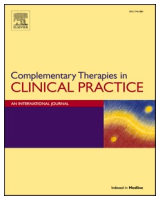
Complementary Therapies in Clinical Practice 59 (2025) 101949

Contents lists available at ScienceDirect

Complementary Therapies in Clinical Practice

journal homepage: www.elsevier.com/locate/ctcp



# Efficacy and safety of olive leaf extract (*Olea europaea* L.) for glycaemic control in adults with type 2 diabetes mellitus (ESOLED): A pilot randomised controlled trial

Matthew J. Leach [a,b,*], Ian Breakspear [c]

[a] JBI, University of Adelaide, King William Road, North Adelaide, SA, 5005, Australia
[b] Faculty of Health, Southern Cross University, Military Road, Lismore, NSW, 2480, Australia
[c] Faculty of Health & Education, Torrens University Australia, Bowen Terrace, Fortitude Valley, QLD, 4006, Australia

ARTICLE INFO

*Keywords:*
Clinical trial
Glycaemic control
Olive leaf
Plant extract
Type 2 diabetes

ABSTRACT

*Background:* Maintaining optimum glycaemic control is essential to reducing comorbidity and mortality in diabetes. However, research indicates that <50 % of patients achieve their target HbA1c ranges. Laboratory studies suggest that olive leaf extract (OLE) may improve glycaemic control, however clinical studies in persons with diabetes are lacking.

*Methods:* ESOLED is a pilot, randomised, placebo-controlled trial. Adults with a diagnosis of type 2 diabetes of ≥12 months duration, and not receiving insulin therapy, were eligible to participate. Participants were randomised to receive OLE or placebo capsules for 24 weeks. The primary outcome was change in HbA1c. Secondary outcomes included changes in the homeostasis model assessment of insulin resistance, diabetes-related stress, health-related quality of life, and safety.

*Results:* Thirty-one participants were randomly assigned to the OLE (n = 16) and placebo (n = 15) groups. Analyses found no statistically significant time-group interactions for HbA1c, diabetes-related distress or health-related quality of life. Although participants receiving OLE demonstrated greater improvements in insulin sensitivity than those on placebo, there was no significant difference between groups over time. OLE and placebo were found to be well-tolerated, with no severe or serious adverse events reported in either group.

*Conclusion:* The ESOLED trial has provided preliminary evidence on the tolerability of OLE in adults with type 2 diabetes, but was inconclusive in determining whether OLE is effective at improving glycaemic control, insulin sensitivity, diabetes-related distress and quality of life. Larger trials and further exploration of the bioavailability of OLE are needed to fully assess the therapeutic potential of OLE in diabetes.

*Trial registration:* Australian New Zealand Clinical Trials Registry (ACTRN12622000616774).

## 1. Introduction

Diabetes mellitus is a chronic metabolic disorder affecting an estimated 529 million adults worldwide. The global cost of managing diabetes was US$966 billion in 2021, with costs expected to climb to US $1054 billion by 2045 [1]. A cornerstone of effective diabetes management is maintaining optimum glycaemic control. Findings from large epidemiological studies demonstrate a close association between tight glycaemic control and decreased risk of comorbidity and mortality in people with diabetes [2–4]. Despite this evidence, the direction provided by clinical guidelines, and advances in the treatment of diabetes, between 45 % and 93 % of individuals with type 2 diabetes mellitus (T2DM) across the globe fail to achieve recommended target ranges for glycosylated haemoglobin (HbA1c) [5], with no indication that rates are improving [6].

Many first-line pharmacological agents have been shown to be effective in improving glycaemic control in type 2 diabetes [7], although the magnitude and duration of effect, and the quality of the evidence does vary [8,9]. These oral hypoglycaemic agents are also associated with frequent adverse effects, poor medication adherence [10,11], and high economic burden (costing Australia AU$598 million in 2019, and the United States US$24.7 billion in 2022) [12,13]. The spiralling costs of diabetes management, together with scarcer resources, indicate the current approach to managing diabetes is unsustainable, and that safer,

* Corresponding author. JBI - University of Adelaide, King William Road North Adelaide, SA, 5005, Australia.
*E-mail address:* dr.matt.leach@gmail.com (M.J. Leach).

https://doi.org/10.1016/j.ctcp.2025.101949
Received 3 December 2024; Received in revised form 6 January 2025; Accepted 12 January 2025
Available online 13 January 2025

equally efficacious and cost-effective diabetes treatments are urgently needed.

A relatively safe and low-cost therapy that is emerging as a promising treatment for diabetes is Olive Leaf Extract (OLE). The leaves of the olive tree (*Olea europaea* L.) have a long history of use as an antidiabetic agent [14]. More recently, the antidiabetic effects of OLE have been supported by *in vitro*, in *vivo* and human studies. These studies indicate the extract acts on multiple metabolic pathways to improve glycaemic control [15], including increasing insulin sensitivity, pancreatic beta-cell activity, insulin-like growth factor binding protein-1 and glucagon-like peptide-1 concentration, and decreasing alpha glucosidase activity, intestinal glucose uptake, cortisol levels and psychological stress [15–17]. While the effects of OLE on HbA1c, blood lipids and fasting blood glucose levels have been supported in human studies [18–20], the evidence from these studies has been limited by high risk of bias, the use of non-standardised extracts, and short treatment periods.

