

Effects of Curcumin Plus Piperine Supplementation on Metabolic Syndrome and Body Mass Index in Children: Protocol for Randomized Controlled Trial

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Abstract

Background: The incidence of obesity and metabolic syndrome has been rising among the pediatric population, and these metabolic disturbances are associated with complications that persist into adulthood. Regulating energy intake is therefore fundamental for both prevention and treatment. Curcumin, a compound derived from turmeric with anti-inflammatory and antioxidant properties, and piperine, a bioavailability-enhancing alkaloid from black pepper, have both been explored for use in various non-communicable diseases in adults.

Objectives: This study aims to evaluate the effects of curcumin-piperine supplementation on metabolic syndrome and body mass index in children.

Methods: This is a randomized, triple-blind, placebo-controlled trial with a parallel two-arm design. Participants aged 7–18 years who meet at least three Cook criteria for metabolic syndrome will be recruited from a pediatric endocrinology clinic. The intervention group will receive one tablet daily containing 500 mg curcumin and 5 mg piperine for three months, while the control group will receive a microcrystalline cellulose placebo. The primary outcomes are improvement in metabolic syndrome status and body mass index (BMI). Secondary outcomes include other anthropometric indices, laboratory parameters (triglycerides, fasting glucose, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), liver enzymes (ALT and AST), fasting insulin, and HbA1c), insulin resistance indices (HOMA-IR and QUICKI), and blood pressure.

Conclusion: While findings on inflammatory markers and metabolic syndrome in adults are promising, they are heterogeneous, and pediatric studies are limited. The use of curcumin with piperine may produce more discernible effects on lipid and metabolic profiles due to improved bioavailability. The results of this trial may help generate hypotheses for developing safe and effective nutritional and therapeutic strategies for children with metabolic syndrome.

Keywords: Metabolic syndrome, Children, Curcumin, Piperine, Childhood obesity

1. Introduction

The rising prevalence of obesity in children and adolescents is one of the most concerning public health issues worldwide and a major predictor of future health problems (1, 2). Estimates indicate that by

2050, the number of children and adolescents with obesity globally will reach approximately 360 million (3). Moreover, obese children are three times more likely to become obese adults than their normal-weight peers (4). According to Professor

Emanuela Gakidou, "the unprecedented global epidemic of overweight and obesity represents a profound tragedy and a massive societal failure" (3).

Pediatric metabolic syndrome is characterized by central obesity, dyslipidemia, hypertension, and impaired glucose metabolism during childhood and adolescence (1). Childhood obesity is associated with a wide range of adverse health outcomes and is a primary risk factor for significant morbidity and mortality in adulthood (5, 6). Individuals whose obesity persists into adulthood face a substantially increased risk of type 2 diabetes, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease (5). The clustering of these metabolic and cardiovascular disorders is commonly classified as metabolic syndrome (7).

Epidemiological evidence suggests that the prevalence of metabolic syndrome in children and adolescents has increased significantly in parallel with the global rise in childhood obesity, particularly in low- and middle-income countries (8). Current management strategies for pediatric metabolic syndrome primarily emphasize lifestyle modification, including dietary changes and increased physical activity. However, long-term adherence to these interventions is often limited, and pharmacological options remain scarce due to safety concerns in children (9).

Curcumin, a bioactive polyphenolic compound extracted from turmeric (*Curcuma longa*), has garnered attention for its potential to modulate key pathways in the pathogenesis of metabolic syndrome, owing to its significant anti-inflammatory and antioxidant properties (10-13). As the principal curcuminoid in turmeric, it exerts a wide range of biological effects by regulating inflammatory signaling pathways, modulating oxidative stress responses, and improving metabolic homeostasis, making it a promising

candidate for the prevention and management of metabolic disorders (10, 14). Experimental and clinical evidence suggests that curcumin can modulate several important molecular targets, including nuclear factor kappa B (NF- κ B), peroxisome proliferator-activated receptors (PPARs), and inflammatory cytokines, which collectively may improve metabolic regulation (15). Findings from several randomized controlled trials in adults with metabolic syndrome suggest that curcumin supplementation can favorably modulate various components of the syndrome, leading to reductions in waist circumference, fasting blood glucose, and diastolic blood pressure, alongside improvements in HDL cholesterol and reductions in inflammatory markers. However, results are not always consistent, and considerable heterogeneity exists across studies (16-19).

