CLINICAL TRIAL EVIDENCE ON CURCUMIN POTENTIAL FOR TYPE 2 DIABETES MELLITUS TREATMENT: A SYSTEMATIC REVIEW FROM 2015-2020

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ABSTRACT

Regardless of the availability of diabetes medicines, diabetes mellitus and its complications are increasing and still a major global problem. This study aims to review the potential of curcumin to prevent diabetes mellitus complications in humans. A literature search with a systematic method was carried out across four databases (PubMed, Cochrane, ScienceDirect, and Taylor and Francis) from 2015-2020. Triglyceride (TG), Low-Density Lipoprotein-cholesterol (LDL-c), Body Mass Index (BMI), and body weight are the top four outcome parameters that have significant changes compared with the baseline condition. Meanwhile, when comparing the results with the control group, only TG, BMI, and body weight were observed to be significantly improved. Curcumin supplements administered through oral route, with their medicinal properties such as anti-inflammatory and antioxidant, have a significant role in preventing the development of cardiovascular, neurological, and nephrological complications in the diabetic patient through improving lipid profile, vascular stiffness, inflammation, and oxidative stress.

Keywords: Type 2 Diabetes Mellitus, Curcumin, Curcuma Longa, Anti-inflammatory, Triglyceride, Body Mass Index

INTRODUCTION

As the most common metabolic disorder, diabetes mellitus has been categorized as a significant challenge health sector.¹ The prevalence of diabetes increases drastically from 1980 to 2014 (108 to 422 million people)¹ and more rapidly in low to middle-income countries.²,³ Diabetes mellitus is a chronic disease with inflammation caused by the pancreas that can not produce inadequate insulin or insulin resistance. In 2016, diabetes had caused 1.6 million deaths, becoming the major cause of heart diseases, kidney failure, stroke, blindness, and lower limb amputation.⁴ To answer this global challenge, several experiments have been conducted to discover potential plant-based medicine with anti-diabetic properties.⁵ Indeed, several developed drugs have been used for diabetes treatment to substitute insulin therapy, such as secretagogues, biguanides, insulin sensitizer, and so on;⁶ but plant-based medicine such as that of genus Curcuma still gain a lot of researchers’ attention due to its high potential.⁷–⁹

Turmeric or Curcumin longa (Fig.-1a) is an herbaceous plant found widely in South Asia. Turmeric contains curcumin (Fig.-1b) that is commonly used as spices in Asian dishes and is well known for its anti-inflammatory, antioxidant, antimicrobial, anticancer, and antiseptic properties.¹⁰ Curcumin based on recent research shows many pharmacological actions. Curcumin may be effective in reducing the development and complication of diabetes because it has antioxidant properties and prevents the formation of oxygen free radicals.¹¹ Previous research has shown the effect on animal trials or in vitro models as an anti-inflammatory, blood lipid, and sugar-reducing in turmeric.¹¹ Several reviews have been reported to address the issue of the clinical trial of curcumin supplements to suppress type 2 diabetes mellitus (T2DM).¹²–¹⁴ However, those reports disregard the effect of curcumin to reduce the complication of T2DM, or they were not systematic. Another review only extracted the data from in vivo studies using animal testing.¹⁵ This study aims to review relevant
previous journal articles (from 2015 – 2020) with the clinical trial as the research design to see the potential of curcumin to prevent and cure T2DM and its complication.

EXPERIMENTAL

A systematic review was performed on October 10th, 2020, using the PubMed, ScienceDirect, Taylor, and Francis, and Cochrane Databases according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedures for systematic review for published reports in the English language within the year of 2015-2020. The terms used to generate the search were Type 2 Diabetes Mellitus, Complication, Prevention, and Curcumin. Articles found then were selected with inclusion and exclusion criteria. Articles included in this systematic review should use clinical trial settings performed on humans, study curcumin effects on preventing and treating complications of T2DM, and allow full-text access. Studies on pediatric or adolescent patients, animal studies, and studies in different focus are excluded (Fig.-2).

