria and diabetic nephropathy which are the main causes of kidney failure disease.[16] Meanwhile, there are glomerular pathological changes in long-term DM patients.[17] DM patients have a higher glomerular filtration rate, which in the long term can lead to increased albumin, hypertension and decreased GFR.[18]

The evaluation of medication treatment based on the criteria for drug use that have been determined by the Ministry of Health of the Republic of Indonesia in 2011 regarding the rational use of drugs was showed in Table III.

The right patient

Drug contraindication is a condition where drugs should not be given to patient, so that the patient's accuracy can be seen from the patient's condition or allergies in the medical record.[19] In this study, it shows that 94% of the sample is the right patient. The previous study showed that drug administration was 100% right for the patient, because there was no drug contraindication found in the patient's clinical condition.[20,21]

The result on this point out that there are drugs that contraindicated in the patient's clinical condition. The drugs were gliclazide, gliquidone, and metformin. Gliclazide was contraindicated in patients with chronic

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kidney disease (CKD) stage 3, liver failure and type 1 DM.[22] Patients received gliclazide and gliquidone when the patient had coexisting CKD stage 3. The administration of antidiabetic sulfonylureas requires a dose adjustment in GFR below 30 ml/minute/1.73 m^2.[23]

Metformin was used by patients with GFR <30 ml/min/1.73m^2. Metformin was contraindicated in patients with renal failure GFR <30 ml/min/1.73m^2, Congestive Heart Failure (CHF) NYHA III-IV, diabetic ketoacidosis and lactation.[24,25] In patients with moderate to severe CKD, metformin Cmax increased, which may increase the side effects. In patients with kidney disorders, there was a decrease in the elimination of lactic acid from the kidneys, giving metformin will increase the risk of lactic acidosis.[26]

The right medicine

Appropriate and rational drug need to consider by doctor's diagnosis, benefits, level of safety and side effects. The results show that the right drug has 74 percentage. Previous study at PKU Muhammadiyah Gamping showed that the right drug had to be 33.33%.[27] In this study, inappropriate drugs include the use of a combination of oral antidiabetics with insulin novorapid. Novorapid insulin is an insulin aspart that works rapid-acting.[25] Based on Indonesian Endocrinology Society 2021 algorithm, the use of a combination iral antidiabetic with basal insulin. Rapid-acting or short-acting insulin used to control postprandial blood glucose, which is when the optimal dose of basal insulin has not been able to control blood glucose, and was used in combination with basal insulin.[25]

Another inappropriate drug is the used of monotherapy insulin novorapid. Based on the Indonesian Endocrinology Society 2021 algorithm, the use of insulin monotherapy was basal or premix insulin. Short/rapid acting insulin monotherapy was recommended for patients with kidney disorders,[28] also there were the administration of gliclazide, gliquidone, and metformin therapy in patients with CKD stage >3. The guidelines recommend the use of SGLT-2 or GLP-1 RA inhibitors which have been shown to reduce the progression of CKD. If SGLT-2 or GLP-1 RA was not available, safe therapy for CKD can be chosen, such as insulin.[25]

The right dose

The dosage needs to consider the patient's clinical condition, like kidney function. In patients with decreased kidney function, it very necessary to give the right dose or it will aggravate the disease.[29] Antidiabetics that require dose adjustment in conditions of renal failure are sulfonylureas (glipizide and glimepiride), glinides, and DPP-4 inhibitors. In this study, there were no drugs that required dose adjustment due to renal impairment.

In this study, the right dose ratio is 100%, which support the previous research from Ramdini et al (2020) that showed 100% of the correct antidiabetic dose based on the Indonesian Endocrinology Society 2015.[30] Dosage always be an important aspect that determines the efficacy or therapeutic effect of a drug. If the dose received by the patient is below the therapeutic range, the expected therapeutic effect will not be achieved. If the dose received by the patient is too high, it can cause hypoglycemia or the emergence of toxicity.[31,32]

The right time administration

Antidiabetic can be given before meals, with meals, or after meals. Drug administration can affect the effectiveness of a drug, related to the amount of drug that can be absorbed. The accuracy time administration has been regulated based on Indonesian Endocrinology

Society 2021, DIH 22nd, and information of drug. The result shows that the right time of drug administration was 100%.

In this study, novorapid insulin was given after meals. Novorapid insulin was a rapid-acting insulin analog that belongs to prandial insulin to control blood glucose after eating and was given at any time before eating or 5-15 minutes before eating, when necessary can be used immediately after meal.[25,28] Review articles showed that rapid-acting insulin was administered 15–20 minutes before meals with a good postprandial glucose control. The risk of postprandial hypoglycemia might increase when rapid-acting insulin distributed after meals.[33]

The right dose interval

The right dose interval for drug can affect the duration of drug effectiveness as it was the time difference between onset and the time required for the drug to fall back to the minimum concentration. Inappropriate drug intervals will also cause inappropriate drug frequency.[30] In table III, it can be seen that the time interval for drug administration was 97%. In the other hand, the study by Ramdini et al (2021) found that the time interval for drug administration was 100%.[30] Inappropriate time interval of administration was the use of acarbose. Acarbose was given 100-300mg/ 3 times a day.[25] In this study there were patients who received acarbose 1-2 times a day.

Conclusion

The rationale for the use of antidiabetics in patients with Diabetes Mellitus Type 2 outpatient at PKU Muhammadiyah Yogyakarta are include the right patient by 94%, the right drug by 74%, the right dosage regimen by 100%, the right time of administration by 100 % and interval administration of 97%. This study is expected to be used as a reference in the rational drugs administration, where can reduce the risk of drug side effects and patient treatment costs as well as improve the patient's quality of life.