A major limitation of oral curcumin supplementation is its poor bioavailability, attributed to low intestinal absorption, rapid metabolism, and systemic elimination (20). Co-administration with piperine, an alkaloid from black pepper, has been shown to significantly increase curcumin bioavailability by inhibiting hepatic and intestinal glucuronidation (21-23). Clinical trials in adults have demonstrated that combined curcumin and piperine supplementation is associated with more significant improvements in inflammatory markers and oxidative stress compared to curcumin alone (24). Despite this growing body of evidence in adults, data on the effectiveness of curcumin-based interventions in pediatric populations remain limited. Most existing studies have focused on obesity rather than clinically defined metabolic syndrome (25, 26). Furthermore, no randomized controlled trial has specifically investigated the effects of curcumin-piperine combination on metabolic syndrome in children, indicating a significant gap in the literature (25). Given the progressive nature of pediatric metabolic

syndrome and its long-term effects on future health, there is an urgent need to develop and evaluate safe, evidence-based adjunctive interventions that can complement lifestyle modification strategies (9). Therefore, this study was designed as a randomized, triple-blind, placebo-controlled clinical trial to investigate the effects of curcumin-piperine supplementation on metabolic parameters in children with metabolic syndrome.

2. Methods

2.1. Study Design

This is a randomized, triple-blind, placebo-controlled, parallel-group clinical trial designed to evaluate the efficacy of curcumin-piperine supplementation as an adjunctive intervention for metabolic syndrome in children. The randomized controlled trial design was selected to reduce confounding factors and biases in this pediatric population, where metabolic indices are influenced by physical growth, pubertal development, and behavioral factors. Triple blinding will minimize

expectation and observer bias, a measure particularly important in studies with anthropometric and biochemical outcomes, which may be sensitive to minor procedural variations.

2.2. Study Setting and Participants

Participants will be recruited from a pediatric endocrinology subspecialty clinic in Mashhad, Iran. Children aged 7 to 18 years who meet the criteria for metabolic syndrome as defined by Cook et al. (27) will be eligible for inclusion.

Exclusion criteria include the presence of chronic systemic diseases (e.g., malignancy, chronic liver disease, chronic kidney disease), current or recent use (within the past three months) of corticosteroids, known allergy or intolerance to curcumin, piperine, or turmeric-derived compounds, inability to comply with study procedures, or withdrawal of consent at any stage. Detailed inclusion and exclusion criteria are presented in Table 1.

Table 1. Inclusion and exclusion criteria of the current randomized controlled trial

Inclusion criteria	
Metabolic syndrome according to Cook et al. criteria (≥ 3 out of 5)	waist circumference (WC) $\geq 90^{\text{th}}$ percentile for age
	Blood pressure $\geq 90^{\text{th}}$ percentile for age and height
	Triglycerides ≥ 110 mg/dL
	HDL-cholesterol ≤ 40 mg/dL
	Fasting blood glucose ≥ 100 mg/dL
- Age between 7-18 - Informed consent	
Exclusion criteria	
Chronic systemic diseases	Malignancy
	Chronic liver disease
	Chronic Kidney Disease (CKD)
- Use of corticosteroids - Known allergy to turmeric/black pepper - Intolerance to administered supplement - Withdrawal of consent	

2.3. Randomization and Allocation Concealment

Participants will be randomized 1:1 to the intervention or placebo group using block randomization with variable block sizes of 4 and 6, generated by Sealed Envelope Ltd. This approach ensures balanced group sizes throughout the recruitment period while maintaining unpredictability. The sequence generated by the website will code the intervention and placebo groups as A and B. These codes will be written on separate sheets in sequential order, folded to conceal the contents. After obtaining informed consent from the patient and parents, a sheet will be drawn in sequence, and the participant will be assigned to the corresponding group. Assignment and enrollment will be conducted by a trained nutritionist at the pediatric endocrinology clinic.

2.4. Blinding

The placebo tablets will be identical in shape, color, size, and packaging to the active tablets, ensuring that participants are unaware of their group assignment. Both curcumin and placebo tablets will be film-coated to mask any odor. Identical packaging and coding (A/B) on checklists—rather than labeling groups as curcumin/placebo—will ensure that the physician and outcome assessors are blinded. Data will be entered into SPSS software using codes, so the data analyst will also remain blinded.

2.5. Study Intervention

Participants in the intervention group will receive one tablet containing 500 mg curcumin and 5 mg piperine daily for three months. The dosage was selected based on previous pediatric and adult studies that

demonstrated acceptable biological activity and safety profiles (25, 26). Piperine is included to enhance curcumin bioavailability. The three-month supplementation period is considered sufficient to detect changes in metabolic and biochemical variables while remaining feasible and safe for the pediatric population.

