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Antidiabetic activity evaluation of polyherbal formulation in type 2 diabetes mellitus patients

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ABSTRACT

Objective: The main aim of this research was to evaluate the effect of mixed herbs on blood HbA1c, and the liver function tests in type 2 diabetes mellitus (T2DM) patients.
Methods: This was a quasi-experimental design where no comparison was made with either placebo or control. We examined the effect of herbs namely, coriander leaves (*Coriandrum sativum*), bunching onion (*Allium fistulosum*), curry leaves (Murraya koenigii), and holy basil leave (*Ocimum tenuiflorum*) among T2DM patients. Fresh herbs were cleaned, freeze-dried, ground, mixed (25 % of each), encapsulated and fed at 4 g/day to T2DM patients for 90 days. Blood samples were collected on days 0, 31, 61, 91 and 121. The effect was assessed on the levels of HbA1c, creatinine, blood urea and liver enzymes i.e., alanine transaminase (ALT) or serum glutamic-pyruvic transaminase (SGPT), aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), among the patients. The data were statistically analysed, and the means were regarded as significant at 95 % CI. interval.
Results: Blood HbA1c concentration was highest on Days 0 and 31 and significantly ($p < 0.001$ and $p < 0.01$) reduced on Days 61, 91 and 121. The creatinine and urea concentrations were found to increase but not considerable with larger variation among the subjects. The ALT and AST concentrations were found higher ($p < 0.001$) on Day 60 but started to decline afterwards. The ALP levels were higher on the Days 0 and 31 but started declining from Day 61 onwards.
Conclusion: The consumption of mixed herbs was found to be associated with an improvement of HbA1c level among T2DM patients without having any clinically significant change in blood urea, creatinine, and liver enzymes.

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1. Introduction

The glycated haemoglobin (HbA1c) status of an individual reflects the blood glucose metabolism and can be reflective of the glucose status of a diabetic patient. Therefore, HbA1c is considered as a biomarker with high reliability in diagnosis and prognosis of diabetes even as a single test. However, in some reviews, it has been cautioned that proper application and interpretation of the HbA1c test is important for mastering accurate assessment (Sherwani et al., 2016; Sandler and McDonnell, 2016). Although HbA1c has been known since 1955, HbA1c levels association was not known in diabetes until 1968 (Little and Rohlfi, 2013). The biochemical assessment is due to the monosaccharides like glucose and fructose (Sh. Abdullah et al., 2022). These have strong correlation with type 2 diabetes mellitus (T2DM) and have been used in the screening of prediabetes (Sumner et al., 2016). In general, when assessing T2DM the rule of thumb is persistently elevated blood glucose at multiple occasions which shows the incidence of DM (American Diabetes Association. Diabetes Care 2004).

It is a well-known fact that T2DM patients suffer from higher blood glucose concentration with a greater possibility of abnormal metabolism of carbohydrate, fat, and protein than healthy individuals. Therefore, urea and creatinine are considered useful and simple biomarkers as for predicting or assessing renal function in diabetic patients (Bamanikar et al., 2016). The T2DM may happen without showing any symptoms in many individuals before it is diagnosed or established. Currently, there is no effective screening option available for the early prediction of diabetes (Abid et al., 2016). This may lead to a delay in the establishment of the disease. However, fasting blood glucose (FBG) $\geq$ 126 mg/dL is an easy option although it must be evaluated with multiple tests including repeated FBG on different occasions to confirm T2DM along with HbA1c (Screening for Diabetes, 2002). The T2DM patients remain asymptomatic in most cases for ten years (Harris et al., 1992). In general, the FBG and HbA1c are the common tests being used in the standard clinical practice as reported by the American Diabetic Association (American Diabetes Association 2018) and these were used in the current study as well.