OLE also has been shown in animal studies to reduce advanced glycation end-products, lipid peroxidation, serum cholesterol, serum triglycerides, serum LDL-cholesterol, plasma creatinine and neuropathic pain, and to increase renal excretion of sodium [16,17]. These effects suggest the actions of OLE may extend beyond improving glycaemic control, to aiding the primary and secondary prevention of diabetes-related complications.

Current evidence appears to support the biological plausibility of OLE as a treatment for dysglycaemia in diabetes. This is of critical importance as optimal glycaemic control is imperative to reducing diabetes burden and associated health system costs. Notwithstanding, robust contemporary research examining the long-term clinical safety and effectiveness of OLE for the complementary management of type 2 diabetes is currently lacking. The study described herein aimed to address this evidence gap.

## 2. Material & methods

### 2.1. Design

The Efficacy and Safety of Olive Leaf Extract for Diabetes (ESOLED) trial is a pilot, prospective, randomised placebo-controlled trial with two parallel arms. The trial was reported in accordance with the CONSORT 2010 statement: extension to randomised pilot and feasibility trials [21], CONSORT 2006 statement: extension to randomised controlled trials of herbal interventions [22], and was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622000616774).

### 2.2. Aim

To provide preliminary evidence of the effectiveness of Olive Leaf Extract in improving glycaemic control, insulin resistance, diabetes-related distress and health-related quality of life in adults with type 2 diabetes mellitus.

### 2.3. Hypotheses

#### 2.3.1. Primary hypothesis

1. OLE significantly improves HbA1c in adults with T2DM when compared to placebo.

#### 2.3.2. Secondary hypotheses

1. OLE significantly reduces insulin resistance in adults with T2DM relative to placebo.
2. OLE significantly improves diabetes-related distress in adults with T2DM when compared to placebo.
3. OLE significantly improves health-related quality of life in adults with T2DM when compared to placebo.
4. There is no statistically significant difference in the incidence and severity of adverse events between OLE and placebo in adults with T2DM.

### 2.4. Participants

*Inclusion criteria*: Individuals satisfying the following criteria were eligible to participate in the trial: (a) Diagnosis of type 2 diabetes mellitus (as diagnosed by a medical doctor or nurse); (b) Diabetes ≥12 months duration; (c) Not receiving insulin therapy; (d) Not received OLE within the previous 6 months; (e) Able to provide written consent; (f) Fluent in written and spoken English, (g) Aged ≥18 years, and (h) resided in Australia.

*Exclusion criteria*: Individuals were excluded from participating in the trial if they met any of the following criteria: (a) History of any condition causing moderate to severe cognitive impairment (e.g. dementia, acquired brain injury); (b) Known allergy to olives or olive leaf; (c) Needle phobia or strong aversion to providing a blood sample; (d) Known pregnancy and/or actively breastfeeding; or (e) Participated in a clinical trial within the past 30 days.

*Sample size*: Based on the flat rule-of-thumb for two-armed pilot trials (accounting for 90 % power, medium effect size [.5] and 15 % attrition), the trial required a sample size of 40 participants (20 per arm) [23].

### 2.5. Interventions

Participants were required to self-administer OLE or placebo, at a dose of 2 capsules once daily after breakfast, for 24 weeks. Participants were advised to continue with their usual diabetes care (including prescribed medications, diet, exercise, appointments) throughout the trial period. Details of each intervention are provided below.

- *Intervention*: Olive Leaf Extract capsules were manufactured by Wellgrove Health, Australia. Each capsule contained 733.34 mg of olive leaf extract (equivalent to 3.3g of fresh *Olea europaea* L. leaf, drug extract ratio of 4.5:1, with water as the extraction solvent, standardised to 55 mg oleuropein and 2.5 mg Hydroxytyrosol), together with standard excipients (i.e. colloidal anhydrous silica, hypromellose, magnesium stearate, purified water, silicon dioxide, and sorbitol), in a clear hard-shell capsule containing hypromellose and purified water. The product was included on the Australian Register of Therapeutic Goods (AUST L 327922). The dosage was chosen to achieve double the daily oleuropein dosage employed in a previous clinical trial that demonstrated improved insulin sensitivity in overweight middle-aged men [24].
- *Control*: Placebo capsules were manufactured by Biohealth Pharmaceuticals, Australia. Placebo capsules contained microcrystalline cellulose and colouring agents yellow iron oxide, red iron oxide, and black iron oxide (in order to replicate the appearance of the intervention), but contained no OLE, in a clear hard-shell capsule containing hypromellose and purified water. Further details of the placebo and intervention are provided in Supplementary File 1.

### 2.6. Outcomes

The outcomes of the trial were conceptualised and operationally defined as below.

#### 2.6.1. Primary outcome

1 Glycosylated Haemoglobin (HbA1c) is a long-term measure of an individuals' average glucose level, over approximately 90 days [25]. HbA1c was measured using High-Performance Liquid Chromatography from a venous blood sample collected at weeks 0 (baseline), 12 (mid-intervention) and 24 (post-intervention). Specimen collection

and pathology testing were undertaken by QML Pathology, Australia.

