

*Original Research Article*

## Traditional and Complementary Medicine Use in Patients With Type 2 Diabetes: Findings From A Multicenter Cross-Sectional Questionnaire Survey in Selangor, Malaysia

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**Abstract:** Current global estimates of traditional and complementary medicine (T&CM) utilization range from 9.8% to 76%, with high rates of use being documented in Japan, South Korea, and Malaysia. Previous research has shown that patients with diabetes are more likely to use T&CM than individuals without diabetes. A multicenter cross-sectional survey of patients with type 2 diabetes mellitus was conducted at five primary care health clinics in Petaling district of Selangor, Malaysia from June 1, 2020 through September 30, 2020. A total of 476 patients were enrolled. 58.0% of men and 64.8% of women reported having used at least one type of T&CM. The prevalence of T&CM use among Malays, Chinese, and Indians was 71.1%, 33.3%, and 62.9% respectively. The most commonly used T&CM were herbal remedies (45.2%), followed by nutritional supplements (9.9%). 80.0% of the patients would follow their doctor's instructions if the doctor asked them not to use T&CM, whereas 70.2% would consult their doctor about using T&CM. Factors associated with higher tendency for T&CM use included increased age, unemployment, oral antidiabetic monotherapy, presence of family history of diabetes, and coexisting chronic disease. T&CM therapies were common among the multi-ethnic patient population with type 2 diabetes. The high rate of use warranted clinical attention and intervention to prevent adverse drug events.

**Keywords:** Traditional and complementary medicine, Complementary and alternative medicine, Diabetes, Drug-herb interaction, Dietary supplement, Prescription medication.

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## 1. Introduction

Traditional and complementary medicine (T&CM) refers to a wide variety of clinical therapies that are not currently considered as an integral part of conventional medicine<sup>[1]</sup>. The prevalence of T&CM use by populations across the world ranges from 9.8% to 76%, with high rates being documented in Japan (76%), South Korea (75%), and Malaysia (30%)<sup>[2,3]</sup>. However, previous studies have revealed that about half of T&CM users do not disclose their use of T&CM with their primary care providers. This problem is compounded by the issue that, very often, physicians rarely initiate conversations or discuss with patients about T&CM. A better understanding of practices, attitudes, and beliefs of patients towards T&CM can facilitate better coordination of care, decrease the risk of potential interactions between prescription medications and T&CM therapies, and lead to better patient outcomes<sup>[4]</sup>.

Diabetes mellitus is one of the most widespread and morbid chronic diseases worldwide and over 90% of the diagnoses are type 2<sup>[5]</sup>. While conventional medical therapies prevent some of its devastating complications, patients do not usually restore normoglycemia or eliminate all the adverse consequences. Hence, it is not surprising that individuals with diabetes are more likely to utilize T&CM in conjunction with standard medical care than those without diabetes<sup>[6]</sup>. Although several T&CM therapies have been suggested to have promising roles in diabetes, their safety concerns, clinical efficacy, and mechanism of action are still less understood. Patients with diabetes are often prescribed with multiple medications. Thus, there exists a substantial risk for clinically significant drug-herb and drug-supplement interactions<sup>[1]</sup>.

Sociocultural factors have been reported to influence the utilization of T&CM<sup>[7]</sup>. There have been limited studies to elucidate the prevalence, knowledge, attitude, and pattern of T&CM use among the multi-ethnic population in Malaysia. Consequently, we conducted a multicenter cross-sectional study to better understand the use of T&CM among patients with type 2 diabetes.

## 2. Materials and Methods

### 2.1 Study Population

From June 1, 2020 until September 30, 2020, a cross-sectional questionnaire survey was administered via face-to-face interviews to patients with type 2 diabetes of 18 years of age or older who were receiving medical care at five primary care health clinics situated in

the district of Petaling, Selangor, Malaysia. Potential participants were recruited using convenience sampling, i.e., non-random (non-probability) sampling when they were waiting or collecting their medications at the pharmacy unit. All participants who agreed to participate in the research had to provide a written informed consent. The survey took approximately 10 minutes to complete. The exclusion criteria included gestational diabetes, type 1 diabetes, and inability to comprehend the survey.

## *2.2 Survey Instrument*

The questionnaire was developed by our team in dual language (English and Malay) and consisted of 25 questions to glean sociodemographic information, clinical characteristics, knowledge, attitude, and perception towards T&CM, type of T&CM used, and reasons for use of T&CM. It was adopted from two validated questionnaire tools in previous studies<sup>[8,9]</sup>. The questions were further reviewed by four pharmacists for clarity and ease of administration.