The ALT (alanine transaminase), AST (aspartate aminotransferase) and ALP (alkaline phosphatase) are the enzyme tests that are routinely performed in the assessment of diseases and when any intervention to be made in the patients with diabetes, hyperlipidaemia, etc. These enzymes increase with certain drug use and in disease conditions, so they are used as biomarkers. These enzymes are released in the liver in response to the damage caused by the disease(s) or intervention (Zentella and Muñoz, 2016). The ALP enzyme is measured to assess the bile system of the patient's liver. Having abnormal results on any of these liver tests typically requires a follow-up to determine the cause of the abnormalities. Even mildly elevated results can be associated with liver disease. The clinical significance of ALT and AST is due to their involvement in aminotransferases reaction. In general, they are the markers of liver diseases or damages, however, AST is lesser than ALT (Kunutsor et al., 2013). In muscles, skeletal disorders and embolism, ALT levels are higher than AST, which primarily relates to ALT's half-life. The higher circulating concentration of ALT is associated with mortalities (Ruhl and Everhart, 2009). The ALP enzyme has been reported as the only biochemical substitute marker of cholangitis which is an important indication for the damage of the bile ducts. This, however, is still questionable and open for investigation (Sun et al., 2019). In the present study, we relied on a single measurement of HbA1c to evaluate the blood glucose status of the T2DM patients.

Several indigenous or folk medicines as herbal remedies derived from traditional medicinal plants have been well documented and described in ancient traditional literature for the treatment of various types of chronic ailments like diabetes, asthma, hypertension among others (Shen et al., 2019). Herbal remedies are generally considered safe and do not have much deleterious effects in comparison to synthetic drugs (Mia et al., 2022; Khan et al., 2023). Hence, studying the therapeutic efficacy of herbal remedies has become important regarding providing humans with safer alternatives to synthetically prepared medicines. More recently, there is a vast progression in the field of herbal medicines in their herbal mixture forms to discover safe and affordable therapeutic agents to cure different diseases efficiently. These multiple plant-based herbal remedies are receiving higher recognition both in developing and developed countries owing to their natural origin and less side effects. The main obstacle in blending plants-based remedies in mainstream medicine practices (i.e., allopathic medicine, conventional medicine, Western medicine etc.) is lack of genuine scientific and clinical data proving their efficacy and safety. Hence, there is a need for conducting clinical research in multiple plant based herbal remedies to confirm their safety and efficacy to treat several diseases. Moreover, it is also important to confirm the active principles of these herbal remedies responsible for synergistic and toxicological effects if any (Amin et al., 2015; Sarian et al., 2017; Ahmed et al., 2018; Palla et al., 2021).

Coriander leaves (*Coriandrum sativum* L.), bunching onion (*Allium fistulosum* L.), curry leaves (*Murraya koenigii* (L.) Sprengel), and holy basil leaves (*Ocimum tenuiflorum* L.) (see Figs. 1–4) are well-known herbs available throughout Malaysia including neighbouring countries and they are commonly used for the treatment of various diseases including diabetes mellitus (Kajal and Singh, 2019; Airaodion et al., 2020; Husna et al., 2018; Antora and Salleh, 2017; Ahmed et al., 2018; Hasan et al., 2023). The antidiabetic activity of the individual plant parts is well proven (Sarian et al., 2017; Mia et al., 2022) but the synergistic or combined effects of multiple plant based herbal therapy are still unclear and uncertain. Hence, this research study was designed due to the concept of polyherbal way of traditional practices that have been exclusively highlighted in *Sharangdhar Samhita*, an Ayurvedic literature dating back to 1300 CE. Polyherbal formulations have been reported to improve the medicinal action and decrease the concentrations of single herbs, thus lowering harmful events (Palla et al., 2021). Therefore, the aim of the present study was to formulate a polyherbal formulation comprising *C. sativum*, *A. fistulosum*, *M. koenigii*, *O. tenuiflorum* and evaluate its antidiabetic potential in diabetic patients to discover a new combination of daily used herbs as herbal remedies to manage type 2 diabetes mellitus more effectively.