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Conflict of Interest

Non declared

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Pharmacokinetic Changes and Dosage Adjustment of Digoxin in Elderly Patients with Atrial Fibrillation: A Narrative Review

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Abstract

Digoxin is a cardiac glycoside medication commonly used to control rapid heart rates in Atrial Fibrillation (AF). However, digoxin has a narrow therapeutic range and can be associated with adverse effects, including increased mortality risk, especially in the elderly. Pharmacokinetic changes occur with aging, affecting the way drugs are absorbed, distributed, metabolized, and eliminated from the body. Thus, this narrative review aimed to assess the optimization of digoxin dosing in elderly patients with AF while considering pharmacokinetic changes due to aging. We performed a comprehensive computerized search of relevant English articles and a manual examination of reference lists from primary sources formed the basis of this scoping review. This involved an extensive computerized search of relevant articles in English and a manual search of the reference lists of original articles. The review highlighted the need to carefully monitor digoxin levels in elderly patients due to changes in body composition, protein binding, hepatic clearance, renal excretion, and other factors affecting drug metabolism. Furthermore, we summarized guidelines and recommendations for optimizing digoxin dosing in elderly patients with AF. By shedding light on the intricacies of optimizing digoxin dosing in the elderly with atrial AF and emphasizing the significance of accounting for age-related pharmacokinetic changes, this review offers valuable insights for healthcare practitioners and researchers in the field. Addressing these aspects is crucial to enhancing therapeutic outcomes and minimizing potential risks associated with digoxin therapy in this vulnerable patient population

Keywords*:* digoxin, pharmacokinetics, atrial fibrillation, aged, elder

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Introduction

Digoxin is a medication that belongs to a group of drugs known as cardiac glycosides. It is frequently employed to control rapid heart rates in Atrial Fibrillation (AF). William Withering initially brought digitalis to clinical cardiology in Birmingham in 1785. Since then, it has been frequently utilized to decrease heart rate in AF.[1,2] The most frequent type of arrhythmia seen in clinical settings.[3] Digoxin's therapeutic range is limited, and other medical conditions can substantially impact its levels.[4]

Observational studies have reported a higher risk of mortality associated with using digoxin,[5–7] which has led to decreased usage due to safety concerns.[8–10] The safety and effectiveness of digoxin can also be affected by aging. As people age, their body undergoes various physiological changes.[11,12] In addition to having altered function, older people may also react differently to medications in terms of mechanical reactions, receptor mechanisms, homeostatic alterations, and brain function.[13] As a result, drug therapy in an elderly patient is unpredictable. Thus, medication should be carefully monitored, especially with drugs with narrow therapeutic indexes such as digoxin.

Our research aimed to conduct a narrative scoping review of the existing literature on optimizing digoxin dosing in elderly patients with AF while considering the changes in pharmacokinetics that occur due to aging. To achieve this, we performed a computerized search of relevant articles written in English. We identified references of interest by searching PubMed and Google Scholar using various combinations of search terms, such as "Digoxin", "Pharmacokinetic", "Atrial Fibrillation", and "Aged", either alone or in combination. Furthermore, we manually searched the reference lists of original articles for additional relevant articles.

Pharmacology and Mechanism of Action

Digoxin originated from the foxgloves, *Digitalis lanata*. It is a cardiotonic glycoside and belongs to the *digitalis* class. The chemical formula of digoxin is C41 H64 O14. In 1954, the FDA approved using cardiac glycosides, including digitalis and digoxin, to treat various heart problems, including atrial flutter and AF.[14] Digoxin is also widely used to manage congestive heart failure and arrhythmia[15,16] in spite of its narrow therapeutic index and potentially fatal toxicity, especially in the elderly.

The incidence and prevalence of heart failure in the elderly are relatively high, and digoxin is the most frequently prescribed in the over-65-year population.[17,18] Digoxin is usually combined with diuretic therapy to reduce heart failure symptoms and increase exercise ability.[15] In the oral route, digoxin is absorbed incompletely. The bioavailability of digoxin ranged from 50% to more than 90% of the oral dose.[19] This aspect should be carefully considered, as it directly affects the drug's concentration in the bloodstream and its efficacy at the intended site of action.

Digoxin plays a role in the different levels of heart cells. It has positive inotropic effects and negative chronotropic and dromotropic action.[20] It also increases the availability of calcium and inhibits the sodium-potassium pump (Na+ /K+ -ATPase). Consequently, an increase in the intracellular Na^+ concentration facilitates the entry of Ca^{2+} into the cell, which increases cardiac inotropic.[21] Thus, it will shorten the cardiac action and increase calcium for the sarcomeric excitation-contraction coupling.[22] Moreover, *digitalis* compounds increase vagal efferent activity in the heart. Its parasympathomimetic action lowered the conduction velocity of electrical impulses in the atrioventricular node, thus slowing the ventricular response rate in AF.[18] (Fig.1)

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Pharmacokinetic Changes with Aging

Aging is shown by a progressive change in the physiological and functional capacities of the human body, a reduction in homeostatic mechanisms, and an impaired response to receptor stimulation. This might alter the pharmacokinetics of drugs, leading to clinically relevant consequences concerning safety and efficacy.[23,24] Elder people are at higher risk of experiencing adverse drug reactions due to age-related changes in how drugs are absorbed, distributed, metabolized, and eliminated from their bodies, as summarized in Table 1.[25]

The impact of pharmacokinetics on the body depends on various properties of a drug, including its pH-dependent ionization, lipid solubility, binding affinity to proteins, metabolic pathways, and renal excretion rate. Drugs undergoing significant first-pass metabolism may have higher bioavailability when impaired hepatic clearance. As people age, their body composition changes, with an increase in body fat and a decrease in both lean body mass and total body water. These changes can cause an increase in the volume of distribution for lipophilic drugs and a decrease for hydrophilic drugs.[26] The impact of drugs on the body is linked to the amount of unattached drug molecules in the blood. Therefore, modifications in how drugs attach to proteins in the blood can have considerable effects on patients. This is particularly crucial for drugs that strongly bind to proteins and require precise dosing. Although changes in protein binding that occur in older adults are often ascribed to aging, they are usually caused by accompanying medical conditions such as kidney or liver disease, as well as diabetes, that modify how drugs bind to proteins.[27]