## *2.3 Sample Size*

According to the Malaysian National Health and Morbidity Survey 2019, the estimated adult population with known diabetes in the state of Selangor was 408,113<sup>[10]</sup>. Using the Raosoft calculator, the sample size of the study was enumerated based upon a margin of error of 5%, a confidence level of 95%, a response distribution of 50%, and a total population of diabetic patients of approximately 408,113<sup>[11]</sup>. The recommended sample size was 384 patients.

## *2.4 Statistical Analysis*

Data were summarized by the calculation of frequency and percentage for categorical variables. Chi-square tests were carried out to assess sociodemographic and clinical predictors of T&CM use. Additionally, multivariable logistic regression analyses were performed to compute the odds ratio (OR) and 95% confidence intervals (CI) for the use of T&CM among patients with type 2 diabetes. A P value of less than 0.05 was considered to indicate statistical significance. All analyses were undertaken with the use of SPSS Statistics software, version 26 (IBM Corp., Armonk, NY, USA).

## *2.5 Ethics Statement*

The research was conducted in accordance with the principles of the Malaysian Guideline for Good Clinical Practice, following the International Council for Harmonization of Good Clinical Practice Guidance. All study subjects gave written informed consent. The

study protocol was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (KKM/NIHSEC/ P20-984 [6]).

### 3. Results

476 patients participated in the study. A total of 123 of 212 men (58.0%) reported having used at least one type of T&CM, as compared with 171 of 264 women (64.8%). Nearly three quarters of all T&CM users were aged 51 years and older. The prevalence of T&CM use among Malays, Chinese, and Indians was 71.1%, 33.3%, and 62.9% respectively. Of 294 patients with type 2 diabetes reported using T&CM, the majority attained secondary education (56.5%), were married (94.2%), or were non-smokers (73.5%). In terms of clinical characteristics, most of the T&CM users had a family history of diabetes (74.5%), received oral antidiabetic monotherapy (51.7%), had no diabetic complications (70.7%), and had coexisting hypertension (74.8%) or dyslipidemia (65.0%). Further details are presented in Table 1.

More than one quarter of patients believed T&CM was safe and effective for diabetes. 80.0% would follow their doctor's instructions if the doctor asked them not to use it, whereas 70.2% would discuss T&CM use with their primary care physician before taking it. The main reasons for T&CM use were belief in its efficacy in diabetes control (41.8%) and wide availability with low costs (10.1%). Herbal remedies were the most frequently used T&CM (45.2%) and the varieties reported encompassed finished products such as *Momordica charantia* (bitter melon), *Trigonella foenum-graecum* (fenugreek), *Swietenia macrophylla* (sky fruit), green apple herb, *Allium sativum* (garlic), *Azadirachta indica* (neem), Ayurvedic polyherbal formulation, *Orthosiphon stamineus Benth* (cat's whiskers), and *Kaempferia parviflora* (black ginger); and raw herbs such as *Panax ginseng* (Asian or Korean ginseng), *Panax quinquefolius* (American ginseng), *Kasini veppalai*, and *Andrographis paniculata*. Other T&CM practices used by the patients included nutritional supplements (9.9%), treatment based on a specific diet (2.5%), wet cupping (1.7%), honeybee products (1.7%), Roqia (1.3%), medical massage (1.1%), and acupuncture (0.8%).

Study participants were largely influenced by their friends (33.0%) and family members (18.7%) when making a decision to use T&CM. A third of them were satisfied with current T&CM and would continue using it for a long period of time (Table 2). Chi-square analysis showed that T&CM use in type 2 diabetes was significantly associated with ethnicity, employment status, smoking status, coexisting chronic conditions, duration of diabetes diagnosis (All  $P < 0.001$ ), presence of a diabetes complication ( $P = 0.002$ ), educational attainment ( $P = 0.002$ ), pharmacotherapy prescribed ( $P = 0.003$ ), and age ( $P = 0.014$ ) (Table 1).

Multivariate logistic regression analysis depicted elevated rates of T&CM usage among age groups of 31 to 60 years, unemployed, oral antidiabetic monotherapy, presence of family history of diabetes, and coexisting illness (Table 3).