2. Material and methods

2.1. Location of the study

This study was carried out at the Medical Outpatient Department (M−OPD), Hospital Tengku Ampuan Afzan (HTAA), Kuantan, Malaysia

Fig. 1. *Coriandrum sativum* L.

Fig. 2. *Allium fistulosum* L.

Fig. 3. *Murraya koenigii* L.

in collaboration with the Department of Nutrition Sciences, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia (IIUM), Kuantan, Malaysia.

2.2. Subjects: Population and interventions

In the present study, ten T2DM patients were recruited and enrolled from the M−OPD, HTAA. They were subjected to 4 g/d of encapsulated mixed herbs i.e., coriander, bunching onion, curry leaves and holy basil and underwent blood HbA1c and liver function tests.

2.3. Inclusion and exclusion criteria

Adult male and female patients having confirmed T2DM were included in the study. Whereas the patients who had type 1 diabetes mellitus, allergy, or intolerance to herbs, were consuming other herbal supplements, were pregnant with/without gestational diabetes mellitus (GDM) and/or were having any other disease, were excluded from the study.

Fig. 4. *Ocimum tenuiflorum* L.

2.4. Ethical clearance

This study protocol was approved by the Kulliyyah Postgraduate and Research Committee (KPGRC) and subsequently by the IIUM Research Ethics Committee (IREC) and Clinical Research Committee (CRC) and was registered in the National Medical Research Registry (NMRR) Research ID: 17783.

2.5. Consent of the patients

Informed consent was obtained from all patients on the day of briefing/recruitment of the patients for the study. The purpose of the study was explained, and they were included in the study only with their willingness and approval.

2.6. Processing of the herbs

The fresh (recently harvested) herbs were purchased from the local market Kuantan, Pahang, Malaysia and thoroughly cleaned, weighed, freeze-dried, and weighed again. All herbs (Figs. 1–4) were identified by one of the the botanists from IIUM. The equivalency of dry-to-wet weight was determined from the fresh freeze-dried difference. The freeze-dried herbs were ground with a coffee mill and appropriate amounts were encapsulated in the capsule to be offered to the patients (Ahmed et al., 2017).

2.7. Feeding protocol

The consumption of the capsules was spread over the day and the numbers of capsules to be consumed per day were tailored to 4 g of wet herbs (6 capsules in a day containing 25 % of each herb in a mixture). The total duration of the trial was 90 days and a follow up period 30 days. The feeding dose of 4 g was based on our previous observations of herbs fed to T2DM patients which seems to be well tolerated among the subjects.

2.8. Measurements and data collection

All the patients were requested to provide the blood samples on Days 0 and 31, 61, 91 and 121 for the analysis of various parameters, to assess any possible changes induced by the consumption of mixed spices and herbs.

2.9. Blood sample analysis

The blood samples collected were immediately processed and examined at the Biochemistry Laboratory of HTAA, for HbA1c, creatinine, urea, ALT or SGPT, AST or SGOT, and ALP concentrations using clinical analyser with appropriate kits accordingly.

2.10. Statistics

The collected data were statistically analysed using SPSS statistical software (version 27.0) One-way analysis of variance (ANOVA) was used. The data was expressed as mean ± SD and the difference in the means was ascertained at 95 % confidence interval ($P < 0.05$).

3. Results and discussion

In the present study, the respondents remained well and there were no fluctuations in the blood electrolyte's concentration. The uric acid concentration was higher but remained in the normal ranges during the entire clinical trial as shown in Table 1.

The study results for the other parameters namely HbA1c, ALT, AST, ALP, creatinine, and blood urea for the patients are shown in Figs. 5A, 5B & 5C and 6A, 6B & 6C. It was found out that the blood HbA1c levels were reduced until Day 121. The levels were found to be the highest on Days 0 and 31 but significantly ($p < 0.001$ & $p < 0.01$) reduced on Days 61, 91 and 121 (Fig. 5A). This decline of HbA1c is of clinical significance in the management of patients with T2DM and needs further investigation.