The liver's microsomal cytochrome P450 (CYP) enzymes are essential for breaking down various drugs, with CYP3A being particularly significant due to its vast range of pharmacological substrates. Several studies indicate that the elderly population experiences decreased clearance of drugs metabolized by CYP3A.[28] One way to estimate the degree of impairment in kidney function is by measuring the level of creatinine in the blood and using it to calculate creatinine clearance. This can be done using formulas such as the Cockcroft and Gault equation.[29]

Digoxin toxicity is a frequent occurrence among older individuals and is linked to various factors such as reduced lean body mass, a decline in glomerular filtration rate (GFR), reduced muscle mass, potassium depletion

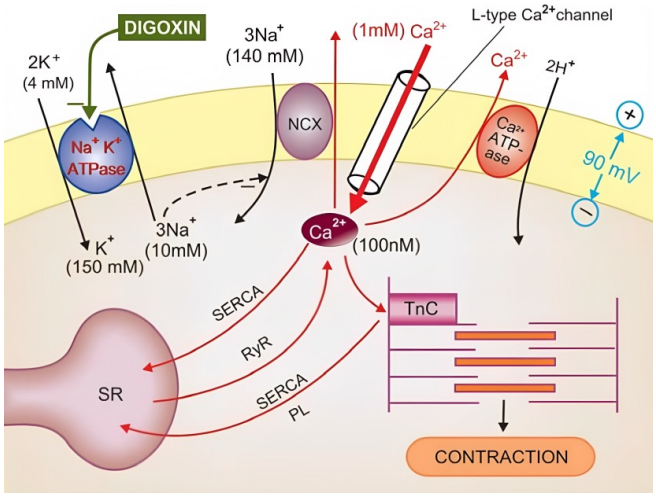

Figure 1. Mechanism of Action of Digoxin[46]

Table 1. Age-related Changes that Affect Drug Pharmacokinetics[25]

Pharmacokinetic Parameter	Physiological Parameter	Effects in Older People compared to Younger Ones
Absorption	Acid secretory capacity of gastric mucosa	↓ resulting in ↑ gastric pH and more rapid emptying of stomach
	Gastrointestinal blood flow	↓
	Gastrointestinal motility	↓
Bioavailability	First-pass effect	↓ as a result of ↓ hepatic clearance
Distribution	Body fat	↑
	Lean body mass	↓
	Total body water	↓
	Serum albumin concentration	↓
	α1-Glycoprotein concentration	↑
Hepatic clearance	Size of the liver and hepatic blood flow	↓ resulting in ↓ oxidation and reduction capacity
Renal clearance	Glomerular filtration rate	↓
	Renal plasma flow	↓
	Filtration fraction	↑
	Tubular function	↓ resulting in ↓ reabsorptive capacity

↑ indicates increase; ↓indicates decrease.

resulting from diuretic use, drug interactions, and the presence of other medical conditions. As the body ages, the elimination half-life of digoxin is prolonged and the volume of distribution is reduced.[30] A study of more than 1,000 nursing home residents in Canada found that 32% of elderly patients with heart failure were treated with digoxin. Of these patients, 80% received doses that exceeded recommended levels. Serum digoxin levels were higher than toxic in 30% of patients, and 26% were also taking medications known to interact with digoxin, increasing the risk of adverse effects.

Guidelines and Recommendations

Digoxin is recommended by the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) for heart rate control in AF with left ventricular dysfunction at a dose of 0.25 mg I.V. with repeat dosing to a maximum of 1.5 mg over 24 hours and for maintenance doses, namely oral doses of 0.125-0.25 mg once daily.[31] Similarly, the 2020 European Society of Cardiology (ESC) Guidelines, in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), recommend the use of digoxin for heart rate reduction in AF patients. For IV formulations, the suggested dose is 0.5 mg IV bolus (0.75-1.5 mg over 24 hours in divided doses). As for maintenance therapy, oral doses of 0.0625 mg to 0.25 mg are typically prescribed once daily.[32]

Digoxin appears to minimize the risk of hospitalization in individuals with an ejection fraction (EF) of < 45% who cannot tolerate beta-blockers. For patients with a pulse rate of 70 beats per minute or higher, an alternative option is ivabradine. Additionally, patients should receive an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin

receptor blocker (ARB), along with a mineralocorticoid receptor antagonist. During long-term therapy with digoxin, it is essential to monitor plasma digoxin levels regularly. The therapeutic dosage of digoxin is typically maintained between 0.6 to 1.2 ng/mL in the blood. However, caution should be exercised as certain medications, such as amiodarone, diltiazem, verapamil, and quinidine, can elevate digoxin levels in the bloodstream. Digoxin levels are used as a good toxicity marker but must be interpreted clinically because serum levels are not always a good indicator of toxicity.[33]

Digoxin remains a prevalent pharmacological agent in contemporary clinical practice, with frequent prescription for elderly patients. The aging process entails continuous structural and functional changes in aging populations, profoundly impacting critical organ systems. The decline in homeostatic capacity and functional reserve bears significant pharmacokinetic implications. Consequently, the elderly become more vulnerable to diseases and drug toxicity. To ensure safe and effective use of digoxin in older adults, specific recommendations include: optimizing polypharmacy by reducing the total number of drugs administered, discontinuing if deemed ineffective, taking into account potential drug-drug interactions and comorbidities, conducting regular medication reviews, implementing therapeutic drug monitoring, considering drug kinetics, and emphasizing compliance through appropriate dosage forms. These practices are vital for enhancing the clinical outcomes and well-being of elderly patients receiving digoxin therapy.[30]

Adverse Events and Monitoring

Aging causes changes in body condition, which, when combined with decreased kidney function and volume of distribution, prolongs digoxin elimination in plasma and increases bioavailability. Digoxin's increased pharmacodynamic sensitivity exacerbates the increased pharmacokinetic toxicity risk. The increased risk of pharmacokinetic toxicity is exacerbated by increased pharmacodynamic sensitivity to digoxin.[30] Rich et al. reported 7,788 patients in the Digitalis Investigation Group (DIG) study divided into 5 age categories: < 50 years (n = 5,841), 50 to 59 years (n = 1,545), 60 to 69 years (n = 2,885), 70 to 79 years (n = 2,092) and ≥ 80 years (n = 425) used digoxin with an average dose of 0.25 mg. The average serum digoxin level tends to be higher in older patients. Increasing age strongly predicts digoxin side effects in patients with HF.[34] Based on the study report, it was found that in elderly patients, digoxin is difficult to manage because there are many complications, and administration of digoxin to older patients increases hospitalization risk.[35,36]

