The Effects of Curcuma longa in Insulin Resistance

Lais Maria Pescinini Salzedas¹, Giulia Trevisan Covre Simão Batista¹ and Sandra Maria Barbalho¹,²,³*

¹Department of Biochemistry and Pharmacology, School of Medicine, University of Marília (UNIMAR), Avenida Higino Muzzi Filho, 1001, Marília, São Paulo, Brazil.
²Postgraduate Program in Structural and Functional Interactions in Rehabilitation, UNIMAR-Marília, São Paulo, Brazil.
³Department of Biochemistry and Nutrition, Faculty of Food Technology of Marília, Marília, São Paulo, Brazil.

Authors’ contributions

This work was carried out in collaboration among all authors. Authors SMB and LMPS designed the study and wrote the first draft of the manuscript. Authors SMB, LMPS and GTCSB managed literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/EJMP/2020/v31i1030286

Editor(s):
(1) Dr. Shanfa Lu, Chinese Academy of Medical Sciences & Peking Union Medical College, China.
(2) Prof. Marcello Iriti, University of Milan, Italy.

Reviewers:
(1) Prince Chikwere, All Nations University, Ghana.
(2) U. S. Mahadeva Rao, Universiti Sultan Zainal Abidin (UniSZA), Malaysia.

Complete Peer review History: http://www.sdiarticle4.com/review-history/58892

Received 01 May 2020
Accepted 06 July 2020
Published 15 July 2020

ABSTRACT

Background: Curcumin is seen as an anti-hyperglycemic agent that acts by improving the expression of glucose transporters. It is also related to the reduction of glycosylated hemoglobin, improvement of insulin sensitivity, plasma lipids, and blood pressure.

Aim: The purpose of this article is to review the effects of Curcuma longa in insulin resistance.

Methodology: PUBMED and EMBASE databases were searched, and PRISMA (Preferred Reporting Items for a Systematic Review and Meta-analysis) guidelines were followed to build the review.

Results: Nineteen Randomized Clinical Trials (RCTs) met the inclusion criteria and were described according to PICO (Population, Intervention, Comparison, and Outcomes).

Conclusion: Curcumin could be considered in the therapeutic approach of patients with Insulin Resistance.

*Corresponding author: E-mail: smbarbalho@gmail.com, silmaraebarbalho@gmail.com
Resistance, once it is related to the reduction of oxidative stress, inflammation, serum fasting blood glucose, HOMA-IR, blood pressure, serum lipids, and liver transaminases. However, the results depend on the dose, intervention time, and formulation of the compound.

Keywords: Insulin resistance; type 2 diabetes mellitus; glycemia; Curcuma longa; curcumin.

1. INTRODUCTION

Insulin resistance (IR) is a consequence of abnormal functioning and signaling of insulin receptors, an excessively high level of insulin-binding antibodies, or an abnormal insulin molecule structure [1]. This condition manifests impaired insulin action in all insulin target organs and tissues as skeletal muscle, cardiac muscle, liver, adipose tissue, the brain as well as the vasculature [2,3]. Therefore it is clinically seen as metabolic stress that leads to high blood glucose, obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome (MS), and cardiovascular diseases (CVD) [1,4,5].

The usual metabolism is disturbed in the state of IR due to elevated plasma free fatty acids and inflammatory cytokines, like tumor necrosis factor-alpha (TNFα), which induces microvascular IR, seen in obesity and T2DM [2]. Furthermore, the p110α, catalytic subunit of phosphatidylinositol 3- kinase, mediates the cellular responses to insulin [5,6]. Its inhibition blocks insulin signaling, leading to glycogen breakdown in the liver and decreased glucose uptake in skeletal muscle and adipose tissue, resulting in a state of IR, hyperglycemia, and hyperinsulinemia [3].

According to recent studies, curcumin can act as an anti-hyperglycemic agent by improving the expression of Glucose Transporter-1 (GLUT-1), GLUT-3, and GLUT-4, reducing blood glucose levels, inhibiting the effects of leptin in overweight patients, and increasing β-oxidation. Its administration can also reduce glycosylated hemoglobin (HbA1C) levels in the blood, improve insulin sensitivity, and reduce the increased levels of fasting blood glucose (FBG) [4-7].