It was noticed that there was a significant ($p < 0.001$) increase in ALT and AST levels on Day 61, but these levels started to decline afterwards (Figs. 5B & 5C). This decline is also an indication of a positive effect on liver function which needs further experimentation on the herbs under investigation. However, it was discovered that this change was not clinically significant in terms of herbal intervention since it was already on decline after two months of herbal mixture consumption. Similarly, the ALP concentration was not found to be affected and started to be declining from Day 61 onwards (Fig. 6A).

Moreover, the level of creatinine was found to be the highest on Day 61, followed by Day 91 and Day 121 (Fig. 6B). There were fluctuations in the creatinine in the study period among the patients. However, these concentrations in the blood remained in the normal ranges on the days of assessment. Among the patients, blood urea concentration was also not significantly affected (Fig. 6C) with the consumption of the mixed herbs under investigation in the study duration period.

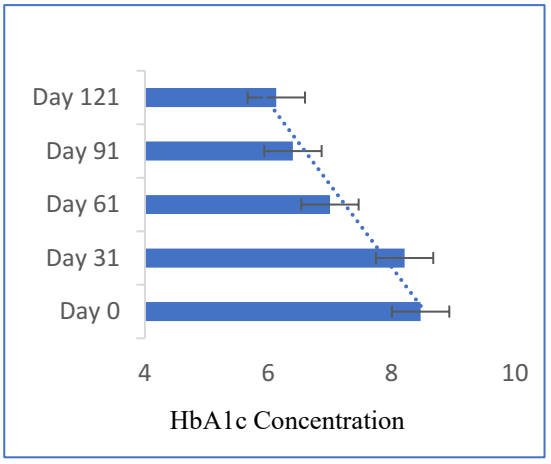
Synergistic therapeutic actions of mixed herbs are probably through underlying mechanisms such as regulation of same or different targets in various pathways hence in combination augment efficacy, regulation of enzymes and transporters to enhance oral drug bioavailability, neutralize deleterious effects and overcome drug resistance mechanisms. Synergism is observed when multiple phytoconstituents are present in single or in combination of herbs, which are potential therapeutic options for various disease targets particularly diabetes mellitus. This forms the basis of mixed herbs therapies and is considered rational and more efficacious in multi-targeted diseases (Amin et al., 2015).

The observed effects of these mixed herbs (coriander leaves, bunching onion, curry leaves and holy basil leaves) are of greater clinical significance in T2DM patients. It appears that the consumption of these herbs at the dosage of 4 g/d is the most suitable dose for a longer period i.e., three months or beyond. It also brings effective control of blood glucose in the T2DM patients as evident from blood HbA1c concentration (Fig. 5A). We also observed that these herbs in its original form did not affect the liver and kidney functions and were also not associated with any adverse effect (Figs. 5B & 5C and Figs. 6A, B & C). Now the question is why the herbs under investigation were effective in maintaining blood HbA1c at the lowest level on the Day 91 and beyond? There are various suppositions/inferences made by researchers while investigating the effect of herbs in T2DM patients.

Table 1
The effect of herbs on the body weight, electrolytes, and uric acid concentrations among the subjects.