Digoxin's elimination half-life is prolonged with age, and its volume of distribution is reduced.[37] Digoxin toxicity symptoms in the elderly are varied with the more common features, including anorexia, cognitive changes, hazy vision, and arrhythmia.[38–40] Moreover, the most important age-related change is decreased renal function, especially for digoxin, where poorer renal excretion requires lower doses to avoid toxicity.[41]

A previous study in a meta-analysis of 19 studies evaluated the correlation between digoxin use and mortality.[42] The Digitalis Investigation Group (DIG) study showed that serum concentrations equal to or greater than 1.2 ng/ml were correlated with a 56% increase in death risk compared to patients without taking the drug.[15] Subsequent posthoc analysis of the same DIG study indicated that digoxin treatment was considered safe when serum levels ranged from 0.5 to 0.9 ng/mL, as opposed to levels above 1.0 ng/mL.[43] Moreover,

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patients with AF using anticoagulants showed serum digoxin correlated with higher urinary excretion of thromboxane B2. In addition, in vitro experiments demonstrated that digoxin escalated platelet activation in a prestimulated stage in patients with serum digoxin levels of 1.2 ng/mL. These findings indicate the importance of maintaining digoxin levels below 1 ng/mL.[44]

Furthermore, the combination of digoxin therapy was found to elevate the risk of overall mortality in patients with end-stage renal disease on hemodialysis. As a result, guidelines have recommended that serum digoxin concentrations should ideally be maintained below 1.0 ng/mL, with a preferred range of 0.7 to 0.9 ng/mL.[45] Although current U.S. and European guidelines do not specifically recommend measuring serum digoxin levels in patients with AF, the measurement may help the monitoring to reach the goal of therapy.

Further Directions

Several potential areas for future research exist to optimize digoxin dosing in elderly patients with AF. These may include the development of novel biomarkers to predict better digoxin pharmacokinetics and dosing requirements, pharmacogenomic studies to identify genetic factors that influence digoxin metabolism and response, and using non-invasive monitoring techniques to monitor digoxin efficacy and toxicity. Additional randomized controlled trials may be conducted to compare the efficacy and safety of different digoxin dosing strategies and refine individualized dosing approaches.

Long-term outcomes associated with digoxin use in elderly patients with AF, such as the risk of adverse events like digoxin toxicity, hospitalization, and mortality, should also be investigated. Furthermore, researchers may explore ways to implement optimal digoxin dosing strategies in clinical practice, including interventions to improve prescriber education and adherence to evidence-based dosing recommendations.

Conclusion

Digoxin, a commonly used medication for controlling rapid heart rates in AF patients, encounters significant pharmacokinetic changes with age, complicating dosage adjustment for the elderly who are at higher risk of adverse reactions. To ensure safety and effectiveness, healthcare professionals should regularly monitor renal and hepatic function in elderly patients. Medication reconciliation is also crucial to identify potential drug interactions that may lead to toxicity. While current guidelines recommend a low maintenance dose for heart rate control, individualized dosing based on patients' unique clinical characteristics and response to treatment is essential. By carefully tailoring treatment and monitoring, healthcare providers can strike a balance between therapeutic benefits and risks, optimizing digoxin usage in elderly AF patients.

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Conflit of Interest

The authors declare no conflicts of interest.

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Usability of mHealth in Patient with Type 1 and Type 2 Diabetes Mellitus: A Review

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Abstract

Diabetes mellitus (DM) is a group of metabolic illnesses identified by elevated blood glucose levels. The glycated hemoglobin (HbA1C) test is used to evaluate a person's control of their blood glucose levels. According to a recent study, mHealth interventions may be particularly helpful for assisting patients with diabetes mellitus to self-monitor their status on their HbA1c level. Therefore, this systematic review aims to provide an overview of how mHealth affects individuals with diabetes mellitus, concentrating on HbA1c evaluation. A systematic review was conducted by reviewing the PubMed, Google Scholar, and Mendeley databases for randomized control trials published between February 2017 and September 2023. The studies of mHealth on the result of HbA1c were then examined. A drop in HbA1c was seen in all intervention groups. The overall average reduction in HbA1c across all intervention groups was - 0.79%, while the reduction in control groups was - 0.42%. The influence of mHealth could significantly reduce HbA1c levels. Studies show that HbA1c decreased more in patients who underwent a 3 to 6-month intervention. This study discovered 12 papers that discuss health for people with diabetes mellitus type 1 and 2. This study found that mHealth interventions significantly lower HbA1c in DM patients. For further research, bigger sample sizes and data on self-care results are needed. The views and perspectives of patients regarding the physical characteristics and design aspects of different interventions—mobile applications, texts, and phone calls—need to be further investigated.

Keywords: Diabetes mellitus, HbA1c, mHealth

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Introduction

DM is a group of metabolic illnesses defined by increased blood glucose levels, which leads to major consequences and major mortality and morbidity worldwide over time.[1] Increasing levels of obesity and body mass index, unhealthy eating habits, inactivity and lack of physical activity, increasing smoking, and other factors are the main contributors to DM. The term "mHealth" was first defined and introduced as "mobile computing, medical sensors, and communications technologies for health care". Since 2003, mHealth has become one of the most critical fields of technology that reflects the significant advancements in computing, sensors, mobile communications, and the internet to enhance the execution of healthcare.[2]

From a clinical perspective, all diabetes mellitus treatment recommendations suggest self-care of blood glucose levels as an important extra strategy for improving diabetes mellitus treatment and quality of life as well as reducing long-term effects and HbA1C levels.[2] One way to evaluate someone's glucose management is with the HbA1C test. The test provides a percentage of the mean blood sugar level for the previous ninety days.[3] Hemoglobin gets coated with glucose from the bloodstream and becomes glycated. Higher blood glucose levels reflect on the hemoglobin protein's surface, where they bond to the hemoglobin protein and cause an increase in the A1c score.[4]