#### 2.6.2. Secondary outcomes

1 Insulin resistance is defined as the "inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population" [26]. This outcome was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), which generates an estimate of insulin sensitivity and β-cell function from fasting plasma insulin and glucose concentrations. Specimen collection and pathology testing were undertaken by QML Pathology, Australia. HOMA-IR was calculated at weeks 0, 12 and 24.
2 Safety referred to the monitoring and reporting of any potential adverse events associated with the trial intervention or placebo. Safety was assessed using an adverse event record (as completed by participants), and reported at weeks 0, 12 and 24.
3 Diabetes-related distress (DRD) is the negative emotional reaction attributed to living with the diagnosis, threat of complications, and self-management demands of diabetes [27]. Elevated DRD is associated with poorer glycaemic control, lower quality of life, and increased comorbidity [28]. DRD was measured using the 17-item Diabetes Distress Scale (DDS), and was self-administered by participants at weeks 0, 12 and 24.
4 Health-related quality of life (HRQOL) refers to an individuals' sense of wellbeing and an ability to enjoy normal life activities. Given that persons with diabetes demonstrate considerably poorer quality of life than persons without the condition [29,30], it is important to recognise the participants' perception of change in response to each treatment in order to capture any patient-centred benefits resulting from each intervention. HRQOL was measured using the Assessment of Quality of Life 8-dimension (AQoL-8D) instrument, which was self-administered by participants at weeks 0, 12 and 24.

### 2.7. Recruitment

Participant recruitment was undertaken between February 2023 and January 2024. Adults with T2DM were invited to participate in the study using diverse media. This included posting flyers across university campuses, public libraries, general practices, diabetes educator clinics, and community centres; regularly posting social media messages (via Facebook, Twitter and LinkedIn); and promoting the trial on local radio stations, television and newspapers. A 6-month targeted Facebook Ads campaign was also conducted. Individuals interested in participating in the study were advised to contact the researchers to ask questions, undergo telephone screening for eligibility, and to obtain a consent form.

### 2.8. Randomisation and allocation

Participants were randomly assigned to OLE or placebo at a ratio of 1:1. Block randomisation was used with computer-generated randomly permuted blocks of random sizes. Randomisation codes were held in sequentially-numbered opaque sealed envelopes, and each envelope selected in consecutive order at the time of participant enrolment. This process was undertaken by a third party not directly involved in the administration of the trial. Block sizes were not be disclosed to the third party to ensure allocation concealment.

### 2.9. Blinding

Participants and researchers were blinded to group assignment. Further, the OLE and placebo products were packaged in identical containers, with similar labels. The OLE and placebo capsules also matched in size, shape, consistency and colour, and were similar in taste and odour.

### 2.10. Procedures

Participants were required to attend the Southern Cross University Clinical Trial Unit at three timepoints during the trial: week 0, week 12 and week 24. Three days prior to each appointment, participants attended a pathology laboratory collection centre to provide a 10 ml venous blood specimen. During each appointment, participants completed the DDS and AQoL-8D. Following this, the researcher measured the participant's weight, height and blood pressure, discussed the pathology test results, assessed the participant's compliance and tolerance with the intervention, and answered any participant questions. At the week 0 and week 24 appointment, participants also completed a trial enrolment form and trial exit form, respectively. Between trial appointments, participants were required to record the administration of the intervention on a daily administration record, and to report any adverse effects/events on an adverse event record. These records were reviewed and discussed at each appointment.

### 2.11. Statistical analysis

Data were entered into SPSS (v.26) and analysed by intention-to-treat. Missing data were handled using the multiple imputation method. Baseline differences between groups were examined using the *t*-test for independent samples, median test for independent samples, or Fisher's Exact tests. Differences in trial outcomes between groups, across all timepoints, were examined using linear mixed-effects models. The model used restricted maximum likelihood estimation, with group, time and time-group interaction used as fixed effects, and participant ID as the random effect. The level of statistical significance was set at $p < .05$.

### 2.12. Ethics

The trial was reviewed and approved by the Southern Cross University Human Research Ethics Committee (Approval No. 2022/034).

## 3. Results

Fifty-three individuals were screened for eligibility (Fig. 1). Of these, 22 were excluded as they were unable to commit to the study schedule (n = 16), were advised against taking OLE by a medical specialist (n = 2), had a needle phobia (n = 1), had diabetes for less than 12 months duration (n = 1), had used OLE within the past 6 months (n = 1), or had type 1 diabetes (n = 1). The remaining 31 participants were randomly assigned to the intervention (n = 16) and control (n = 15) groups. Data from all randomised participants were analysed.

### 3.1. Characteristics of participants

Participants were aged 63.3 ± 8.7 years (mean ± SD), and 71.0 % were male (Table 1). Most participants were non-smokers (96.8 %) and non-drinkers (51.6 %). Across both groups, mean HbA1c (%) at baseline was 7.1 ± 1.6, BMI was 27.4 ± 5.7, and HOMA-IR was 5.1 ± 3.5. Median DDS total score at baseline was 1.5 (IQR 1.2,2.7), and AQoL-8D utility score was .8 (IQR .5,.9). There were no statistically significant differences between groups in demographic variables or trial outcomes at baseline.