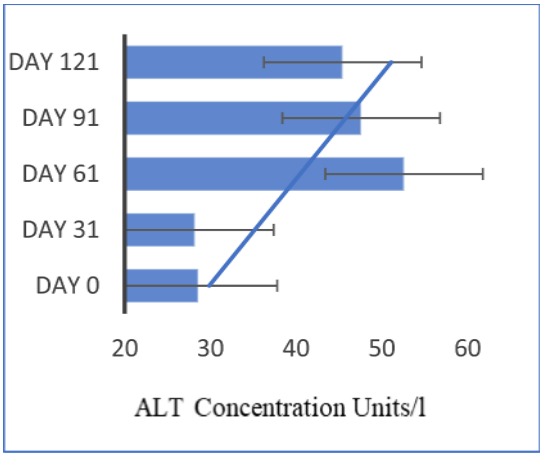
Duration					
Variables	Day 0 Mean ± Std (n = 10)	Day 31 Mean ± Std (n = 10)	Day 61 Mean ± Std (n = 10)	Day 91 Mean ± Std (n = 10)	Day 121 Mean ± Std (n = 9)
Body Weight (kgs)	75 ± 9.6	74 ± 10.6	73 ± 12.4	79 ± 0	73 ± 11.0
Sodium (mmol/l)	140 ± 2.68	140 ± 2.54	139 ± 2.63	138 ± 2.53	138 ± 3.00
Chloride (mmol/l)	101 ± 6.90	100 ± 6.20	100 ± 6.23	101 ± 3.97	100 ± 3.96
Potassium (mmol/l)	4.11 ± 0.45	4.15 ± 0.37	4.07 ± 0.45	3.89 ± 0.60	3.93 ± 0.49
Uric Acid (umol/l)	409 ± 99	399 ± 94	431 ± 75	428 ± 64	419 ± 60

Note: Statistically, none of the values are different in the clinical trial at 95% CI.



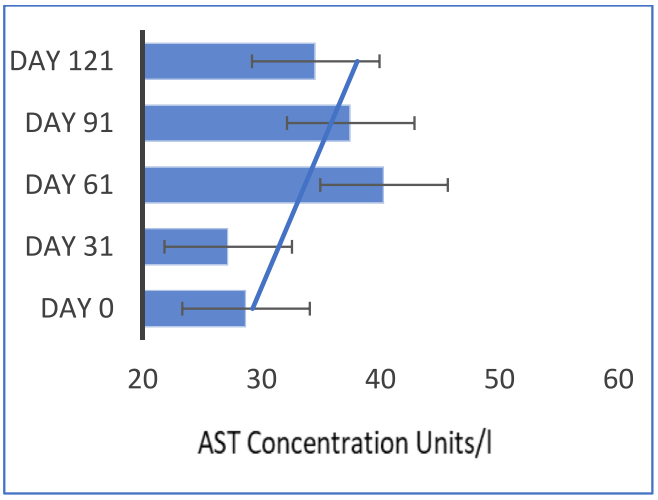
A

Fig. 5A. HbA1c concentration among T2DM patients from Day 0——121 after the consumption of mixed herb formulation.



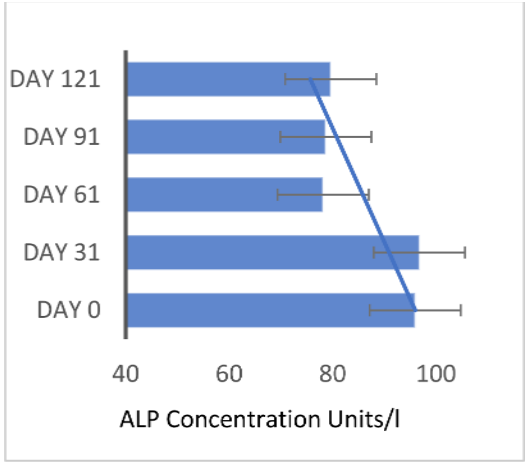
B

Fig. 5B. Alanine Transaminase (ALT) or serum glutamic-pyruvic transaminase (SGPT) concentration among T2DM patients from Day 0——121 after the consumption of mixed herb formulation.



C

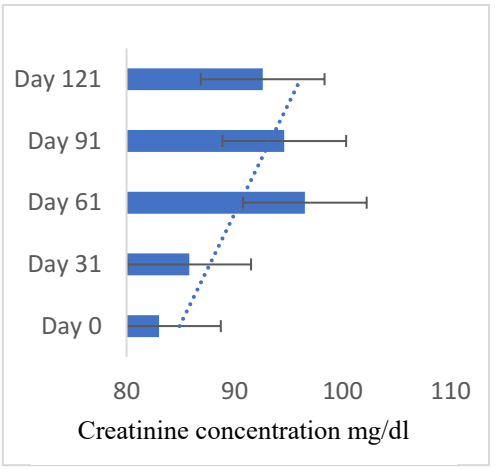
Fig. 5C. Aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGOT) concentration among T2DM patients from Day 0——121 after the consumption of mixed herb formulation.