Good self-management can prevent diabetic complications.[5] Strategies for self-management include keeping an eye on blood sugar levels, taking prescription drugs as directed, starting and maintaining lifestyle changes, and adjusting to the psychological and physical effects of the condition.[6–8] This element of DM treatment is still underdeveloped globally. Improving mechanisms for and actively supporting patient self-management can encourage long-term behavior change, reduce health consequences, and lower associated costs.[9]

DM currently affects 573 million adults globally, with that figure estimated to increase to 643 million by 2030 and 783 million by 2045.[10,11] Throughout the next 30 years, there is expected to be a sharp increase in the number of diabetes mellitus diagnoses. As a result, it puts increasing strain on care delivery systems and necessitates the development of low-cost solutions to assist DM patient self-management.[12] People with DM may enhance their ability to take care of themselves and control their blood sugar levels by participating in traditional DM education programs, such as doctor visits. Conversely, people may not interact with medical professionals very often because of scheduling limitations, transportation issues, expensive office visits, or longer intervals between appointments. Additionally, data indicates that web-based or mobile solutions are particularly helpful for patients living in remote places with limited access to clinics and hospitals.[13]

According to recent study, mHealth interventions may be especially beneficial for promoting diabetic self-management practices.[1,2,5,14] Mobile technology (for example, cell phones) enables highly adaptable new approaches to diabetes mellitus management.[15] A number of mHealth have been developed to assist patients with diabetes mellitus in self-monitoring their condition and providing DM knowledge and guidance.[9] The potential for mHealth to promote self-management has expanded due to its convenience, low cost, and accessibility.[7,11]

Over 6.5 billion individuals globally currently own smartphones. About five hundred million of them use smartphone apps to manage

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chronic health conditions, diets, and exercise.[16] In both developed and developing countries, smartphones are widely used. They've shown a lot of potential in offering individualized medical guidance.[17]

Approximately 1800 of more than 50,000 healthcare apps were created specifically for DM management.[1,14] Publishers and developers of mobile apps believe that DM treatment has the largest prospective market of any health field in digital health.[7] Features involving blood glucose meter connectivity, real-time feedback, medicine, fitness tracking, DM education, emotional support, tracking of sugar and glucose levels, food composition and menu change recommendations are currently included in DM management applications.[1,7,9,14]
Therefore, the purpose of this systematic review is to summarize the available literature on the effects of applying mHealth on laboratory-examined HbA1c in persons with DM. Focusing on HbA1c because it is a reliable measure of the result of all treatments.

Methods

The inclusion criteria for articles were as follows: (1) articles written in English; (2) original research; (2) full accessed articles; (3) issued between February 2017 and September 2023; (4) published in PubMed, Google Scholar, and Mendeley databases; (5) keywords developed around "mHealth", "diabetes mellitus", iii) "HbA1c", and other common diabetes mellitus terms. The exclusion criteria were: (1) non-English articles; (2) duplicate publications; (3) inability to access full text or extracted data; (4) review articles.

A two-step process was used for study selection. Reviewers independently assessed all identified titles and abstracts using the specified inclusion and exclusion criteria. After initial abstract screening, reviewers independently screened the full text of potentially relevant articles.

Articles discussing randomized control trials showing that diabetes mellitus-specific mHealth can be therapeutically beneficial for individuals with the disease. Given the rapid improvements in the mHealth field, included studies were published between 2017 and 2023 to ensure the most up-to-date material was included. Since HbA1c is the most often examined and evaluated clinical outcome related to DM technology therapy, studies reporting HbA1c as one of the key outcomes were included in this comprehensive review.

Supporting data, such as author, year, study design, intervention and control groups, baseline and follow-up HbA1c values, type of DM, sample size, and main findings are included in the Table 1.

Results and Discussion

The primary study features of the 12 included trials are summarized in Table 1. All studies used HbA1c levels as either the primary or secondary outcome of the experiment. The difference in mean average HbA1c was determined by compiling relevant research containing intervention groups (by applying mHealth interventions) and control groups (usual care). The changes in HbA1c for both the intervention and control groups as a percentage from the beginning to the end of the experiment.

All studies were randomized control trials, as required by the review inclusion criteria, with distinct digital mHealth treatments investigated in each clinical investigation. Additional patient outcomes included in the trials were glucose, Postprandial Blood Glucose (PBG) level, body mass index or body weight, Fasting Blood Glucose (FBG) concentrations, and hypoglycemic events,

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vital signs, anthropometry, fructosamine level, and fasting lipids level, user satisfaction to the app, Diabetes Knowledge Test (DBK), Self-Efficacy Scale (SES), self-management, psychosocial monitoring.

A total of 1650 people were involved in the 12 included trials; 1352 of them received a mHealth intervention, whereas 298 were part of the control group. There were between 10 and 693 participants in the experiment. The mean age of the intervention group was 48.29 years, while that of the control group was 50.84 years.

In the intervention group, there were 52.11% male participants, while in the control group, there were 548.52% male participants. Based on the statistics, the intervention group's average length of diabetes mellitus was 14.78 years, while the control group's average duration was 14.67 years.

Table 2 compares HbA1c levels between intervention and control groups in the 12 trials included in this review. Across the 12 included studies, a drop in HbA1c was seen in all intervention groups. 5 out of 6 studies found an increase in HbA1c in the control group. In all 12 trials, the intervention favored the control group. The overall average reduction in HbA1c across all intervention groups was - 0.79%, while the reduction in control groups was - 0.42%.