**Table 1.** Sociodemographic and clinical characteristics of patients in the study and T&CM use ( $n=476$ ).

Characteristic	Total number of study participants, $n$ (%)	Number of patients reported having used T&CM for diabetes, $n$ (%)	$P$ value (Chi-square test)
<i>Age (years)</i>			
<30	14 (2.9)	9 (1.9)	0.014
31–40	31 (6.5)	25 (5.3)	
41–50	80 (16.8)	49 (10.3)	
51–60	156 (32.8)	106 (22.3)	
>60	195 (41.0)	105 (22.1)	
<i>Gender</i>			
Male	212 (44.5)	123 (25.8)	0.132
Female	264 (55.5)	171 (35.9)	
<i>Marital status</i>			
Single	22 (4.6)	11 (2.3)	0.223
Married	447 (93.9)	277 (58.2)	
Other	7 (1.5)	6 (1.3)	
<i>Ethnicity</i>			
Malay	235 (49.4)	167 (35.1)	<0.001
Chinese	87 (18.3)	29 (6.1)	
Indian	151 (31.7)	95 (20.0)	
Other	3 (0.6)	3 (0.6)	
<i>Educational level</i>			
Primary	99 (20.8)	48 (10.1)	0.002
Secondary	271 (56.9)	166 (34.9)	
Diploma	66 (13.9)	48 (10.1)	
Undergraduate degree	36 (7.6)	28 (5.9)	
Postgraduate degree	4 (0.8)	4 (0.8)	
<i>Employment status</i>			
Employed	213 (44.7)	125 (26.3)	<0.001
Unemployed	82 (17.2)	69 (14.5)	
Retired	181 (38.0)	100 (21.0)	
<i>Smoking status</i>			
Daily smoker	72 (15.1)	30 (6.3)	<0.001
Non-daily smoker	45 (9.5)	34 (7.1)	
Former smoker	26 (5.5)	14 (2.9)	
Non-smoker	333 (70.0)	216 (45.4)	
<i>Duration of diagnosed type 2 diabetes</i>			
Newly diagnosed	41 (8.6)	26 (5.5)	<0.001
<5 years	114 (23.9)	82 (17.2)	
5–10 years	161 (33.8)	94 (19.7)	
10–15 years	109 (22.9)	52 (10.9)	
>15 years	51 (10.7)	40 (8.4)	
<i>Family history of diabetes</i>			
Yes	351 (73.7)	219 (46.0)	0.125
No	109 (22.9)	69 (14.5)	
Unsure	16 (3.4)	6 (1.3)	
<i>Diabetes pharmacotherapy</i>			
Oral antidiabetic drugs alone	217 (45.6)	152 (31.9)	0.003
Insulin alone	53 (11.1)	29 (6.1)	

Characteristic	Total number of study participants, n (%)	Number of patients reported having used T&CM for diabetes, n (%)	P value (Chi-square test)
Combination of oral hypoglycemic drugs and insulin	206 (43.3)	113 (23.7)	
<i>Diabetes complications</i>			
Neuropathy	97 (20.4)	60 (12.6)	
Cardiovascular complications	36 (7.6)	17 (3.6)	
Retinopathy	47 (9.9)	16 (3.4)	
Diabetic foot	12 (0.2)	1 (0.2)	0.002
Nephropathy	26 (2.5)	5 (1.1)	
Multiple complications	45 (9.5)	12 (2.5)	
No complications	311 (65.3)	208 (43.7)	
<i>Concomitant chronic disease</i>			
Hypertension	357 (75.0)	220 (46.2)	
Dyslipidemia	290 (60.9)	191 (40.1)	
Asthma	20 (4.2)	7 (1.5)	
Coronary heart disease	60 (12.6)	22 (4.6)	<0.001
Other	11 (2.3)	10 (2.1)	
Multiple coexisting diseases	256 (53.8)	146 (30.7)	
No coexisting disease	27 (5.7)	10 (2.1)	