A

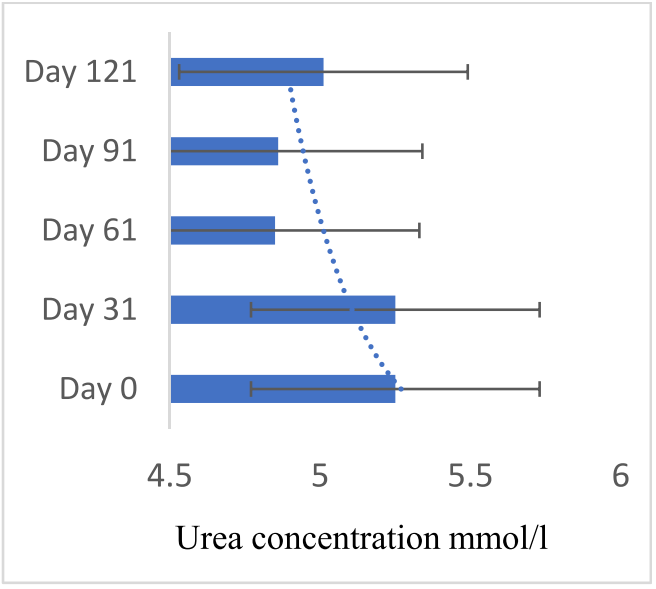
Fig. 6A. Alkaline phosphatase (ALP) concentration among T2DM patients from Day 0——121 after the consumption of mixed herb formulation.

The observed effect in these patients might be due to the possibility of the antioxidants (preserved with the freeze-drying procedure) in the herbs under investigation. As it is well known that in T2DM patients, oxidative stress (OS) is the major aetiology of diabetes besides lower secretion of insulin or insulin insensitivity (Montonen et al., 2004). Some dietary antioxidants improve free radical-scavenging activity (Nimse and Pal, 2015), enhance glucose transport by stimulating the translocation of GLUT4 from internal pools to the plasma membrane (Hajiaghaalipour et al., 2015), protect insulin receptors from oxidative deterioration and maintaining its functional integrity (Ruhe and McDonald, 2001). And possibly the same thing happened with the consumption of these mixed herbs in the T2DM patients. All four herbs have been reported to possess different types of antioxidants in the form of several polyphenolic compounds namely pinocembrin, apigenin, luteolin, kaempferol, quercetin, baicalein (5,6,7-trihydroxyflavone), isorhamnetin, rutin (quercetin-3-O-rutinoside), daidzein, genistein, pseudobaptigenin, pectolinarigenin, diosmetin, rosmarinic acid, caffeic acid (hydroxycinnamic acid), ferulic acid (derivative of hydroxycinnamic acid), 3,4-dimethoxycinnamic acid, eugenol, chlorogenic acid



B

Fig. 6B. Creatinine concentration among T2DM patients from Day 0——121 after the consumption of mixed herb formulation.



C

Fig. 6C. Urea concentration among T2DM patients from Day 0——121 after the consumption of mixed herb formulation.