RESULTS AND DISCUSSION

Subject’s Characteristics

From 6 selected clinical trials, there were 2 kinds of age groups; adolescent to elderly and adult to elderly. A clinical trial from Panahi et al.16 recruited patients from adolescent to elderly. Meanwhile, the rest recruited – adults to elderly (Table-1).
Study Outcome
This review has selected 6 studies that only use clinical trials on the patient with Diabetes Mellitus with the comparison between Curcumin and placebo or only curcumin (Table-1). A study shows a significant reduction in BMI, body weight, LDL-c, and TG.\(^1\) Another study shows a sharp decrease in TG, hs-CRP, as well as a significant elevation of adiponectin.\(^1\) A clinical trial study achieved an enourmous decrease in the total symptom score, total reflex score, the total score of neuropathy, temperature, waist circumstance, FBS, and HbA1c.\(^17\) A group led by Panahi reported a significant decrease in body weight, BMI, TG, non-HDL-C, LDL-c, TC, and lipoprotein (a).\(^16\) Srinivasan \textit{et al.} obtained a remarkable lowering of diastolic blood pressure, pulse pressure, systolic blood pressure, right and left brachial-ankle PWV, aortic pulse pressure, aortic systolic pressure, aortic augmentation pressure, aortic augmentation index, carotid-femoral PWV, and VCAM.\(^10\) Another clinical trial reported a significant reduction in U-mAlb excretion, MDA level, LPS level, and a significant increase in inflammation inhibitory protein 1kB.\(^18\) Significant outcome parameters from these studies have been metaanlyzed and presented in Fig.-3. TG, BMI, body weight, and LDL-c are the top four outcome parameters that have significant changes compared with the baseline condition. Meanwhile, when it comes in comparing the results with the control group, only TG, BMI, and body weight that are observed with the greater portion than the others.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Participant Characteristics</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Age: 30-70 years old Hyperlipidemic Diabetes Type 2 Did not follow undergo insulin therapy and consume multivitamin, antioxidants, or polyphenols supplements in the last 3 months before the trial. (HbA1C) &gt; 6%, TG &gt; 150 mg/dl, LDL-c &gt; 100 mg/dl, body mass index (BMI) between 20 and 35 kg/m(^2), or Fasting blood sugar &lt; 200 mg/dl, hemoglobin A1c</td>
<td>Turmeric powder (capsule) Dose: 700mg/meal (2100 mg/day) in 8 weeks No diet change</td>
<td>Significant reduction on: Bodyweight, BMI, TG, and LDL-c Significant differences in: BMI, TG, and total cholesterol,</td>
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<tr>
<td>1</td>
<td>Age: 40-70 years old Diabetes Mellitus Type 2 (up to 10 years) BMI ranges 18.5-30 kg/m(^2) Using oral hypoglycemic agents</td>
<td>Curcumin capsule (500 mg) containing 347 mg curcumin, 84 mg demethoxycurcumin, and 9 mg bisdemethoxy curcumin, and 38 mg turmeric oil. 1500 mg/day in 10 weeks</td>
<td>Significant reduction on: TG and hs-CRP Significant increase in adiponectin Significant differences in hs-CRP, adiponectin, and body weight</td>
</tr>
<tr>
<td>17</td>
<td>Age: 30-60 years old Patients Patients with Diabetic Sensorimotor Polyneuropathy (DSPN). Some patients were Non–Insulin-Dependent Diabetes Mellitus (NIDDM)</td>
<td>Nano curcumin supplements with 72% curcumin, 25% demethoxycurcumin and 3% bisdemethoxycurcumin</td>
<td>Significant reduction on: Total score of neuropathy, total symptom score, total reflex score, temperature, waist circumstance, FBS, and HbA1c Significant differences on FBS, HbA1c, and total score of neuropathy</td>
</tr>
</tbody>
</table>
## Effects on Hyperlipidemia and Hyperglycemia

<table>
<thead>
<tr>
<th>Age</th>
<th>Diabetes Type</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>18-65 yrs old</td>
<td>Diabetes Type 2</td>
<td>Curcuminoids capsule (500 mg) consisting curcumin, demethoxycurcumin, and bisdemethoxycurcumin; added with 5 mg piperine</td>
<td>Significant decrease on: Bodyweight, BMI TC, TG, LDL-c, non-HDL-C, lipoprotein (a)</td>
</tr>
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<td></td>
<td></td>
<td>Glycated hemoglobin (HbA1C) ≥ 6.5%, Fasting plasma glucose (FPG) ≥ 126 mg/dL, Treated with anti-diabetic medication. N=50 for intervention and N=50 for placebo</td>
<td></td>
<td>Insignificant increase on: HDL-c</td>
</tr>
<tr>
<td>10</td>
<td>30-65 yrs old</td>
<td>Diabetes Type 2</td>
<td>Curcuma longa (400 mg) Use of metformin, with or without, sulfonylureas.</td>
<td>Significant reduction on: Systolic blood pressure, pulse pressure, right and left brachial-ankle PWV, diastolic blood pressure, aortic pulse pressure, aortic augmentation index, aortic systolic pressure, carotid-femoral PWV, and VCAM, aortic augmentation pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2 within 3 months – 10 years priorly. Consuming metformin, regardless the addition of sulfonylureas for 3 months priorly. N=60 for intervention and N=54 for placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>47-85 yrs old</td>
<td>Diabetes Type 2</td>
<td>From ORGANIKA Health Product (Canada) (capsule) Dose 500mg/day in 15 days For DKD (diabetic kidney disease) patient, extended to 30 days</td>
<td>Significant reduction on: U- mAlb excretion, MDA level, LPS level</td>
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<td></td>
<td></td>
<td>14 patients (4 patients diagnosed with Diabetic Kidney Disease (DKD), 3 patients with pre DKD, and the others were T2D with normal U-mAlb excretion)</td>
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</tr>
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</table>