### 3.2. Glycosylated haemoglobin

Changes in HbA1C levels were relatively larger in the control group than the intervention group over the 24 weeks. However, the linear mixed model found no significant difference in HbA1c levels over time, by group assignment, or by time-group interaction (Table 2). Time-group interactions for HbA1c levels also failed to reach statistical significance after accounting for random effects.

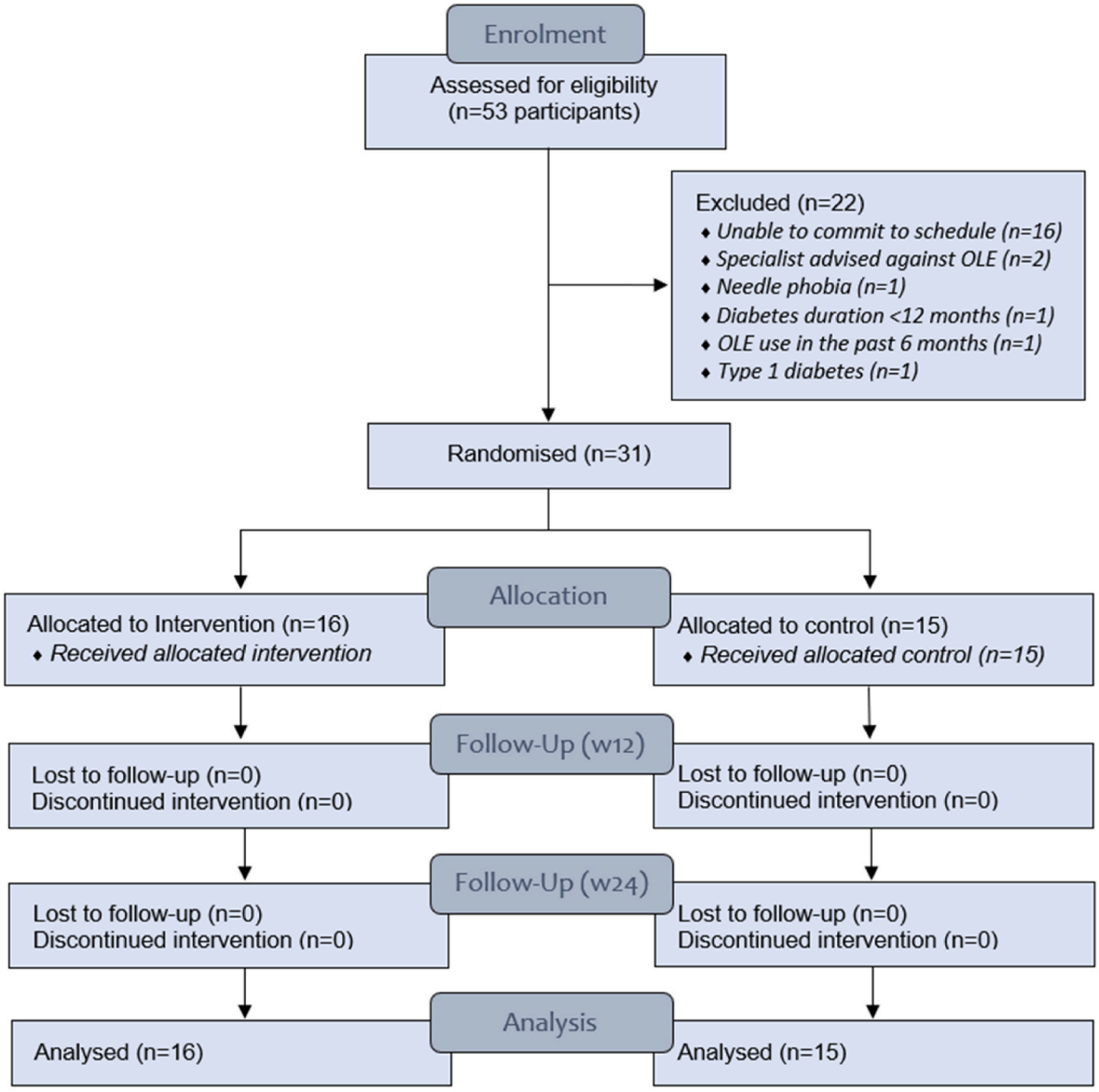



**Fig. 1.** Participant flow chart.

### 3.3. Insulin resistance

While changes in HOMA-IR over the 24 weeks were considerably greater in the intervention group compared to the control group, there were no significant differences in HOMA-IR over time, by group assignment, or by time-group interaction, according to the linear mixed model (Table 2). Accounting for random effects, time-group interaction effects for HOMA-IR remained statistically non-significant.

### 3.4. Diabetes distress

Reductions in DDS total scores, and all four DDS subscores were observed in both groups over the 24 weeks. However, the linear mixed model found no statistically significant differences in DDS scores over time, by group assignment, or by time-group interaction (Table 3). Time-group interactions for DDS scores also did not reach statistical significance when accounting for random effects.

### 3.5. Quality of life

AQoL-8D utility scores over the 24 weeks improved slightly in the control group relative to the intervention group. Yet, there were no significant differences in AQoL-8D utility scores over time, by group assignment, or by time-group interaction, according to the linear mixed model (Table 3). Accounting for random effects, time-group interaction effects for AQoL-8D utility scores remained statistically non-significant.