(ester of (–)-quinic acid and caffeic acid), gallic acid (3,4,5-trihydroxybenzoic acid), koenine, koenigine, mukoeic acid and isomahanine (Mahleyuddin et al., 2022; Choi et al., 2017; Rengasamy et al., 2020; Mousavi et al., 2018). Among the isolated compounds, majority of the phenolic compounds reported are flavonoids (Fig. 7) that have been experimentally proven to exert their antioxidant effects through different mechanisms of actions which mainly include their capability to decrease free radical generation and to scavenge free radicals. Several *in vitro* and structure – activity relationships studies have clearly proven the phenolic compounds particularly flavonoids to act as antioxidants. Moreover, the antioxidant effects of the flavonoids *in vivo* have also been confirmed experimentally by the increase of the plasma antioxidant status. Furthermore, research studies have demonstrated that flavonoids have the ability to prevent DM by improving the pathogenesis of DM through the regulation of hepatic enzymes activities, lipid profile and a glucose metabolism (Hasan et al., 2017; AL-Ishaq et al., 2019; Alhassan

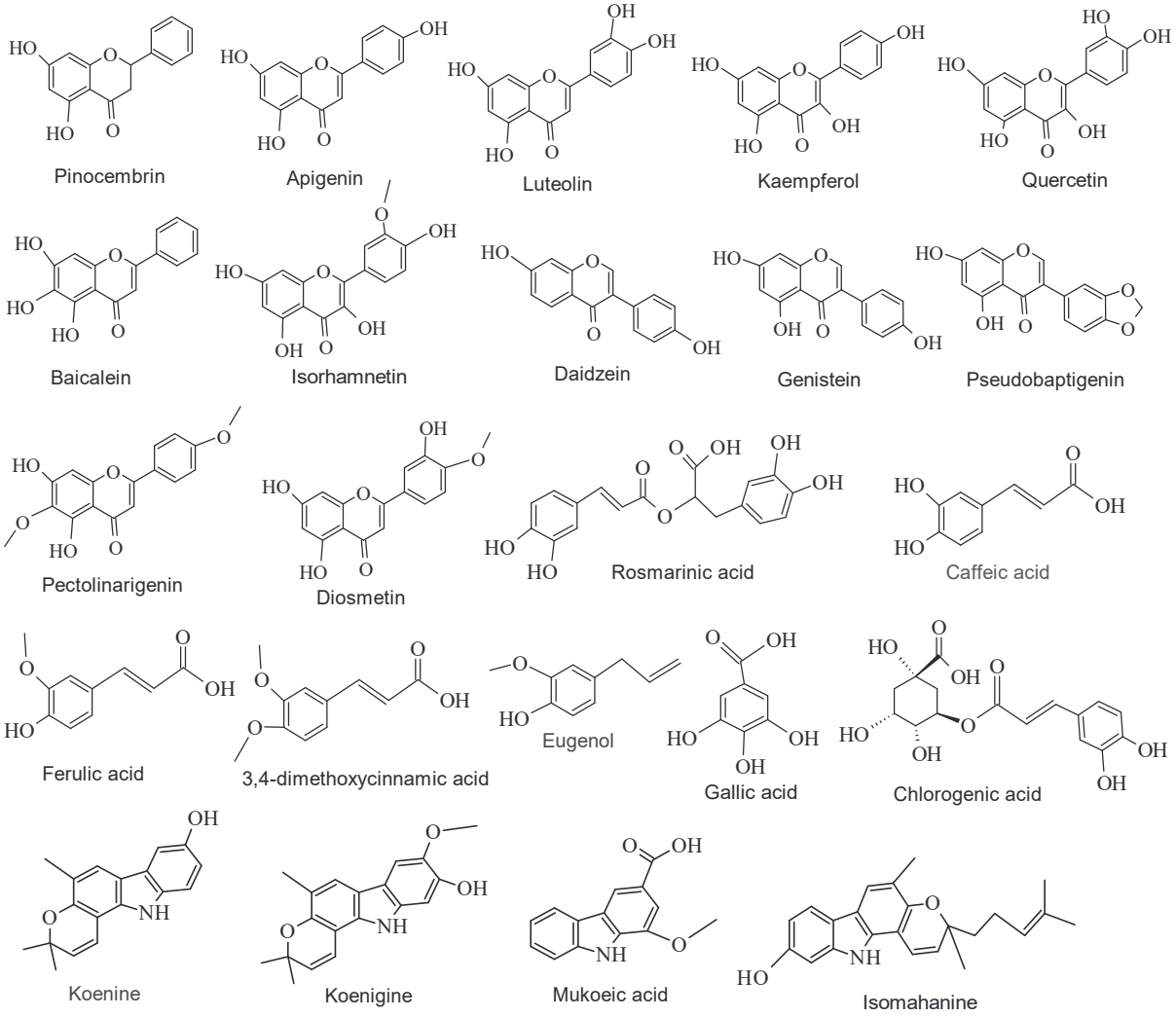


Fig. 7. Structures of some important antioxidants reported in coriander leaves, bunching onion, curry leaves and holy basil leaves (Mahleyuddin et al., 2022; Choi et al., 2017; Rengasamy et al., 2020; Mousavi et al., 2018).

et al., 2019; Ullah et al., 2020). Therefore, it can be inferred that these mixed herbs are involved in the protection of cellular activity or a combination of the events that in turn improve the hyperglycaemic status of the patients under investigation. Alternatively, these herbs are rich sources of minerals namely K, Ca, Mg, Cr, Mn, Zn, Cu, and Fe, which are considered vital for good health. These were previously studied in the mixed herbs formulations from the same sources for T2DM management (Shirazi et al, 2016). Among these, Cr and Zn were reportedly involved in the sensitivity of insulin. Moreover, Cr is considered an important insulin-potentiating factor. The mineral Cr is part of the insulin molecule structure which is crucial for glucose sensitivity to be utilized for energy purposes in the cell (Marreiro et al., 2017).