To improve HbA1c, good eating habits, physical activity, and medication adherence are all critical in diabetes mellitus, but self-management apps might help and effectively motivate the patients.[18] The findings of this study have found that mHealth can help diabetes mellitus patients to improve their self-management and HbA1c levels from a total of 1650 participants across 12 RCTs. The various interventions, such as text messages, mobile apps, interactive telephone, websites, video conferences, and devices, may also explain the impact of mHealth on HbA1c.[9,12,19] A previous study found similar results, hypothesizing that interactive treatment could help remote management of diabetes mellitus healthcare better. Research revealed that receiving text messages (whether motivational or instructive) or being interactive with the physicians resulted in a high level of patient satisfaction and that patients found this useful and beneficial.[9] A statistically significant HbA1c reduction for patients in the intervention group was achieved with the use of mHealth and phone-based therapies that allow for bidirectional patient-provider contact.[12,20]

Although every method of intervention revealed significant HbA1c improvement, this review found that coaching groups with interactive physicians showed a larger HbA1c reduction than other forms of intervention. Without remote supervision and continued assistance, it is difficult to attain long-term effectiveness. Consequently, long-term follow-up is crucial for elderly diabetic patients.[21]

Based on the data on the average age of the diabetes mellitus patients, diabetes mellitus itself is more common in older people. Because of this, certain patients might have encountered issues utilizing certain applications, such as inputting blood glucose readings to the website or gaining access to online learning resources. A study shows that elderly patients need time to become familiarized with the mHealth system. However, following self-training and remote help from the medical team, the patients began using the portable smart gadget independently, which resulted in favorable outcomes.[21]

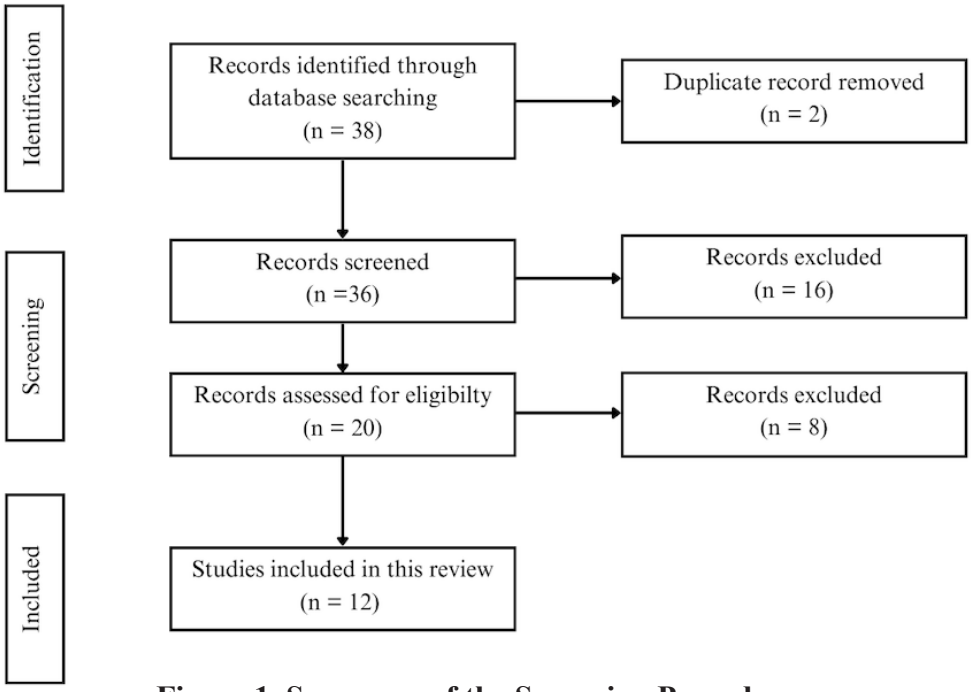

Figure 1. Summary of the Screening Procedure

Patients who underwent a 3 to 6-month intervention showed a greater decrease in HbA1c. These data showed that mHealth intervention might help with HbA1c management for at least 6 months.[2,19,20,22] A prior study revealed similar findings, indicating that 6 months of digital healthcare intervention significantly decreases HbA1c levels in diabetes mellitus patients.[23] mHealth allows patients to get remote diagnosis, therapy, and consultation while also lowering medical costs and preventing cross-infection during outpatient appointments.[24–26]

Liu et al explored the impact of participants' educational backgrounds on the decrease in HbA1c levels, noting a correlation with involvement in mobile peer support. The most actively engaged group predominantly consisted of individuals with at least a college education. This observation suggests that participants with higher educational levels might possess more positive attitudes toward utilizing mobile apps for diabetes self-management and demonstrate a more favorable response within mobile communities.[27]

The Welltang application introduced a team of external medical experts who engage with patients online and offer thorough guidance. Findings indicated that, following a six-month follow-up, the group receiving assistance from the external medical team exhibited notably lower HbA1c levels compared to other groups. This implies that combining app-based self-management with the support of a professional medical team can enhance the management of blood sugar and lipids. Interactive management models, like this one, have the potential to be a significant driving force in the future of diabetes management.[28]

The Wellthy CARE mobile app program implemented a digital persuasion model that concentrated on boosting patient motivation, easing the difficulty of task completion, and offering appropriate incentives to encourage

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action. The program provided coaching in seven key areas: promoting healthy eating, increasing physical activity, enhancing self-monitoring, ensuring medication adherence, fostering problem-solving skills, reducing risk factors, and promoting healthy coping mechanisms.

These areas were tailored to the individual's entered data and were informed by prior clinical, lifestyle, and behavioral information. Participants utilizing the digital therapy for 16 weeks experienced a reduction of 0.49% in HbA1c levels. Furthermore, a correlation was observed between increased program participation and notable decreases in HbA1c levels.[29]

The ¡Sí, Yo Puedo! program, designed for adults with Type 2 Diabetes, resulted in a noteworthy enhancement of diabetes self-efficacy and indicated a potential improvement in HbA1c levels within the treatment group after 6 months, compared to the control group. The program's success in maintaining high attendance and low attrition could be attributed to intervention elements such as customizing content to the local context, reinforcing information and motivation through methods like text messages, group sessions, and follow-up phone calls led by class leaders. The significance of group-based session attendance as a moderator of program effectiveness was underscored. Additionally, participants in the treatment group exhibited a substantial increase in diabetes self-efficacy, potentially acting as a mediating factor contributing to the observed improvement in HbA1c levels. [19]

Conclusion

This research found 12 articles that reported the findings of RCTs of mHealth for patients with type 1 and 2 DM patients. In general, this study concluded that mHealth interventions improve HbA1c in diabetes mellitus patients considerably. Our study's limitations include the fact that every outcome and most subgroups show notable heterogeneity. The intricacy of telemedicine treatments—including the duration, strategies, combinations, and quality of mobile applications—may be a factor in the variance. Second, we found that research number limitations put doubt on the effectiveness of self-care outcomes. For future research, further studies with bigger sample sizes and data on the results of self-care are needed.