### 3.6. Adverse events

Fourteen adverse events were reported by 3 participants in the intervention group. These events were of mild-moderate severity and transient in nature (i.e. loose bowel actions; nausea; abdominal discomfort; dark stools). Eight adverse events were reported by 3 participants in the control group. These events were transient and mild (i.e. loose bowel actions; nausea; abdominal bloating; urinary frequency; weight gain). No severe or serious adverse events were reported in either study group. The frequency of adverse events was not statistically significantly different between groups ($\chi^2 = 2.010$, $p = .570$).

**Table 1**
Characteristics of participants at baseline (n = 31).

| Characteristic | Intervention group (n = 16) | Control group (n = 15) | P value[a] |
|---|---|---|---|
| **Age**, *mean (SD)* | 63.4 (10.3) | 63.2 (7.0) | .940 |
| ***Sex***, *n (%)* | | | .616 |
| *Male* | 11 (68.8) | 11 (73.3) | |
| *Female* | 4 (25.0) | 4 (26.7) | |
| *Other* | 1 (6.3) | 0 (.0) | |
| **Non-smoker (tobacco)**, *n (%)* | 16 (100.0) | 14 (93.3) | .484 |
| **Non-drinker (alcohol)**, *n (%)* | 10 (62.5) | 6 (40.0) | .257 |
| **HbA1c (%)**, *mean (SD)* | 7.1 (1.8) | 7.0 (1.4) | .772 |
| **BMI**, *mean (SD)* | 27.2 (7.2) | 27.7 (3.8) | .839 |
| **HOMA-IR**, *mean (SD)* | 5.6 (4.6) | 4.6 (1.6) | .411 |
| **Baseline DDS Total score**, *median (IQR)* | 1.4 (1.2,2.7) | 1.7 (1.4,2.7) | .862 |
| **Baseline DDS Emotional burden subscore**, *median (IQR)* | 1.4 (1.2,2.7) | 1.6 (1.2,3.0) | .862 |
| **Baseline DDS Physician-related distress subscore**, *median (IQR)* | 1.3 (1.0,2.3) | 1.5 (1.0,2.8) | .372 |
| **Baseline DDS Regimen-related distress subscore**, *median (IQR)* | 1.7 (1.2,3.2) | 2.2 (1.4,3.4) | .378 |
| **Baseline DDS Interpersonal distress subscore**, *median (IQR)* | 1.7 (1.3,2.7) | 2.0 (1.3,2.3) | .862 |
| **Baseline AQoL-8D utility score**, *median (IQR)* | .8 (.5,.9) | .7 (.5,.9) | .862 |

AQoL-8D – Australian Quality of Life (8-dimension); BMI – Body Mass Index; DDS – Diabetes distress scale; HbA1c - Haemoglobin A1c; HOMA-IR - Homeostatic Model Assessment for Insulin Resistance.
[a] means compared using independent samples *t*-test; medians compared using independent samples median test with Yate's continuity correction; categorical data compared using Fisher's Exact test.

**Table 2**
HbA1c and HOMA-IR results over time, by group (n = 31).

| Measurement | Intervention group (n = 16) | Control group (n = 15) | P value[a] | Mixed model analysis with interactions | |
|---|---|---|---|---|---|
| | | | | Fixed effect | P value[b] |
| **HbA1c (%)**, *mean (SD)* | | | | | |
| Week 0 | 7.14 (1.83) | 6.97 (1.39) | .772 | Time | .196 |
| Week 12 | 7.03 (1.40) | 6.85 (1.37) | .722 | Group | .541 |
| Week 24 | 7.17 (1.40) | 6.61 (.95) | .207 | Time[a]Group | .196 |
| **HOMA-IR**, *mean (SD)* | | | | | |
| Week 0 | 5.64 (4.63) | 4.61 (1.61) | .411 | Time | .796 |
| Week 12 | 4.58 (2.55) | 4.47 (2.55) | .897 | Group | .702 |
| Week 24 | 4.45 (2.94) | 4.64 (2.58) | .851 | Time[b]Group | .620 |

HbA1c – Haemoglobin A1c; HOMA-IR - Homeostatic Model Assessment for Insulin Resistance; SD – Standard deviation.
[a] means compared using independent samples *t*-test.
[b] p values associated with type III tests of fixed effects.

### 3.7. Intervention adherence

The median rate of adherence to the trial intervention (i.e. number of capsules administered divided by number of capsules dispensed) was 99.7 % (IQR 98.2,100) in the intervention group, and 98.8 % (96.3,100) in the control group. The difference in intervention adherence rates between the two groups was not statistically significant (Yates $\chi^2 = .929$, p = .335).

### 3.8. Testing of blinding

Two-thirds (68.8 %) of participants in the intervention group, and less than half (40.0 %) of participants in the control group were uncertain of the intervention assigned to them during the trial. The participant's best guess of the intervention received (i.e. placebo vs OLE vs don't know) were not significantly different between groups ($\chi^2 = 2.608$, p = .456).