Curcumin is the main biological compound found in Curcuma longa. The plant is a natural Indian spice that belongs to the family Zingiberaceae. It contains proteins (6.3%), carbohydrates (69.4%), essential oils (5.8%), fat (5.1%), and curcuminoids (3-6%) [8]. Studies involving the medicinal properties of Curcuma longa suggest that it possesses activity against viral infection, amyloid aggregation, arthritis, cancer, oxidation, and inflammation, along with correlated therapeutic effects on IR and T2DM [5]. Therefore, the purpose of this article is to review the effects of Curcuma longa in IR.

2. METHODS

2.1 Data Sources

The MEDLINE-PubMed and EMBASE databases were searched following the PRISMA guidelines (Preferred Reporting Items for a Systematic Review and Meta-analysis). This survey was conducted to answer the following question: Does Curcuma longa show positive effects on IR?

2.2 Research

The research included Randomized Clinical Trials (RCTs), and the combination of terms and mesh-terms used for this search was Hyperglycemia or Diabetes or IR and Curcuma longa or curcumin or turmeric.

Based on the studies resulting from the combination of these keywords, a flow diagram (Fig. 1) was constructed to summarize the selection process. Other studies on curcumin and IR were used for discussion purposes.

2.3 Eligible Criteria and Study Selection

Our research included only RCTs that discussed the use of curcumin and its effects on IR (the primary outcomes were improvement in glycemia) and were described according to PICO. Only articles written in English from May, 2016 to May 2020, that showed correspondence with the mesh-terms were selected.

Articles in languages other than English were excluded. Also, cross-sectional studies, cohort studies, case reports, poster presentations, animals or in-vitro studies, and letters to the editor were excluded.

2.4 Extraction of Data

The extraction of the data was carried out independently by two authors (LMPS and
GTCSB) who used the predefined inclusion and exclusion criteria, as well as mesh terms. Where necessary, SMB evaluated to address discrepancies. Data were extracted from eligible articles that included the author, date, sample size, study design, and information related to the use of curcumin and its relationship with IR. Only original articles were selected (Table 1).

3. RESULTS AND DISCUSSION

At the end of the selection process, 19 articles involving 1494 subjects were included. The age range of subjects was 18-85 years. Fig. 1 summarizes the selection process of the studies.

3.1 Insulin Resistance: General Aspects

IR is related to lower insulin sensitivity of the body tissues composed of insulin-dependent cells, such as skeletal muscle and adipocytes. The insulin plays a crucial role in glucose entry into cells, and any disturbance in insulin signal transduction is associated with hyperglycemia [9,10].

This disorder that has been shown to be correlated to stress and overstimulation of the sympathetic nervous system is strongly linked to inflammation states [1] that occur due to metabolic disturbances involving glucose intolerance, leptin resistance, dyslipidemias, mitochondrial dysfunction, an increase in pro-inflammatory mediators, and oxidative stress [9,11]. It can also be explained by the creation of advanced glycation end products (AGEs) due to chronic hyperglycemia. These AGEs stimulate inflammatory reactions and oxidative stress by acting through specific receptors leading to cell damage [12,13].

AGEs are generated due to glycoxidation reactions, giving rise to a complex mixture of interrelated compounds [14], that, so far, is considered as irreversible [15]. The formation of AGEs is consistently high due to hyperglycemia [14,16], once the high glucose concentration activates the polyol pathway, and its intermediates can glycated proteins leading to AGEs creation [14]. Tissues composed of long-lasting proteins, such as collagen, are more likely to accumulate AGEs and become altered by this accumulation. Increased levels of these
compounds can be potential markers that directly correlate T2DM with hypertension and ischemic heart disease [15-17].

The interaction between the receptor for advanced glycation end products (RAGE) with its ligands increases inflammation and oxidation, playing a role in age-related chronic diseases such as chronic/acute inflammation, neurodegenerative disorders, atherosclerosis and vascular complications of diabetes mellitus (DM). This can be explained by the interaction of the complex mixture of compounds with free amino groups, causing covalent modification, cross-linking, oligomerization and aggregation, that leads to intracellular damage, impaired cell functions and, ultimately, cell death [14,15,18]. Moreover, previous studies suggest that AGEs decrease glucose uptake by the adipocytes through the stimulation of intracellular reactive oxygen species production, and RAGEs may impair insulin signal transduction by toll-like receptor 2 activation [12].