**Table 2.** Knowledge, attitude, and pattern of T&CM use (n=476).

Variable	Total number of patients, n (%)
<i>Knowledge</i>	
Hear of T&CM	373 (78.4)
Believe T&CM is effective for diabetes	167 (35.1)
Believe T&CM is safe	141 (29.6)
<i>Attitude</i>	
Follow a doctor's instructions if the doctor asks you not to use T&CM	381 (80.0)
Discuss with a doctor if you want to use T&CM	334 (70.2)
Combine T&CM with antidiabetic medication	263 (55.3)
Advise or encourage family member(s) to use T&CM	152 (31.9)
<i>Reason to use T&amp;CM</i>	
Lack of confidence towards prescription medication	18 (3.8)
Long appointment intervals to see a doctor	12 (2.5)
Believe T&CM has fewer side effects than conventional medicine	47 (9.9)
Believe T&CM helps in diabetes control	199 (41.8)
Poor physician-patient communication	4 (0.8)
T&CM is easily available and cheaper	48 (10.1)
Doctor suggests to use T&CM	27 (5.7)
Other	21 (4.4)
Multiple reasons	68 (14.3)
<i>Type of T&amp;CM</i>	
Herbal remedies	215 (45.2)
Wet cupping	8 (1.7)
Nutritional supplements	47 (9.9)
Cautery	0 (0.0)
Roqia	6 (1.3)
Honeybee products	8 (1.7)
Medical massage	5 (1.1)
Treatment based on a specific diet	12 (2.5)
Acupuncture	4 (0.8)
Other	27 (5.7)
Multiple types of T&CM	26 (5.5)

Variable	Total number of patients, <i>n</i> (%)
<i>Influencer of T&amp;CM use</i>	
Friend	157 (33.0)
Traditional healer	8 (1.7)
Pharmacist	9 (1.9)
Herbalist	5 (1.1)
Dietitian	4 (0.8)
Physician	9 (1.9)
Family member	89 (18.7)
Other	31 (6.5)
Neighbor	2 (0.4)
Salesman	2 (0.4)
Online advertisement, TV, YouTube, or newspaper	16 (3.4)
Multiple sources of influence	32 (6.7)
<i>Perception</i>	
Satisfied with current T&CM used	153 (32.1)
Will continue using T&CM for the long term	157 (33.0)
Ever used T&CM for medical conditions other than diabetes	74 (15.5)

**Table 3.** Multivariate adjusted association between patients' characteristics and T&CM use for type 2 diabetes (*n*=476).

Characteristic	T&CM use for type 2 diabetes	
	OR (95% CI)	<i>P</i> value
<i>Age (years)</i>		
<30	1.983 (0.504–7.805)	0.327
31–40	6.864 (2.105–22.380)	0.001
41–50	3.255 (1.601–6.616)	0.001
51–60	3.403 (1.848–6.264)	0.000
>60	1 (ref)	-
<i>Gender</i>		
Male	1.251 (0.775–2.019)	0.359
Female	1 (ref)	-
<i>Marital status</i>		
Single	0.081 (0.007–0.894)	0.040
Married	0.227 (0.026–2.013)	0.183
Other	1 (ref)	-
<i>Employment status</i>		
Employed	0.468 (0.263–0.833)	0.010
Unemployed	2.950 (1.370–6.350)	0.006
Retired	1 (ref)	-
<i>Smoking status</i>		
Daily smoker	0.617 (0.220–1.729)	0.359
Non-daily smoker	2.922 (0.863–9.888)	0.085
Non-smoker	1.549 (0.592–4.051)	0.372
Former smoker	1 (ref)	-
<i>Duration of diagnosed type 2 diabetes</i>		
Newly diagnosed	0.261 (0.088–0.771)	0.015
<5 years	0.368 (0.148–0.912)	0.031
5–10 years	0.248 (0.106–0.579)	0.001
10–15 years	0.226 (0.096–0.534)	0.001
>15 years	1 (ref)	-
<i>Family history of diabetes</i>		
Yes	3.465 (1.073–11.189)	0.038
No	3.248 (0.946–11.153)	0.061
Unsure	1 (ref)	-
<i>Diabetes pharmacotherapy</i>		
Oral antidiabetic drugs alone	1.985 (1.236–3.188)	0.005

Characteristic	T&CM use for type 2 diabetes	
	OR (95% CI)	P value
Insulin alone	1.631 (0.812–3.273)	0.169
Combination of oral hypoglycemic drugs and insulin	1 (ref)	-
<i>Diabetes complications</i>		
Yes	0.600 (0.377–0.955)	0.031
No	1 (ref)	-
<i>Concomitant chronic disease</i>		
Yes	2.949 (1.175–7.403)	0.021
No	1 (ref)	-

The model used was adjusted for age, gender, marital status, employment status, smoking status, duration of diagnosis of type 2 diabetes, family history of diabetes, pharmacotherapy received, presence of diabetes complications, and coexisting chronic disease. The results were based on  $n=476$  participants with complete data for all covariates (no missing data).