**Table 3**
AQoL-8D and DDS results over time, by group (n = 31).

| Measurement | Intervention group (n = 16) | Control group (n = 15) | P value[a] | Mixed model analysis with interactions | |
|---|---|---|---|---|---|
| | | | | Fixed effect | P value[b] |
| **AQoL-8D Utility Score**, *mean (SD)* | | | | | |
| Week 0 | 0.72 (0.24) | 0.72 (0.22) | .974 | Time | .321 |
| Week 12 | 0.73 (0.25) | 0.75 (0.20) | .786 | Group | .836 |
| Week 24 | 0.72 (0.25) | 0.75 (0.20) | .704 | Time[a]Group | .460 |
| **DDS – Total Score**, *mean (SD)* | | | | | |
| Week 0 | 1.89 (0.92) | 2.20 (1.11) | .412 | Time | .376 |
| Week 12 | 1.71 (0.73) | 1.95 (0.93) | .442 | Group | .467 |
| Week 24 | 1.68 (0.70) | 1.78 (0.92) | .729 | Time[a]Group | .734 |
| **DDS – Emotional burden subscore**, *mean (SD)* | | | | | |
| Week 0 | 1.94 (0.96) | 2.17 (1.13) | .537 | Time | .502 |
| Week 12 | 1.79 (0.90) | 1.93 (0.93) | .660 | Group | .607 |
| Week 24 | 1.71 (0.78) | 1.81 (0.97) | .753 | Time[a]Group | .876 |
| **DDS – Physician-related distress subscore**, *mean (SD)* | | | | | |
| Week 0 | 1.61 (0.90) | 1.95 (1.26) | .397 | Time | .356 |
| Week 12 | 1.38 (0.68) | 1.75 (1.13) | .279 | Group | .407 |
| Week 24 | 1.48 (0.72) | 1.57 (0.99) | .794 | Time[a]Group | .479 |
| **DDS – Regimen-related distress subscore**, *mean (SD)* | | | | | |
| Week 0 | 2.03 (1.04) | 2.37 (1.06) | .365 | Time | .303 |
| Week 12 | 1.90 (0.84) | 2.08 (0.95) | .581 | Group | .514 |
| Week 24 | 1.78 (0.76) | 1.85 (0.92) | .799 | Time[a]Group | .694 |
| **DDS – DDS Interpersonal distress subscore**, *mean (SD)* | | | | | |
| Week 0 | 1.98 (0.94) | 2.29 (1.35) | .468 | Time | .540 |
| Week 12 | 1.71 (0.86) | 2.00 (1.02) | .397 | Group | .427 |
| Week 24 | 1.71 (0.79) | 1.89 (0.93) | .566 | Time[a]Group | .815 |

AQoL-8D – Australian Quality of Life (8-dimension); DDS – Diabetes distress scale; SD – Standard deviation.
[a] means compared using independent samples *t*-test.
[b] p values associated with type III tests of fixed effects.

## 4. Discussion

The ESOLED trial addresses an important evidence gap by providing preliminary evidence of the effectiveness of OLE in improving glycaemic control, insulin resistance, diabetes-related distress and health-related quality of life in adults with type 2 diabetes mellitus. Although the findings of the trial indicate that OLE is well tolerated when compared with placebo, the trial did not find OLE to be more effective than placebo at improving glycosylated haemoglobin, insulin sensitivity, diabetes-related distress or health-related quality of life.

A number of factors may help explain why the ESOLED trial did not find statistically significant differences in trial outcomes between OLE and placebo. The first consideration is sample size. Although the sample size of the study (n = 31) was close to the required number of participants determined a priori (n = 40), it is possible that the sample size may not have been sufficient to detect a statistically significant difference between groups (noting that the study was only powered to detect a medium effect size). Thus, the ESOLED trial may have been underpowered, meaning that it may be premature to claim that OLE is ineffective in improving glycaemic control in diabetes without further exploration of its effectiveness in larger clinical trials [31].

Another factor potentially impacting the outcomes of the ESOLED trial is the bioavailability of OLE and its active constituents. The phenolic compounds of OLE (such as hydroxytyrosol and oleuropein) are shown to be absorbed dose-dependently [32], with absorption rates increased when administered in liquid versus capsule form [33], and reduced when exposed to gastric and intestinal fluid [34]. Studies administering OLE, hydroxytyrosol and/or oleuropein at doses above that utilised in the ESOLED trial have demonstrated positive therapeutic

effects on metabolic parameters such as blood pressure and plasma lipids [35]. Thus, it could be hypothesised that high doses of liquid OLE preparations maybe required to exert clinically meaningful effects in humans, particularly for metabolic disorders such as diabetes. Notwithstanding, given that it is currently unclear how foods, prescribed medications and other ingested substances interact with the pharmacokinetics and pharmacodynamics of OLE, robust pharmacokinetic studies of OLE are also urgently required in order to determine how best to optimise the bioavailability of OLE for clinical use.

The ESOLED trial was a rigorously designed pilot, prospective, randomised placebo-controlled trial, using validated outcome measures and demonstrably effective blinding, with high participant retention, and good adherence to treatment. However, as noted above, there are some limitations to the study that should be taken into consideration when interpreting the findings, including the possibility that the trial was underpowered. Another consideration is the gender profile of participants, with the majority (71 %) of participants being male. According to the findings of a small bioavailability study [33], males yield substantially lower plasma oleuropein levels post-OLE ingestion relative to women, which could mean that males require higher doses of oleuropein to induce a therapeutic effect. Alternatively, it may be that males require liquid forms of OLE given that liquid forms are shown to produce sixfold higher peak oleuropein concentrations than capsulated forms of OLE [33]. Although this proposition seems plausible, it does warrant further investigation.