Therefore IR can lead to atherosclerotic CVD, increase the incidence of atrial fibrillation, obesity, early T2DM [19] dyslipidemia, MS, and non-alcoholic fatty liver disorder (NAFLD) [9].

Besides that, the impaired insulin signaling promotes hypertension and atherogenesis, once insulin signaling plays a pivotal role in activating nitric oxide, which is a potent vasodilator and anti-atherogenic agent [19]. Also, IR is a mediator of neurological complications, neuropsychiatric disorders, and age-related cognitive decline because insulin acts directly in the central nervous system regulating blood and cerebrospinal fluid glucose levels, as well as cerebral metabolism [11].

### 3.2 Curcuma longa

*Curcuma longa* Linn., commonly called turmeric, belongs to the Zingiberaceae family. It is a perennial plant, extensively grown in Asia and tropical countries like Brazil [20]. The characteristic yellow golden color is due to the presence of curcuminoids, mainly curcumin (75-81%), demethoxycurcumin (15-19%), and bisdemethoxycurcumin (2.2-6.6%). Roots of *Curcuma longa* have been used for millennia as medicine for many purposes [20,21] as treatment of arthritis, amenorrhea, atherosclerosis, and cancer [22-25].

Curcumin or diferuloylmethane is the principal compound in the rhizomes and is associated with potential anti-inflammatory, antioxidant, antimitagenic, antidiabetic, antibacterial, hepatoprotective, expectorant, anticancer [22,26] anti-malarial, anti-HIV, anti-obesity, lipid-lowering, immunomodulating, [20,27] antiviral, antifungal, and wound healing effects [21,28].

The inhibition of the inflammatory response and release of cytokines promoted by curcumin is modulated by suppressing nuclear factor kappa-B (NF-kB) activation through inhibition of phosphorylation and degradation of NF-kB inhibitor alpha (I-kBα) and blockade of phosphorylation of I-kBα kinase [21,29,30].

Besides the beneficial effects of curcumin as antioxidant, anticancer, neuroprotective, and mainly anti-inflammatory properties, it is considered safe, nontoxic and mediates the anti-inflammatory transcription factors, protein kinase, cytokines, and enzymes that promote inflammation. Therefore, it is a possible safe therapy for IR [22].

### 3.3 Curcumin and Insulin Resistance

The main goal of IR treatment is to control inflammation through lifestyle interventions [31] such as a low carbohydrate diet [32,33], increased physical activity, and weight loss [34], that may improve insulin sensitivity and preserve β-cell function, and insulin-sensitizing to antidiabetic medication as thiazolidinediones [19] or metformin if necessary [33-35].

Many studies in animal models have shown that *Curcuma longa* and curcumin can improve glycemia and other risk factors for MS and Cardiovascular diseases [36-39]. Randomized Clinical Trials, as described in this review, have also shown similar effects. Table 1 summarizes the population, intervention, comparison, and outcomes (PICO) of these studies.

The study of Panahi et al. [40] showed that the intervention with curcumin resulted in significant reductions in the body weight, body mass index (BMI), serum levels of malondialdehyde, and significant elevations in serum superoxide dismutase and total antioxidant capacity. The authors included patients with 18 to 65 years, which could be a bias considering that young and older people present different metabolic rates and may use different medications that can influence the IR and on the effect of the treatment.
Table 1. Studies showing the effects of *Curcuma longa* and its compounds in subjects with insulin resistance