It is suggested that more research be performed on the relationship between various intervention strategies and their constituent parts. The views and perspectives of patients regarding the physical characteristics and design aspects of different interventions—mobile applications, texts, and phone calls—need to be further investigated. Future research must address the elements affecting mHealth's acceptance and utility after examining patients' opinions about its use. It is essential for their impact and application in clinical practice that these therapies are evaluated based on their cost-effectiveness factor.

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Table 1. Characteristic of the Included Studies

Authors	Years	Diabetes Mellitus Type	Study				Participants				Methods	Findings
			App	Control	Interventions (n)	Control (n)	Age (Years, mean % and SD)	Gender (%)	Duration of Diabetes Mellitus (years, mean % and SD)	Ethnic Groups		
Liu et al[27]	2022	T1D	TangTang-Quan	N/A	693	N/A	3 Intervention; 1.00 ± 9.50	Intervention; Male = 33.90, Female = 66.10	Intervention: 8.30 ± 6.80	Chinese	The change in mean fasting blood sugar (FBG), postprandial blood sugar (PBG), and glycosylated hemoglobin (HbA1c) from baseline to the 12th month was evaluated.	HbA1c among the 693 people improved in the 12th month.
Tack et al[30]	2018	T1D	Mobile app	N/A	19	N/A	Intervention; 43.80 ± 14.10	Intervention; Male = 36.84; Female = 63.15	Intervention: 22.80 ± 14	Dutch	Adults with diabetes mellitus attempted the app for six weeks and their HbA1c were evaluated through surveys.	The patient's hemoglobin A1c dropped from 7.9% to 7.6% after six weeks.
Ryan et al[31]	2017	T1D	Intelligent Diabetes Management	N/A	18	N/A	Intervention; 40 ± 13.90	Intervention; Male = 27.78; Female = 72.22	Intervention: 27.3 ± 14.90	Caucasian	The participant's diabetic regimens were entered on the synchronized IDM website after the app had been downloaded by the patients. Their data were examined online at 2, 4, 8, 12, and 16 weeks during the active period, and feedback was given electronically. The glycated hemoglobin (A1C) level change was the main outcome.	The median HbA1C value decreased from 8.10% to 7.80%.

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Table 1. Characteristic of the Included Studies (cont...)

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			App	Control	Interventions (n)	Control (n)	Age (Years, mean % and SD)	Gender (%)	Duration of Diabetes Mellitus (years, mean % and SD)	Ethnic Groups		
Zhang et al[32]	2019	T1D and T2D	Welltang	Patients received standard care and did not download Welltang on their smartphone.	184	92	Intervention; App Self Management Group: 52 ± 10, App Interactive Management Group: 52 ± 12 Control: 55 ± 11	Intervention; App Self Management Group: Male = 64.10, Female = 35.90, App Interactive Management Group: Male = 59, Female = 41 Control; Male = 62.80, Female = 37.20	Intervention: App Self Management Group = 11.20 ± 5.60, App Interactive Management Group = 10.10 ± 5.50 Control: 12.70 ± 7.10	Chinese	This study was a 6-month long and change in glycated hemoglobin (HbA1c) level was the main result.	At months six, the HbA1c levels of patients in the app interactive management group were considerably lower than those in the app self-management and control group.

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Potter et al [9]	2022	T2D	*GLOOK!* app	N/A	15	N/A	54.07	Intervention; Male = 73.33, Female = 26.66	N/A	Australian	The patients used a glucose monitor and an Apple Watch to sensor patient's behavior, food intake, medication, and insulin use for 12 days. The submitted data were linked into the *GLOOK!* software on the patients' smartphones. Participants were also interviewed at both the beginning and end of the study to evaluate their acceptance of the intervention and its potential impact on promoting positive behavior change.	The HbA1c level was reduced by 0.22% in 12-day research. The *GLOOK!* system received excellent feedback from patients, such as the patients were excited in continuing to use the app system if some usability and reliability issues were addressed and felt that adopting the method encouraged long-term behavior improvements.
Koot et al [33]	2019	2019	GlycoLeap	N/A	100	N/A	53.50	Intervention; Male = 53, Female = 47	Intervention: 8.80	Chinese 45, Malay 29, Indian 18 and another ethnicity 8	Participants were accessed to GlycoLeap and completed a survey during the follow-up to assess self-reported changes in diabetic self-care, nutritional consumption, physical activity, program participation, and user satisfaction after ≥12 weeks.	HbA1c improvements were clinically significant in the intervention group.

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Xu et al [12]	2019	2019	EpxDiabetes	No provider-initiated follow-up based on the self-reported FBG data.	33	32	Intervention: 54.60 ± 1.82 Control: 55.34 ± 1.94	Intervention; Male = 37.50, Female = 62.50 Control; Male = 25, Female = 75	N/A	Intervention: Caucasia = 6, African American = 27 Control; Caucasian = 2, African American = 29	EpxDiabetes automated phone calls or text messages were used to obtain self-reported FBG data. Only responses from the intervention groups were shared with providers, enabling follow-up and bidirectional contact.	After 6 months, HbA1c levels were measured. The intervention group had an absolute HbA1c drop of 0.69% whereas the control group had a reduction of 0.03%.
Krishnakumar et al [29]	2021	2021	Wellthy CARE mobile app	N/A	102	N/A	50.80	Interventions; Male = 68.60, Female = 31.40	N/A	Indian	Patients used Wellthy CARE mobile app to track meals, weight, physical activity, and blood sugar levels. They also received lessons, feedback from an artificial intelligence-powered chatbot, and periodic interactions with certified diabetes mellitus educators via voice calls and chats. The study included pre- and post-intervention HbA1c measurements.	The average change in HbA1c after 16 weeks was - 0.49%. 63.70% of all patients had improved HbA1c readings, with a mean change of 1.16%.