## 5. Conclusions

The ESOLED trial has provided important preliminary evidence on the tolerability of OLE in adults with type 2 diabetes, but was inconclusive in determining whether OLE is more effective than placebo in improving glycaemic control, insulin sensitivity, diabetes-related distress and health-related quality of life. Factors such as the small sample size and potential issues with OLE bioavailability may have influenced the outcomes of the trial, suggesting that larger trials and further exploration of OLE dosage and delivery methods are needed to fully assess its therapeutic potential in metabolic disorders like diabetes.

## CRediT authorship contribution statement

**Matthew J. Leach:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ian Breakspear:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization.

## Ethical statement

The trial was reviewed and approved by the Southern Cross University Human Research Ethics Committee (Approval No. 2022/034). Informed consent was obtained from all participants.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Funding

The project was supported by an Olive Wellness Institute Research Grant, as well as donations from Vital.ly Pty Ltd and Oborne Health Supplies.

## Declaration of competing interest

IB was a member of the Boundary Bend Olives Expert Scientific Steering Committee from 2017 to 2022, is an Expert Contributor to the Olive Wellness Institute (2019 ongoing) and was a paid consultant to Wellgrove Health between 2021 and 2022.

## Acknowledgments

The authors would like to thank the study participants for their time and commitment to the project; and Legacy Health for facilitating the preparation and packaging of the intervention and placebo capsules.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2025.101949.

## References

[1] GBD 2021 Diabetes Collaborators, Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021, Lancet 402 (2023) 203–234.
[2] L. Agrawal, N. Azad, G.D. Bahn, L. Ge, P.D. Reaven, R.A. Hayward, D.J. Reda, N. V. Emanuele, VADT Study Group, Long-term follow-up of intensive glycaemic control on renal outcomes in the veterans affairs diabetes trial (VADT), Diabetologia 61 (2018) 295–299.
[3] C.H. Chang, J.L. Wang, L.C. Wu, L.M. Chuang, H.H. Lin, Diabetes, glycemic control, and risk of infection morbidity and mortality: a cohort study, Open Forum Infect. Dis. 6 (2019) ofz358.
[4] M. Mongraw-Chaffin, A.G. Bertoni, S.H. Golden, N. Mathioudakis, D.D. Sears, M. Szklo, C.A.M. Anderson, Association of low fasting glucose and HbA1c with cardiovascular disease and mortality, Diab Care 40 (2019) 800–807.
[5] SA Sr Bin Rakhis, N.M. AlDuwayhis, N. Aleid, A.N. AlBarrak, A.A. Aloraini, Glycemic control for type 2 diabetes mellitus patients: a systematic review, Cureus 14 (2022) e26180.
[6] K. Khunti, A. Ceriello, X. Cos, C. De Block, Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: a meta-analysis, Diab Res Clin Pract 137 (2018) 137–148.
[7] S. Oh, S. Purja, H. Shin, M. Kim, E. Kim, Hypoglycemic agents and glycemic variability in individuals with type 2 diabetes: a systematic review and network meta-analysis, Diab Vasc Dis Res 19 (2022) 14791641221106866.
[8] F. Gnesin, A.C. Thuesen, L.K. Kähler, S. Madsbad, B. Hemmingsen, Metformin monotherapy for adults with type 2 diabetes mellitus, Cochrane Database System Rev 6 (2020) CD012906.
[9] E. Mannucci, L. Naletto, G. Vaccaro, A. Silverii, I. Dicembrini, B. Pintaudi, M. Monami, Efficacy and safety of glucose-lowering agents in patients with type 2 diabetes: a network meta-analysis of randomized, active comparator-controlled trials, Nutr Metab Cardiovasc Dis 31 (2021) 1027–1034.
[10] A.T. Larkin, C. Hoffman, A. Stevens, A. Douglas, Z. Bloomgarden, Determinants of adherence to diabetes treatment, J. Diabetes 7 (2015) 864–871.
[11] E. Piragine, D. Petri, A. Martelli, V. Calderone, E. Lucenteforte, Adherence to oral antidiabetic drugs in patients with type 2 diabetes: systematic review and meta-analysis, J. Clin. Med. 12 (2023) 1981.
[12] L.K. Cieslik, N.R. Cresswell, D. Fineberg, J.A. Mariani, H.C. Patel, Prescription trends and costs of diabetes medications in Australia between 2003 and 2019: an analysis and review of the literature, Intern. Med. J. 52 (2022) 841–847.
[13] E.D. Parker, J. Lin, T. Mahoney, N. Ume, G. Yang, R.A. Gabbay, N.A. ElSayed, R. R. Bannuru, Economic costs of diabetes in the U.S. in 2022, Diab Care 47 (2024) 26–43.
[14] M.A. Hashmi, A. Khan, M. Hanif, U. Farooq, S. Perveen, Traditional uses, phytochemistry, and pharmacology of Olea europaea (olive), Evid Based Complement Alternat Med 2015 (2015) 541591.
[15] M.A. Temiz, A. Temur, The effect of olive leaf extract on digestive enzyme inhibition and insulin production in streptozotocin-induced diabetic rats, Ankara Univ. Vet. Fak. Derg. 66 (2019) 163–169.
[16] N. Acar-Tek, D. Ağagündüz, Olive Leaf (Olea europaea L. folium): potential effects on glycemia and lipidemia, Ann. Nutr. Metab. 76 (2020) 10–15.
[17] H.M.M. Mansour, A.A. Zeitoun, H.S. Abd-Rabou, H.A. El Enshasy, D.J. Dailin, M.A. A. Zeitoun, S.A. El-Sohaimy, Antioxidant and anti-diabetic properties of olive (*Olea europaea*) leaf extracts: in vitro and in vivo evaluation, Antioxidants 12 (2023) 1275.
[18] R. Araki, K. Fujie, N. Yuine, Y. Watabe, Y. Nakata, H. Suzuki, H. Isoda, K. Hashimoto, Olive leaf tea is beneficial for lipid metabolism in adults with prediabetes: an exploratory randomized controlled trial, Nutr. Res. 67 (2019) 60–66.
[19] E. Razmpoosh, S. Abdollahi, M. Mousavirad, C.C.T. Clark, S. Soltani, The effects of olive leaf extract on cardiovascular risk factors in the general adult population: a systematic review and meta-analysis of randomized controlled trials, Diabetol. Metab. Syndrome 14 (2022) 151.
[20] J. Wainstein, T. Ganz, M. Boaz, Y. Bar Dayan, E. Dolev, Z. Kerem, Z. Madar, Olive leaf extract as a hypoglycemic agent in both human diabetic subjects and in rats, J. Med. Food 15 (2012) 605–610.