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Model</th>
<th>Intervention</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>[40]</td>
<td>Randomized double-blind placebo-controlled trial with a parallel-group design.</td>
<td>100 individuals (51 men and 49 women), 18-65y with T2DM.</td>
<td>1000 mg/day of curcumin co-administered with piperine 10 mg/day and a placebo group for 8 weeks.</td>
<td>In the treated group, serum total antioxidant concentrations increased compared to the placebo group.</td>
</tr>
<tr>
<td>[41]</td>
<td>Randomized clinical trial study.</td>
<td>120 individuals (45 men and 75 women, 18-65y) with MS.</td>
<td>3 groups: 40 individuals taking lecithin zed curcumin (1 g/day); 40 individuals taking unformulated curcumin (1 g/day); 40 individuals taking placebo for 6 weeks.</td>
<td>The curcumin did not interfere on serum levels of vitamin E, but decreased LDL-c, and TC pre and post trials.</td>
</tr>
<tr>
<td>[43]</td>
<td>Randomized, double-blind, placebo-controlled trial with a parallel-group design.</td>
<td>100 individuals (51 men and 49 women, 18-65 y) with T2DM.</td>
<td>The patients were divided into 2 groups (n=50 each). One group received a placebo, and the other received 1000 mg/day and 10mg/day of piperine for 12 weeks.</td>
<td>There was a decrease of TC, non-HDL-c levels, and an increase of HDL-c levels in the curcuminoid group.</td>
</tr>
<tr>
<td>[44]</td>
<td>Double-blind randomized controlled clinical trial.</td>
<td>42 individuals, 18 men, and 24 women, 20-60 y, with body mass index 24.9- 40 kg/m² and diagnosed with NAFLD.</td>
<td>Turmeric group received 6 turmeric capsules (500 mg)/day for 12 weeks.</td>
<td>The results showed that turmeric group reduced glycemia, insulin, leptin, HOMA-IR levels, and may be useful to control NAFLD complications.</td>
</tr>
<tr>
<td>[45]</td>
<td>Double-blind, parallel-group, placebo-controlled, randomized clinical trial.</td>
<td>40 individuals (17 men and 23 women) between 39 and 66 years with IFG (FBG: 110-125 mg/dL).</td>
<td>The patients were divided into active group (n=20) and placebo group (n=20). The treated group received 2 pills/day (250 mg <em>Lagerstroemia speciosa</em> extract, 155 mg <em>Berberis aristata</em> extract, 125mg <em>Curcuma</em> extract, 1,3 mg chromium picolinate, 0.15mg folic acid, and 110 mg solvent-free alpha lipoic acid) for 8 weeks.</td>
<td>The study showed an improvement in non-HDL-c and FBG in both groups. The treated group also presented an improvement in TG, FPI, and HOMA-index.</td>
</tr>
<tr>
<td>[42]</td>
<td>Double-blind, randomized, placebo-controlled trial.</td>
<td>120 individuals (34 men and 86 women; 18-65 y) with MS.</td>
<td>The patients were divided into group 1 that received 1 g/curcumin/day, group 2 that received 1 g of phospholipidated curcumin/day, and the control group/ 6 weeks.</td>
<td>The analysis showed that the curcumin group increased the PAB serum; however, in the phospholipidated curcumin group, it was not significant.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Model</td>
<td>Intervention</td>
<td>Main Results</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>[46]</td>
<td>Prospective cohort study.</td>
<td>100 individuals with MS, 35-70 y; 65 woman and 35 men.</td>
<td>The patients were divided into group A that used curcumin 400 mg/day, and group B (control group). The group A was subdivided into subgroup A1 (MS and pre-diabetes status), and subgroup A2 (MS and T2DM). The treatment effects were monitored by ultrasound of the liver at the beginning and after 12 months.</td>
<td>The study shows that the use of 400 mg/day of curcumin during a year can improve the morphological characteristics of the liver in the MS patients. Curcumin had stronger effects on subjects with MS and T2DM than placebo.</td>
</tr>
<tr>
<td>[47]</td>
<td>Randomized, double blind, placebo-controlled clinical trial.</td>
<td>50 participants, 27 men and 23 women; 40-70 y, with T2DM.</td>
<td>The patients were divided into the experimental group that received 1500mg of curcumin/3xd and the control group that received placebo. The treatment period was 10 weeks.</td>