#### 4. Discussion

This study showed T&CM was commonly used among patients with type 2 diabetes in multi-ethnic communities (Figure 1). Of clinical concern, these patients have a high risk of adverse drug events, principally those of older age and have multiple chronic medical conditions<sup>[12]</sup>. The risk is further increased in light of the challenges of determining specific ingredients in T&CM products, no tablet size and shape requirements, and lack of post-marketing surveillance<sup>[13]</sup>.

Notably, the current study identified a popular use of herbal medicine. Such biologically-based T&CM may influence glucose metabolism and interfere with glycemic control<sup>[14,15]</sup>. Reflecting on particular types of herbal remedies consumed by the study participants, bitter melon elicits insulin-mimetic activity, decreases hepatic gluconeogenesis, and is contraindicated in glucose-6-phosphate dehydrogenase deficiency. Garlic increases insulin secretion and potentially interacts with anticoagulant or antiplatelet medications due to its blood thinning effects. Likewise, ginseng causes hypoglycemia by altering hepatic glucose metabolism, interacts with anticoagulant or antiplatelet medications, and causes insomnia, hypertension, and estrogenic effects. Fenugreek decreases carbohydrate absorption, increases insulin secretion, and can cause intestinal gas, bloating, or diarrhea<sup>[1]</sup>. Thus far, most T&CM studies have found conflicting clinical data and lacked sufficient quality to make a recommendation regarding the efficacy and safety of T&CM for patients with type 2 diabetes<sup>[16,17]</sup>. Given the high proportion of patients with type 2 diabetes (61.8%) reporting utilization of T&CM in this representative sample of a state, the potential effects of T&CM use on glycemic control, other cardiometabolic risk factors, and health-related quality of life merit further investigation.



# Traditional and complementary medicine use in patients with type 2 diabetes

## Background



Although evidence from existing literature suggests patients with diabetes are more likely to use traditional and complementary medicine (T&CM) compared to individuals in the general population, less is known about the prevalence and pattern of use within urban, multi-ethnic patient communities with type 2 diabetes.

## Study Design



Multicenter, cross-sectional

Self-administered questionnaire

Primary care health clinics

## Population



476 adults attending government-run primary health care facilities in Petaling district, Malaysia for type 2 diabetes treatment

45% men

41% aged over 60 years

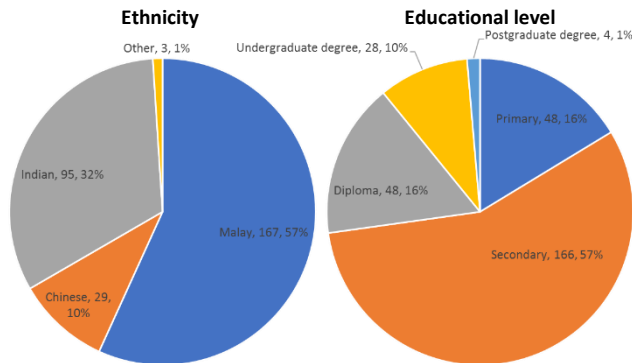
50% Malay ethnicity

## Findings



Age

294 patients (62%) reported having used some form of T&CM. The most commonly used T&CM was herb (215, 73%).



### Knowledge, Attitude & Perception

- 30% believed that T&CM was safe and effective for diabetes.
- 80% would follow a doctor's instructions if the doctor asked them not to use T&CM.
- 70% would discuss T&CM use with their primary care physician before taking it.
- 55% used T&CM and prescription medication together.
- 33% would continue to utilize T&CM for the long term.

### Reasons For T&CM Use

- 42% believed that T&CM was effective in diabetes control.
  - 10% cited that T&CM was easily available and cheaper.
  - 10% believed that T&CM had fewer side effects than conventional medicine.
- ✓ Older age, unemployment, oral antidiabetic monotherapy, family history of diabetes, and coexisting chronic illness were associated with higher odds of T&CM use.

## Conclusion



A high proportion of patients with type 2 diabetes living in urban, multi-ethnic communities reported T&CM use. The safety and efficacy of T&CM modalities, as well as the role of T&CM in conjunction with or as a supplement to conventional means of diabetes care warrant further large-scale investigation.

Figure 1. Research summary of traditional and complementary medicine use in patients with type 2 diabetes in Selangor, Malaysia.