[21] S.M. Eldridge, C.L. Chan, M.J. Campbell, C.M. Bond, S. Hopewell, L. Thabane, G. A. Lancaster, CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Br. Med. J. 355 (2016) i5239.
[22] J.J. Gagnier, H. Boon, P. Rochon, D. Moher, J. Barnes, C. Bombardier, for the CONSORT Group, Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement, Ann. Intern. Med. 144 (2006) 364–367.
[23] A.L. Whitehead, S.A. Julious, C.L. Cooper, M.J. Campbell, Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable, Stat. Methods Med. Res. 25 (2016) 1057–1073.
[24] M. de Bock, J.G.B. Derraik, C.M. Brennan, J.B. Biggs, P.E. Morgan, S. C. Hodgkinson, P.L. Hofman, W.S. Cutfield, Olive (Olea europaea L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial, PLoS One 8 (2013) e57622.
[25] E. Eyth, R. Naik, Hemoglobin A1C, in: StatPearls. Treasure Island (FL), StatPearls Publishing, 2023.
[26] H.E. Lebovitz, Insulin resistance: definition and consequences, Exp. Clin. Endocrinol. Diabetes 109 (2001) S135–S148.
[27] J.S. Gonzalez, L. Fisher, W.H. Polonsky, Depression in diabetes: have we been missing something important? Diab Care 34 (2011) 236–239.
[28] K. Kintzoglanakis, P. Vonta, P. Copanitsanou, Diabetes-related distress and associated characteristics in patients with type 2 diabetes in an urban primary care setting in Greece, Chronic Stress 25 (2020) 2470547020961538.
[29] M.M. Esteban y Peña, V. Hernandez Barrera, X. Fernández Cordero, A. Gil de Miguel, M. Rodríguez Pérez, A. Lopez-de Andres, R. Jiménez-García, Self-perception of health status, mental health and quality of life among adults with diabetes residing in a metropolitan area, Diabetes Metab. 36 (2010) 305–311.
[30] M. Schunk, P. Reitmeir, S. Schipf, H. Völzke, C. Meisinger, B. Thorand, A. Kluttig, K.H. Greiser, K. Berger, G. Müller, U. Ellert, H. Neuhauser, T. Tamayo, W. Rathmann, R. Holle, Health-related quality of life in subjects with and without Type 2 diabetes: pooled analysis of five population-based surveys in Germany, Diabet. Med. 29 (2012) 646–653.
[31] L. Abdullah, D.E. Davis, P.D. Fabricant, K. Baldwin, S. Namdari, Is there truly "no significant difference"? Underpowered randomized controlled trials in the orthopaedic literature, J Bone Joint Surg Am 97 (2015) 2068–2073.
[32] F. Visioli, C. Galli, F. Bornet, A. Mattei, R. Patelli, G. Galli, D. Caruso, Olive oil phenolics are dose-dependently absorbed in humans, FEBS Lett. 468 (2000) 159–160.
[33] M. de Bock, E.B. Thorstensen, J.G. Derraik, H.V. Henderson, P.L. Hofman, W. S. Cutfield, Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (Olea europaea L.) leaf extract, Mol. Nutr. Food Res. 57 (2013) 2079–2085.
[34] D. Martín-Vertedor, M. Garrido, J.A. Pariente, J. Espino, J. Delgado-Adámez, Bioavailability of bioactive molecules from olive leaf extracts and its functional value, Phytother Res. 30 (2016) 1172–1179.
[35] S. Lockyer, I. Rowland, J.P.E. Spencer, P. Yaqoob, W. Stonehouse, Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: a randomised controlled trial, Eur. J. Nutr. 56 (2017) 1421–1432.