<td>The experimental group showed significant changes in body weight, BMI, WC, and FBG. No significant differences were observed in HbA1c, insulin, MDA, TAC, HOMA-IR, and HOMA-B between the groups.</td>
</tr>
<tr>
<td>[48]</td>
<td>Double-blind placebo-controlled parallel group randomized trial.</td>
<td>33 patients, 20-85 y, 23 men and 10 women (with stable IGT; stable non-insulin-dependent DM).</td>
<td>The patients were randomly divided in placebo and Theracurmin group (180 mg daily for 6 months).</td>
<td>The level of AT-LDL-c (the oxidized LDL-c) significantly increased in the placebo group. The percentage change in BMI, adiponectin, and LDL-c tended to be higher in the Theracumin group. The results suggest that the highly absorbable curcumin could potentially inhibit a rise in oxidized LDL-c in patients with IGT or non-insulin-dependent DM.</td>
</tr>
<tr>
<td>[49]</td>
<td>Parallel double-blind randomized placebo-controlled clinical trial.</td>
<td>80 patients, 10 men, 70 women; 30-60 y. with T2DM; diagnosed with Diabetic Sensorimotor Polyneuropathy.</td>
<td>Patients were divided into control and intervention group (80 mg nano-curcumin)/ 8 w. Anthropometric measurements, dietary intake, physical activity, glycemic indices and the severity of DSPN were measured before and after the intervention.</td>
<td>Nano-curcumin reduced HbA1c and FBG. There was also a significant reduction in the total score of neuropathy, total flex score, and temperature compared to placebo group. Curcumin supplementation for 2m improves and reduces the severity of DSPN in patients with T2DM.</td>
</tr>
<tr>
<td>[50]</td>
<td>Randomized double-blind placebo-controlled clinical trial.</td>
<td>51 participants: woman (18-40 years with BMI ≥ 25 and ≥ 35 kg/m2.</td>
<td>The participants were allocated into 2 groups: curcumin (n=27) or placebo group (n=24). Curcumin was administered at a daily dose of 1g (500 mg twice a day) for 6 weeks.</td>
<td>Glycemic indices (serum insulin and QUICKI) were improved significantly in the curcumin treated group.</td>
</tr>
<tr>
<td>[55]</td>
<td>Randomized, double-blind, placebo-controlled, clinical trial.</td>
<td>59 patients, 37 men and 22 women, 28-66 y. with diagnosis of NAFLD.</td>
<td>The participants were allocated into curcumin (n=32) or placebo (n=27) group. The treated group received Phospholipidated curcumin 250mg/day /8w</td>
<td>There was a significant decrease in LDL-c and an increase in HDL-c in curcumin treated group. There was also a significant decrease in serum leptin and increase in serum adiponectin in curcumin group compared to the placebo group.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Model</td>
<td>Intervention</td>
<td>Main Results</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>[56]</td>
<td>Double-blind, randomized, placebo-controlled clinical trial.</td>
<td>84 overweight/obese patients (42 men and 42 women; 25-50 y) with diagnosed NAFLD, BMI 25-35 kg/m².</td>
<td>The patients were randomly divided into nano-curcumin (n=42) and placebo (n=42) groups. Treatment were 40 mg capsules/day after meals / 3m.</td>
<td>In the nano-curcumin group there was a significant increase of HDL-c, QUICKI and nesfastin, and a decrease in fatty liver degree, AST, ALT, WC, FBG, FPI, HbA1c, TG, TC, LDL-c, HOMA-IR, TNF-α, hs-CRP, and IL-6.</td>
</tr>
<tr>
<td>[57]</td>
<td>This was a 2x2 factorial, randomized, double-blind, placebo-controlled study.</td>
<td>64 participants, 26 men, 38 women, (30-70 y), BMI 25-45, diagnosed with IFG, IGT or both, HbA1c levels 5.7 – 6.4% or obtain a score ≥12 in the AUSDRISK tool assessment.</td>
<td>The participants were allocated to either double placebo (PL) (n=16), curcumin + placebo matching for LCn-3PUFA (CC: n=15), LCn-3PUFA + placebo matching for curcumin (FO: n=17), curcumin + LCn-3PUFA (CC-FO: n=16) for 12 weeks. CC group received 180 mg of curcumin + 2x1000 mg corn oil capsules per day. FO group received 1.2 g DHA+EPA + 2x placebo tablets matching curcumin. CC-FO received 180 mg curcumin + 1.2 g DHA+EPA.</td>