Participants in the placebo group will receive tablets identical in appearance, size, color, and packaging, containing microcrystalline cellulose. Both curcumin and placebo tablets will be provided by Sami-Sabinsa Group Limited, India. All participants will receive standard advice on healthy eating habits, physical activity, and sleep, along with nutritional education. The intervention period is three months. Monthly phone calls will reinforce adherence to medication, physical activity, sleep, and nutritional recommendations. To ensure product consumption, participants will be verbally queried about the number of pills taken.

All participants will receive standard advice on healthy eating habits, physical activity in accordance with age-appropriate recommendations. Providing lifestyle advice to both groups is ethically necessary and reflects standard clinical practice. This approach also allows for assessment of whether curcumin-piperine supplementation provides benefits beyond lifestyle modification alone. For blood tests, participants will be asked to fast for 8 hours. To control for circadian effects on biochemical variables, blood samples will be collected between 8:00 and 10:00 AM.

Figure 1 outlines the trial process according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

TRIAL PERIOD					
	Enrollment		Post-Randomization		
TIME-POINT	T ₁ to 0	0	Month 1	Month 2	Month 3
ENROLLMENT					
Eligibility screen (Inclusion/Exclusion criteria)	X				
Informed consent	X				
Randomization		X			
Demographic data and baseline assessment		X			
INTERVENTION/ COMPARATOR					
Piperine -Curcumin		X			X
Placebo		X			X
ASSESSMENTS					
Anthropometric measurements		X			X
Blood pressure		X			X
Fasting blood glucose		X			X
Fasting insulin		X			X
HbA1c		X			X
Lipid profile		X			X
Liver enzymes		X			X
HOMA-IR		X			X
QUICKI		X			X
Adverse events		X	X	X	X
Intervention adherence		X	X	X	X

Figure 1. Trial process (enrollment, randomization, and assessments)

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; QUICKI: quantitative insulin sensitivity check index

2.6. Measurements and Outcomes

At baseline, a checklist will record age, sex, history of underlying disease, and medication use. A physical examination will be performed, and criteria for metabolic syndrome will be assessed. Baseline systolic and diastolic blood pressure, height, weight, waist circumference, and hip circumference will be recorded (weight-for-age percentiles will also be noted). All anthropometric and clinical measurements will be repeated after three months of intervention.

Waist and hip circumferences will be measured according to World Health Organization standard protocols (28). Waist circumference will be measured at the midpoint between the lower edge of the last palpable rib and the top of the iliac crest. Hip circumference will be measured at the maximum prominence of the buttocks. Both measurements will be taken using a tension-resistant tape measure, recorded twice at the end of natural expiration to the nearest 0.1 cm. If the two measurements differ by more than 1 cm, a third measurement will be taken, and the average of the two closest readings will be used. Percentiles for waist and hip circumferences will be calculated using validated reference tables for Iranian children (29).

Blood pressure will be measured using the Arm Style Electronic Blood Pressure Monitor BW-3205. Participants will be seated on a chair with their back fully supported, and the arm placed on a table at heart level, palm facing up, with no tight sleeve constriction. Children will be instructed to remain seated quietly for at least five minutes before measurement. The cuff (size 22–36 cm) will be placed on the arm, 2–3 cm above the elbow crease (30). Primary outcomes include: a) improvement in metabolic syndrome status (according to Cook et al. criteria (27)); and b) body mass index (BMI).

Secondary outcomes include changes in anthropometric indices (height, weight, waist

and hip circumferences and their percentiles); systolic and diastolic blood pressure (and percentiles); and laboratory indices (total cholesterol, LDL-C, HDL-C, triglycerides (TG), fasting blood glucose (FBG), serum insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and HbA1c). We will also calculate the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI) using the following formulas:

$$\text{HOMA IR} = \text{Fasting Insulin } (\mu\text{U/ml}) \times \text{Fasting Glucose (mg/dl)} / 405 \quad (31)$$

$$\text{QUICKI} = 1 / (\log (\text{fasting insulin } (\mu\text{U/mL})) + \log (\text{fasting glucose (mg/dL)})) \quad (32)$$

2.7. Safety Monitoring

Participants will be monitored monthly for adverse events. Parents will be encouraged to report any symptoms or concerns promptly. All adverse events will be recorded and assessed for severity and potential relationship to the intervention. In the event of significant adverse events, study continuation will be re-evaluated by the study physician. To ensure adherence, pill counts and monthly telephone follow-ups with parents or caregivers will be conducted to inquire about missed doses and tolerability.