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			App	Control	Interventions (n)	Control (n)	Age (Years, mean % and SD)	Gender (%)	Duration of Diabetes Mellitus (years, mean % and SD)	Ethnic Groups		
Alanzi et al [34]	2018	2018	Saudi Arabia Networking for Aiding Diabetes system (SANAD system)	Usual medical treatment and management by the health care staff of medical center.	10	10	Intervention: 18-40 years = 80, 41-50 years = 20 Control: 18-40 years = 70, 41-50 years = 30	Intervention; Male = 80, Female = 20 Control; Male = 70, Female = 30	Intervention: ≤ 5 years = 80, 6-10 years = 20 Control: ≤ 5 years = 100	Arabian	The blood glucose sensors were activated and operated by the intervention group using the SANAD system, and the information was sent via the SANAD app for smartphones, using the provided phone. On the other hand, those in the control group were managed by medical center staff and got regular medical therapy. The HbA1c levels of the participants were measured both at enrollment and six months later during the study.	SANAD system among Saudi type 2 diabetes mellitus participants successfully reduced HbA1c levels.
Kim et al [20]	2018	2018	mDiabetes	Record measured glucose levels at the same frequency as the intervention group and continue using the method of	90	82	Intervention: 60 ± 8.40 Control: 56.70 ± 9.10	Intervention: Male = 55.60, Female = 44.40 Control: Male = 47.60, Female = 52.40	Intervention: 13.20 ± 8.00 Control: 12.50 ± 7.30	South Korean	This trial was a 24-week clinical trial. The mDiabetes app and its integration with the activity tracker and glucometer were demonstrated to the intervention group. The insulin dose algorithm recommended by the mDiabetes system was to be followed by those who were in the mDiabetes group. The difference between the baseline and 24-week HbA1c values was the primary outcome. The other	After 24 weeks, the intervention group's HbA1c level drop from baseline was larger than the control group's.

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			App	Control	Interventions (n)	Control (n)	Age (Years, mean % and SD)	Gender (%)	Duration of Diabetes Mellitus (years, mean % and SD)	Ethnic Groups		
Kim et al [20]	2018	2018	mDiabetes	Record measured glucose levels at the same frequency as the intervention group and continue using the method of insulin dose adjustment previously indicated by their physician and nurses.	90	82	Intervention: 60 ± 8.40 Control: 56.70 ± 9.10	Intervention: Male = 55.60, Female = 44.40 Control: Male = 47.60, Female = 52.40	Intervention: 13.20 ± 8.00 Control: 12.50 ± 7.30	South Korean	This trial was a 24-week clinical trial. The mDiabetes app and its integration with the activity tracker and glucometer were demonstrated to the intervention group. The insulin dose algorithm recommended by the mDiabetes system was to be followed by those who were in the mDiabetes group. The difference between the baseline and 24-week HbA1c values was the primary outcome. The other markers including the difference in HbA1c values from baseline after 12 weeks were secondary end goals.	After 24 weeks, the intervention group's HbA1c level drop from baseline was larger than the control group's.
Whittemore et al [19]	2020	2020	*¡Sí, Yo Puedo Vivir Sano con Diabetes!*	The control group were provided usual T2D care at The Seguro	26	21	Intervention: 53.90 ± 9.20 Control:	Intervention; Male = 34.60, Female = 65.40	Intervention: 10.20 ± 7.20 Control: 13.50 ±	Mexican	Participants in the intervention group were given the *¡Sí, Yo Puedo* program which featured seven interactive group-based diabetic self-management educative sessions. The program consisted of daily text/picture	There was a tendency toward decreasing HbA1c at 6 months in the treatment group compared to the control group.

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Table 2. . Trial Results According to HbA1c (%) Values

Authors	Years	Diabetes Mellitus Type	Study				Participants				Methods	Findings
			App	Control	Interventions (n)	Control (n)	Age (Years, mean % and SD)	Gender (%)	Duration of Diabetes Mellitus (years, mean % and SD)	Ethnic Groups		
Whittemore et al [19]	2020	2020	*¡Sí, Yo Puedo Vivir Sano con Diabetes!*	The control group were provided usual T2D care at The Seguro Popular clinic.	26	21	Intervention: 53.90 ± 9.20 Control: 56.80 ± 8.30	Intervention; Male = 34.60, Female = 65.40 Control; Male = 30, Female = 70	Intervention: 10.20 ± 7.20 Control: 13.50 ± 7.30	Mexican	Participants in the intervention group were given the *¡Sí, Yo Puedo* program with seven interactive group-based diabetic self-management educative sessions. The program consisted of daily text/picture messages which were sent out daily for 6 months. Data on primary (HbA1c) and secondary (clinical, psychosocial, and behavioral) outcomes were gathered at baseline, 3 months, and 6 months.	There was a tendency toward decreasing HbA1c at 6 months in the treatment group compared to the control group.
Di Molfetta et al [22]	2022	2022	Glucoonline TM system	Patients were provided with a typical glucose meter and they were instructed to record their glucose readings on a paper diary.	62	61	Intervention: 47.15 ± 14.54 Control: 45.21 ± 14.76	Intervention; Male = 53.20, Female = 46.80 Control; Male = 55.70, Female = 44.30	Intervention: 32.85 ± 15.36 Control: 30.63 ± 15.41	N/A	The experimental group received a smartphone-connected meter and a smartphone with software-implemented real-time data transmission. Web-based electronic GlucoonlineTM enables numerous assessments is available. Participants in the control group were provided with a standard glucose meter and asked to record their glucose readings on a paper diary. Change in HbA1c from Visit 1 measured at Visit 3 was the main outcome.	In comparison to standard of care, the use of the GlucoonlineTM system led to a 0.38% decrese in HbA1c in patients with insulin-treated type 2 diabetes mellitus from baseline and a larger percentage of patients meeting a HbA1c goal level of less than 7%.

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Conflict of Interest
None declared.

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