In this study, we did not ask the patients to stop their routine diabetes medicine consumption during the entire duration of the clinical trial. The hypoglycaemic agent/drug used according to the condition prescribed by the concerned doctor included Metformin, Perindopril, Pravachol, Cardipirin with herbs, Metformin, Gliclazide, Rosiglitazone, Felodipine, Perindopril, Ticlopidine, Simvastatin, Methylcobal, Gemfibrazil used with herbs and Metformin, Gliclazide, Neurobion, Cardipirin, Carvedilol used with herbs. Therefore, there might be some synergistic effect between the medicines and the herbs. In the present study, the patients felt energetic, and no hypoglycaemic episodes were observed in combination with hypoglycaemic drugs like Metformin and the consumption of herbs (Carella et al., 2017). Therefore, it is important to note that the combination of these mixed herbs and hypoglycaemic drug consumption is safe in the management of T2DM. However, it is advised that these combinations must be taken only under the observation of diabetologists with regular monitoring.

As mentioned before, the consumption of these herbs improved the general well-being of the patients. In certain cases, it was associated with improved sexual drive (present study) as normally male T2DM patients suffer from penile erectile dysfunction and low libido (Bal et al., 2015). Among the patients in the present study, it has been indicated that their liver and renal functions remained unaffected. However, some of the enzymes that are involved in the drugs and herbs transport which might have provided further understanding of the effect (Kumolosasi et al., 2022) were not studied.

4. Conclusions

The present study reveals that the consumption of encapsulated mixed herbs i.e., coriander, bunching onion, curry leaves, and holy basil were associated with an improvement in blood HbA1c without having any clinically significant effect on the electrolytes, uric acid, renal, and liver functions among the T2DM patients.

5. Limitations of the study

Execution of research trials among human and T2DM patients is always challenging, and our experimental trial was not an exception. There were a few difficulties with regards to the consents of the participants in the study. These included willingness of the patients, accessibility, and observance to the specified/recommended doses of the capsules. For a successful clinical trial, it is of primary importance to overcome these constraints. We are not confident enough to claim that the compliance was 100 % among the patients.

6. Institutional review board statement

Prior to commencing the research work, the study protocol was initially approved by the Kulliyyah Postgraduate and Research Committee and subsequently by the IIUM Research Ethics Committee and Clinical Research Committee and was finally registered in the National Medical Research Registry Research ID: 17783.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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