Because only adults with type 2 diabetes were recruited in our study, the cohort of patients consisted primarily of Malays (49.4%), Chinese (18.3%), and Indians (31.7%). This ethnic composition appeared quite consistent with the findings in the Malaysian National Health and Morbidity Survey 2019, which indicated that Indians had the highest prevalence of a known diagnosis of diabetes (18.5%), followed by Malays (11.0%), and Chinese (8.5%)<sup>[10]</sup>. The widespread utilization and public interest in T&CM among a multi-ethnic population could be ascribable to ancestral systems of healing, religious practices, and cultural and spiritual beliefs<sup>[7]</sup>. Patients have preferences for their own treatment decisions and health outcomes, and thus, they may opt to try complementary therapies, albeit they lack appropriate information and understanding. Of note, data from our research suggested that use of T&CM was not strongly correlated with the lack of confidence towards prescription medications and long appointment intervals to see a doctor, both of which were typically considered by clinicians to be the key factors. This finding stood in contrast to the common assumption and existing research that patient dissatisfaction with waiting time and treatment at a primary care clinic increased the likelihood of T&CM use<sup>[18]</sup>.

It is important for physicians to enquire whether their patients are using any T&CM, especially when they discover unexpectedly poor diabetic control or adverse events. In view of the trust the public has in health care professionals, clinicians should remain neutral about T&CM use and search for the published medical literature to evaluate the rationale and applicability of T&CM interventions for specific patients' complaints. For T&CM modalities that are unsafe or ineffective, dissuading patients is the most reasonable approach. Patients administering herbal remedies or nutritional supplements concurrently with antidiabetic medications require regular primary care follow-up in order to ascertain potential drug interactions attributable to T&CM use. Health care providers should emphasize the cost of T&CM therapy to patients, particularly when the efficacy is questionable. Physicians may prescribe vitamins or a diet and recommend exercise for general well-being and specific diagnoses. It is not uncommon that simple home remedies to address minor complaints, for instance, tea for cough and chicken soup for upper respiratory flu are favored by some patients, but it is reasonable to avoid potentially expensive or unnecessary T&CM practices<sup>[19]</sup>. Before starting any T&CM, patients should always discuss with their doctor about the possible harmful effects and whether the T&CM interacts with other medications or with any diseases that the patients have. In particular, if patients are older adults and have impaired renal or hepatic functions, elimination of biologically-based T&CM from the body would be reduced, thereby resulting in a higher risk of toxicity. As for acupuncture and related T&CM techniques, currently available evidence has been scarce and varying with

respect to their efficacy and safety in patients with type 2 diabetes<sup>[20]</sup>. Patients should also be informed about the importance of checking whether their T&CM practitioners are appropriately qualified and registered under the government regulatory council to ensure the quality and safety of the complementary practices sought by them<sup>[21]</sup>.

## 5. Conclusions

This study demonstrated a high prevalence of T&CM use among a multi-ethnic patient population with type 2 diabetes. The clinical and sociodemographic characteristics associated with increased T&CM use comprised age, employment status, oral antidiabetic monotherapy, family history of diabetes, and presence of comorbid chronic condition. Most patients utilized T&CM to complement conventional medical care because they believed it would help control blood glucose levels. The extensive use of T&CM, which was reported by 61.8% of patients, might pose pervasive threats to health. The findings would help pharmacists and clinicians to target interventions to reduce the risk of adverse events associated with the concomitant use of T&CM in diabetes. Future observational studies will be needed to evaluate the potential interactions, adverse effects, and clinical outcomes in diabetic patients using T&CM remedies alongside conventional medical treatments.

**Author Contributions:** Yieng Yii Wong, Azizul Hakim bin Sulaiman, and Anis Aaida binti Mat Jaya researched literature and conceived the study. They were also involved in developing the research proposal and the proforma questionnaire to be used for data collection. Yieng Yii Wong, Azizul Hakim bin Sulaiman, Anis Aaida binti Mat Jaya, Pei Zan Wan, Anchaya A/P Eh Wan, Nurieshah Hanim binti Mohd Anuar, and Rajkumar A/L Selvaraju recruited all the patients, collected all the data, and performed data interpretation, analysis, statistical methods, and computation of the results in this study. Yieng Yii Wong wrote the first draft of the manuscript. Kok Pim Kua sought ethics approval, supervised the overall conduct of the study, analyzed and interpreted the results, and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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