*Statistically significant at p = 0.05

**Note.** BMI: body mass index; HbA1c: hemoglobin A1c; FBG: fasting blood glucose; HOMA-ir: homeostatic model assessment of insulin resistance; hs-CRP: high sensitivity C-reactive protein TG: triglyceride; LPS: Lipopolysaccharides; Bs2hp: blood sugar after 2 hours; PWV: pulse wave velocity; U-mAlb: urine-microalbumin; MDA: Malondialdehyde.

**Effects on Hyperlipidemia and Hyperglycemia**

Insulin deficiency in diabetic patients leads to hyperglycemia and dyslipidemia T2DM patients, identified by increased cholesterol parameters. Turmeric and curcumin can significantly decrease body weight and BMI and improve hyperglycemia and hyperlipidemia. Curcumin may induce a weight loss via adipose tissue reduction as the consequence of proinflammatory cytokines suppression and promoting basal metabolic rate. However, the reductions in BMI and body weight were not significant in a clinical trial involving obese women with systemic inflammation and dyslipidemia. T2DM patients with daily curcumin (1500 mg) consumption for 2.5 months, however, experienced a sharp TG level decline. In a clinical trial, the lowered level of lipid and blood glucose did not occur, possibly due to the low dose of curcumin.
curcumin administered. A group led by Adab found that turmeric insignificantly reduced HbA1c, fasting plasma glucose, insulin resistance index (HOMA), and serum insulin compared to a placebo group.

![Diagram of metabolic parameters](image)

(A) and (B) Fig. 3: The most frequently obtained statistically significant outcomes when (A) comparing with baseline condition and (B) comparing with the control group.

Curcumin activates glycolysis, prevents gluconeogenesis, and decreases hepatic lipid metabolism to control glucose homeostasis. Furthermore, it reduces insulin resistance and increases insulin sensitivity, acting as an anti-diabetic agent. In an 8-week long clinical trial, a significant decrease in TG and LDL-c and serum total cholesterol was observed. Additionally, a clinical study reported a significant increase of HDL-c. Turmeric elevates liver cholesterol 7-hydroxylase enzyme activity and suppresses HMG-CoA reductase to inhibit the synthesis of cholesterol and increase cholesterol catabolism. It is worth mentioning that the mixture of curcumin supplements using piperine additive has been reported to enhance its bioavailability. To increase the bioavailability, materials of the carrying capsule can be made from cellulose, chitosan, or others.
Effects on Inflammation
Inflammation is a major cause that can kill the pancreatic beta-cell, associated with the activity redox-sensitive transcription; NF-kb. A study on 100 overweight and obese patients showed decreased TG, TNF-α, and CRP. Several studies have shown positive impacts of curcumin as an anti-inflammation which is a key for the anti-diabetic factor. In *in vivo*, turmeric and curcumin reduced CRP (a sensitive inflammatory biomarker) as well as proinflammation IL-6 and IL-1β, altogether with the improved anti-inflammatory IL-4 and IL-10. In a clinical trial, a decrease of serum hs-CRP was observed. Adiponectin level was observed to be increased significantly upon the treatment using curcumin at the final stage of the investigation. Insulin resistance, cardiovascular disease, obesity, and dyslipidemia have inverted associations with serum adiponectin. Adipokine derived from adiponectin is an antioxidant that can regulate lipid and glucose metabolism and work as an anti-atherosclerotic substance. It is corroborated by the finding of a previous study pertaining to curcumin effect on the increase of adiponectin.