<td>The insulin sensitivity was improved in the CC, FO, and CC-FO supplemented group. TG levels reduced in CC and CC-FO supplementation, and the most significant reduction was in FO.</td>
</tr>
<tr>
<td>[52]</td>
<td>Randomized double-blind clinical trial.</td>
<td>120 participants, 34 men, 86 women, 18–65 y with MS: WC &gt; 94 cm in men and &gt; 80cm in women plus any two of the following: TG &gt; 150 mg/dL, HDL-c &lt;40 mg/dL in men and &lt;50 mg/dL in women, hypertension or FBG 100 mg/dL or diagnosed T2DM.</td>
<td>The participants were divided into 3 groups: group 1 received 500 mg of curcumin/ twice a day, group 2 and 3 received phospholipidated curcumin and placebo respectively in the same amount for 6 weeks.</td>
<td>There were no significant differences in serum levels of anti-HSP 27 antibody, weight, WC, BMI, percentage of TBF, macronutrients, and micronutrients, except saturated fatty acids in the curcumin-treated group.</td>
</tr>
<tr>
<td>[51]</td>
<td>Randomized, double-blind, parallel-arm, placebo-controlled trial.</td>
<td>114 patients, 29 men and 85 women, 30-65 y, with T2DM within the past 3 months to 10y on treatment with stable dose of metformin with or</td>
<td>The participants were randomized into placebo group (n=54) and Curcuma longa (n=60) 400 mg group / 3m.</td>
<td>The differences from baseline in adiponectin, leptin, ICAM, VCAM were compared between the groups, showing no significant differences. In hypertensive patients with T2DM, a significant reduction in carotid-femoral PWV from the baseline was seen in the treated group, and an increase was seen in</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Model</td>
<td>Intervention</td>
<td>Main Results</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>[53]</td>
<td>Randomized, double-blind, placebo-controlled trial.</td>
<td>44 participants, 22 men and 22 women, 40-70 y with T2DM, BMI 18.5-30 kg/m² and intake of oral hypoglycemic agents.</td>
<td>The patients were divided into a placebo group (n=23) and curcumin group (n=21). The treated group received 1500 mg curcumin (500 mg/3xd)/10w.</td>
<td>The treated group showed FBG levels and hs-CRP concentrations reduced compared with the beginning of the study. Adiponectin increased in both groups, but in the curcumin group, the increase was higher. The mean weight in intervention has significantly reduced compared to placebo.</td>
</tr>
<tr>
<td>[54]</td>
<td>Randomized, double-blind, clinical trial.</td>
<td>75 patients (39 women and 36 men, 30-70 y) with T2DM, FBG &lt; 200 mg/dl, HbA1C &gt; 6%, TG &gt; 150mg/dl or LDL-c &gt;100mg/dl, BMI 20-35 kg/m², no insulin therapy.</td>
<td>Patients were divided into placebo group (n=36) and intervention group (n=39) that received 2100mg turmeric powder (700mg/3xd after main meals) /8w.</td>
<td>FBG, HbA1c, insulin, and HOMA-IR reduced in turmeric group. The intervention group had a decrease in BMI compared to the beginning and to the placebo group. The intervention group also had a decrease in TG and TC compared to placebo.</td>
</tr>
<tr>
<td>[58]</td>
<td>Randomized double-blind parallel-group placebo-controlled clinical trial.</td>
<td>80 participants, 40 men and 40 women (18-70 y) with BMI 25-30 kg/m², and FBG levels of 100-125 mg/dL.</td>
<td>After 2 weeks of diet and physical activity for all patients, the treated group received 800 mg phytosomal curcumin (200 mg curcumin, 120 mg phosphatidylserine, 480mg phosphatidylcholine, associated with 8mg piperine) /2xd/8w. Clinical and biochemical data were obtained at the baseline, after 4 weeks and at the end of the trial.</td>
<td>After 28 days, the curcumin group showed improvement of FBG, FPI, HOMA-index, and serum cortisol levels compared to the baseline. The improvement of HOMA-index was also significant when compared to the placebo-treated group. After 56 days, the curcumin group showed a significant improvement in BMI, WC, SBP, TG, HDL-c, FBG, FPI, HOMA-IR, GOT, gGT, LAP, and HSI compared to the baseline. FPI, TG, GOT, GPT, FLI, and serum cortisol level also improved compared with the placebo group.</td>
</tr>
</tbody>
</table>