2.8. Sample Size Calculation

No previous study has specifically investigated the effects of curcumin on metabolic syndrome in children. The study by Di Pierro et al. (18) examined the effects of pure phosphatidylserine and curcumin complexed with phosphatidylserine plus piperine in phytosome form on anthropometric measures in adults with metabolic syndrome. Based on their data, BMI after two months was 26.2 ± 4.2 in the intervention group and 28.7 ± 3.4 in the control group. Assuming an alpha of 0.05 and beta of 0.2, the minimum sample size was calculated as 37 participants per group.

Accounting for a 10% attrition rate, the final recruitment target is 82 participants (41 per group).

2.9. Statistical Analysis

Data will be entered into SPSS software. To compare quantitative variables between the two groups, the t-test or Mann-Whitney U test will be used, depending on the distribution. Qualitative variables will be compared using the chi-square or Fisher's exact test. Analysis of covariance (ANCOVA) will be performed to adjust for potential confounders. A per-protocol analysis will be conducted using data from participants who complete both baseline and follow-up assessments. A significance level of less than 0.05 will be considered statistically significant.

2.10. Confidentiality

All participant information will be collected and maintained confidentially. Upon study entry, each participant will be assigned a unique identification code, and all clinical, laboratory, and questionnaire data will be recorded and analyzed using this code only. Identifiable information (name, contact number, medical record) will be kept separate from research data in a secure, locked location, accessible only to the principal investigator. Electronic files containing raw and analyzed data will be password-protected and accessible only to key research team members. Study results will be reported in aggregate, without individual identification, and no data that could identify participants will be published in articles, presentations, or reports.

3. Discussion

This protocol describes a randomized, triple-blind, placebo-controlled clinical trial. The prevalence of metabolic syndrome in Iranian children is higher than the global average, placing these children at elevated risk for cardiovascular disease in adulthood. Existing pharmacological interventions (e.g.,

metformin) in this age group have limitations. Despite growing interest in curcumin as a potential adjunctive treatment for metabolic disorders, evidence regarding its effects, particularly in combination with piperine, in the pediatric population is scarce. There is a need for a safe, accessible, and effective supplement with anti-inflammatory and antioxidant mechanisms. Therefore, this study is designed to investigate the effects of curcumin-piperine supplementation on anthropometric, clinical, and biochemical indices in children and adolescents with metabolic syndrome.

Curcumin, the active yellow compound in turmeric, is well known for its anti-inflammatory and antioxidant properties. Several studies have shown that curcumin supplementation can reduce BMI, weight, and waist circumference in adults with metabolic syndrome (19). Moreover, the combination of curcumin and piperine, which significantly increases oral curcumin absorption (33), may be effective in suppressing excessive caloric intake. However, several meta-analyses have found no significant changes in fasting blood glucose, insulin, or BMI following curcumin-piperine supplementation compared to placebo (34). Other natural interventions, such as probiotics, have also shown varying effects on metabolic syndrome components (35). For instance, in a clinical trial of obese adolescent girls, curcumin supplementation improved some measures, such as BMI and the triglyceride/HDL ratio, but no significant differences were found between intervention and placebo groups after adjusting for baseline variables (26). Thus, previous findings have been inconsistent.

To our knowledge, this is the first randomized controlled trial to investigate the effect of a curcumin-piperine combination on metabolic syndrome in children. The inclusion of piperine addresses the challenge of curcumin's low bioavailability. The three-

month intervention period is longer than many previous pediatric studies. The triple-blind, randomized, placebo-controlled design will minimize bias. The results of this study may play an important role in shaping future dietary and therapeutic interventions for children with metabolic syndrome. Furthermore, existing evidence suggests that combining curcumin and piperine can improve lipid profiles. For example, a meta-analysis found that this combination lowers total and LDL cholesterol levels in adults with metabolic syndrome (36). If our results support the study hypothesis, curcumin-piperine supplementation could be considered a potential adjunctive strategy for managing metabolic syndrome in children.

3.1. Limitations

This study has several limitations. Recruitment from a single center may limit the generalizability of findings to other settings and populations. In addition, no post-intervention follow-up is planned. The broad age range (7–18 years) includes children and adolescents at different developmental and maturational stages, which may introduce heterogeneity in metabolic responses.

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Ethical Considerations: Written informed consent will be obtained from parents or guardians. The study procedures will be fully explained to eligible participants and their parents, and written consent will be obtained prior to enrollment. The trial is registered before participant enrollment. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences on May 20, 2023 (approval code: IR.MUMS.REC.1402.079). Official registration in the Iranian Registry of Clinical Trials (IRCT) was obtained on June 18, 2023 (registration number: IRCT20181022041407N4).

Conflict of interest: None declared.

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