Effects on Vascular Function
Diabetes mellitus might cause macrovascular (i.e. atherosclerotic cardiovascular and cerebrovascular diseases), as well as microvascular complications (neuropathy, nephropathy, and retinopathy). Under this light, *C. longa* has been proven in a clinical trial to the decline of endothelial function along with arterial stiffness. Other significant improvements included aortic augmentation pressure, Carotid Femoral Pulse Wave Velocity (PWV) and aortic augmentation index. Carotid-femoral PWV has been observed in T2DM patients as an indicator of cerebrovascular and cardiovascular risk factors. Curcumin may reduce arterial stiffness in humans via eNOS enzyme induction to improve nitric oxide activity and increase antioxidant activities. One of the vital risk factors of premature atherosclerosis CVD is the elevation of serum Lp(a) and HDL-c. Currently, drugs such as statin and fibrates have been used to improve HDL-c level in T2D patients, however, they have not been satisfying. On the contrary, a clinical trial has succeeded in reaching satisfying improvement of HDL-c level by the administration of curcumin.

The benefits of curcumin have also been shown through the levels of adiponectin, leptin ICAM, and VCAM. Improvement in adiponectin and leptin levels by curcumin has been achieved after 3 – 6 months of treatment. But, these results were not obtained in the 12 weeks-long clinical trials. These differences might be associated with the length of the treatment and the subject’s health status.

Effects on Nephropathy
The deactivation of Nrf2 in T2DM patients may promote pro-inflammatory mediators leading to the complications development in kidney and renal function. Curcumin has been shown a positive effect on activating Nrf2 in animal studies *in vivo* and can be used to prevent and slower Diabetic Complication such as DKD in humans. In a clinical trial, curcumin was proven to debilitate U-mAlb and activate Nrf2 to suppress inflammatory signaling and LPS level (endotoxin). LPS contributes to systemic inflammation and adipose tissue-derived cytokines, which will lead to DKD development. LPS may generate renal inflammation by binding to toll-like receptor (TLR)-4 in the kidney of a diabetic patient and harm renal podocytes.

Effects on Sensorimotor Polyneuropathy
Chronic hyperglycemia induces systematic oxidative stress and implicates Diabetic Neuropathy. Diabetic Sensorimotor Polyneuropathy (DSPN) affects 25% of people diagnosed with T2DM. Diabetic patients who suffer polyneuropathy may suffer balance loss and chronic pain, sleep disturbance, anxiety, and depression. Curcumin can protect against nerve damage via its antioxidant activities. Based on the studies using animal models, oxidative stress is responsible for causing nerve damages. Based on the *in vivo* study, curcumin has been reported to improve the neuropathic condition. Curcumin also showed effectiveness against heredity neuropathy in *in vitro* experiments. A clinical trial using nano curcumin reported an easier absorption, resulting in significant reductions of DSPN, temperature, and total reflex score. Curcumin may also control DSPN using glycemic management and reduction of serum FBS and HbA1c levels.
CONCLUSION
Turmeric or Curcuma longa, a plant that is commonly used as a spice, was evidenced to have antioxidant anti-inflammation and many other pharmacological benefits which can be used to treat T2DM patients. Based on the clinical trials, curcumin may yield significant effects in preventing T2DM complications through the improvement of lipid profile, vascular condition, an inflammatory marker in diabetic patients. We suggest clinical trials of curcumin as anti-T2DM need to be further carried out with comparable parameters and patients’ characteristics to find a conclusive result of its efficacy.

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REFERENCES
4. https://www.who.int/health-topics/diabetes accessed on March 8th, 2021

49. Ž. Reiner, *Metabolism and Cardiovascular Diseases*, **23**(9), 799(2013), [https://doi.org/10.1016/j.numecd.2013.05.002](https://doi.org/10.1016/j.numecd.2013.05.002)


52. S. M. Tan, A. Sharma, N. Stefanovic, et al. *Diabetes*, **63**(9), 3091(2014), [https://doi.org/10.2337/db13-1743](https://doi.org/10.2337/db13-1743)


61. M. Davies, S. Brophy, R. Williams and A. Taylor, *Diabetes Care*, **29**(7), 1518(2006), [https://doi.org/10.2337/dc05-2228](https://doi.org/10.2337/dc05-2228)


64. A. J. M. Boulton and R. A. Malik, *Diabetes Care*, **33**(1), 207(2010), [https://doi.org/10.2337/dc09-1728](https://doi.org/10.2337/dc09-1728)


68. Y. Zhang, X. Guo, J. Guo, et al., *Scientific Reports*, **4**(1), 5654(2015), [https://doi.org/10.1038/srep05654](https://doi.org/10.1038/srep05654)


70. R. P. Joshi, G. Negi, A. Kumar, et al., *Nanomedicine: Nanotechnology, Biology and Medicine*, **9**(6), 776(2013), [https://doi.org/10.1016/j.nano.2013.01.001](https://doi.org/10.1016/j.nano.2013.01.001)


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