In subjects with Metabolic Syndrome, Mohamadi et al. [41] observed significant differences between pre-trial and post-trial in the Vitamin E/low-density lipoprotein cholesterol ratio, Vitamin E/total cholesterol (TC) ratio, Vitamin E/TG ratio and Vitamin E/high-density lipoprotein cholesterol (HDL-c) ratio when they evaluated three different groups (lecithin zed curcumin (1g/day), or unformulated curcumin (1g/day) or placebo). Mohamadi et al. suggests that the putative antioxidant effects of curcumin are mainly driven by its modulatory effects on enzymatic antioxidant elements. Similarly, Ghazimoradi et al. [42] showed that curcumin and phospholipidated curcumin have positive effects on pro-oxidant-antioxidant balance levels.

In DM patients, Panahi et al. [43] showed significant reductions in weight and BMI in the curcuminoid group while these parameters increased by the end of the trial in the placebo group. There was a significant reduction in triglycerides and LDL-c in both groups. However, only the curcuminoid group resulted in a reduction of serum lipoprotein (a) concentrations. Similar results in BMI were found by Navekar et al. [44].

In the trial performed by Cicero et al. [45], the treatment with a nutraceutical mixture containing curcumin showed an improvement in HDL-c and in other parameters related to IR and MS in patients with impaired FBG. The treated group received extracts of Lagerstroemia speciose, Berberis aristata, Curcuma, chromium picolinate, and folic acid for 8 weeks.

Selmanovic et al. [46] studied the effects of curcumin in patients with MS, pre-diabetes, or T2DM. At the beginning of the study, patients presented with initial and moderate steatosis but after a year of treatment, patients only initial steatosis remained. Selmanovic et al. concluded that curcumin might be used as a therapeutic once it can reduce oxidative stress by increasing liver glutathione concentrations, leading to a reduction in LDL-c levels and reducing inflammation by decreasing interferon-γ, TNF-α and IL-6.

Hodaei et al. [47] showed that the use of curcumin promoted a reduction in the waist circumference (WC) in patients with T2DM. Also, in T2DM patients, Funamoto et al. [48] observed that preparation with curcumin (Theracurmin) decreased the levels of triglycerides and γ-glutamyl transpeptidase. Theracurmin preparation ensures that curcumin is consistently dispersed in an aqueous solution and thus improves its absorption by the intestinal tract. Asadi et al. [49] used a nano-curcumin preparation and found a decrease in WC, glycemia, weight, and BMI compared to placebo. Improvement in glycemia was also found by Sohaei et al. [50] in polycystic ovary syndrome women.

Beneficial effects of curcumin were also found among patients with NAFLD [54,55] and those with systolic and diastolic blood pressure and inflammatory profiles [56]. Also, beneficial effects in the blood pressure were observed by Srinivasan et al [51] in hypertensive patients with T2DM. The other studies found in Table 1 also found beneficial effects of curcumin in patients with MS [52] and T2DM [53,54].

The use of Curcuma longa can bring benefits to patients with insulin resistance and DM2, however, the existing RCTs are very variable as to the formulation and dose administered, making comparisons that would be pertinent difficult.

4. CONCLUSION

Curcumin could be effective in ameliorating the effects of IR and may act through reduction of oxidative stress, inflammation, glycemia, serum FBG, HOMA-IR, blood pressure, serum lipids, and liver transaminases. However, the results depend on the dose, intervention time, and formulation of the compound. For these reasons, we suggest that new RCTs be performed in order to establish the treatment time, formulation and way of delivery of the plant. In addition, the effects on blood glucose should be evaluated over longer periods to assess the effect of the plant as a therapeutic adjuvant for IR or DM patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.
REFERENCES

14. Moldogazieva NT, Mokhosoev IM, Mel'nikova TI, Poro佐v YB, Terentiev AA. Oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in Aging and Age-Related Diseases. Oxid Med Cell Longev. 2019;3085756.
15. Teissier T, Boulanger É. The receptor for advanced glycation end-products (RAGE) is an important pattern recognition receptor (PRR) for inflammaging. Biogerontology. 2019;20(3):279-301.


Kim DW, Choi CH, Park JP, Lee SJ. Nanospheres loaded with curcumin improve the bioactivity of umbilical cord BLOOD-mesenchymal stem cells via c-Src activation during the skin wound healing process. Cells. 2020;9(6).


Taskinen MR, Packard CJ, Borén J. Dietary fructose and the metabolic syndrome. nutrients. 2019;11(9).


Haryuna TSH, Farhat F, Indriany S. Decreased protein kinase C expression in the Cochlear Fibroblasts of Diabetic Rat Models Induced by Curcumin. Turkish journal of pharmaceutical sciences. 2019; 16(2):169-74.


© 2020 Salzedas et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/58892