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Clinical efficacy of the co-administration of Turmeric and Black seeds (Kalongi) in metabolic syndrome — A double blind randomized controlled trial — TAK-MetS trial

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KEYWORDS
Black seeds;
Turmeric;
Co-administration;
Clinical efficacy;
Synergism;
Metabolic syndrome

Summary
Objective: To compare the clinical efficacy of Black seeds and Turmeric alone and its co-administration in lower doses among patients with metabolic syndrome (MetS).
Design: Double-blind-randomized-controlled trial.
Setting: Hijrat colony, Karachi, Pakistan.
Intervention: Apparently healthy males ($n = 250$), who screened positive for MetS, were randomized to either Black seeds (1.5 g/day), Turmeric (2.4 g/day), its combination (900 mg Black seeds and 1.5 g Turmeric/day) or placebo for 8 weeks. Main outcome measures: body-mass-index (BMI), body-fat-percent (BF%), waist-circumference (WC), hip-circumference (HC), blood pressure (BP), lipid-profile (cholesterol, HDL-cholesterol, LDL-cholesterol and TG), fasting blood glucose (FBG) and c-reactive protein (CRP).
Results: At 4 weeks, compared to baseline, Black seed and Turmeric alone showed improvement in BMI, WC and BF%. Combination improved all parameters except HDL-cholesterol with lower FBG and LDL-cholesterol as compared to placebo. At 8 weeks, compared to placebo, Black seeds reduced lipids and FBG, while Turmeric reduced LDL-cholesterol and CRP. Interestingly, combination group with 60% dose of the individual herbs showed an improvement in all parameters from baseline. When compared to placebo, it reduced BF%, FBG, cholesterol, TG, LDL-cholesterol, CRP and raised HDL-cholesterol.

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; HC, hip circumference; BP, blood pressure; Chol, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; BF%, body fat percentage; FBG, fasting blood glucose; CRP, c-reactive protein.

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Conclusion: Turmeric and Black seeds showed improvement in all parameters of metabolic syndrome, when co-administered at 60% of doses of individual herbs with enhanced efficacy and negligible adverse-effects. The combination of Black seeds and Turmeric can therefore, be recommended with lifestyle modification as a starting point for patients with MetS to halt its future complications and progression.

Introduction

Among non-communicable diseases (NCD), metabolic syndrome (MetS) is a major concern globally, specifically in South Asia, as it leads to a 2-fold increase in cardiovascular diseases (CVD) and a 1.5 fold increase in all-cause mortality.[1] Individual components are treated according to different consensus and guidelines, but for prevention and where there is no absolute indication for pharmacological intervention (obesity, pre-hypertension, low HDL-cholesterol and pre-diabetes), the first line of treatment is non-pharmacological which includes a healthy lifestyle, shown to reduce the incidence of MetS by 41% compared with placebo.[2,3]

Introducing early pharmacological treatment is controversial[4,5] as various pharmacological means used to prevent progression of MetS may not be compatible with each other. Several studies have supported the fact that lifestyle modifications are equally if not more effective in primary prevention of MetS and CVD.[6] Therefore, it is important to approach the individual components as a syndrome, rather than targeting clinical risk factors individually with aggressive pharmacological therapy, hence a multidisciplinary approach needs to be employed especially in primary prevention before the development of diabetes, hypertension and hyperlipidemia requiring definitive pharmacological therapies. It is also known that MetS might be more than the sum of its components, therefore, there is a need to use MetS criteria as endpoints for clinical trials. Trials using combinations of therapeutic interventions specifically targeted toward metabolic syndrome need to be conducted.[7]

The concept of complementary medicine is getting strength as evident by the fact that around 80% of the world population relies on complementary therapies mainly the herbs for its healthcare.[8] When dietary modification is of proven benefit as in the management of MetS, medicinal plants may serve as an adjuvant in the treatment and prevention of MetS as they contain a wide range of bioactive phyto-chemicals with diverse metabolic effects. These innovative dietary supplements can be proposed as the safe adjuvant treatments to reduce the progression, morbidity as well as the cost of treating MetS.[9] Moreover, use of complementary therapies is popular among patients with CVD risk as compared to the general population and among the most common complementary modalities used by individuals with CVD risk factors are natural products.[10] Similarly, natural products have contributed immensely in development of the modern medicine for cardiovascular disorders.[11]

Turmeric (*Curcuma longa*) and Black seeds (*Nigella sativa*) are some of the medicinal herbs which have been used for centuries and are acceptable to the public. We recently reported that the co-administration of these herbs produced enhanced effect in animal model of metabolic syndrome compared to when used alone.[12] The hypolipidemic and anti-oxidant effects of both the herbs are known,[13] although the combination has not yet been studied in a clinical trial for MetS.

In a study in Iran, 2 g/day of Black seeds per day given to patients with hypercholesterolemia for 4 weeks significantly reduced total cholesterol (Chol), low density lipoprotein (LDL-cholesterol) and triglycerides (TG) with no beneficial effects on fasting blood glucose (FBG) and high density lipoprotein (HDL-cholesterol).[14] Similarly, a 500 mg/day dose of powdered Black seeds administered with statin in dyslipidemic patients, improved the lipid profile more than with statin alone.[15] Black seed is known to reduce appetite, glucose absorption, hepatic gluconeogenesis, blood glucose, lipids and body weight as well as it simulates secretion of insulin from pancreas. It has also shown to improve glucose tolerance as efficiently as metformin with no significant adverse effects.[16]

Although Turmeric has been found to have some medicinal value in various diseases, but it is not well studied in its natural form; rather curcumin, an active principal of Turmeric has been widely studied.[17,18] Turmeric extract when given to hyperlipidemic obese patients, resulted in favorable effect.[19] Another trial reported that 3 months of Turmeric supplementation can decrease proteinuria, hematuria, and systolic blood pressure in patients suffering lupus nephritis[20] whereas another clinical study reported that ingestion of one dose of 6 g Turmeric increased postprandial serum insulin levels, but did not affect plasma glucose levels or glycemic index, in healthy subjects.[21]

In view of an emerging concept that herbs constituting combination of bioactive compounds possess ''effect enhancing and/or side-effects neutralizing'' properties,[22] we used the Black seeds and Turmeric in their natural form (powder) rather than their active constituents, shown in our lab recently to have synergistic interaction when used in combination.[12] On the other hand, animal studies have their impact on human health only when efficacy is proved in clinical studies.[23] Therefore, this study was aimed translating the beneficial effect of this animal study through a double blind randomized controlled clinical trial. Moreover, we aimed to see the effect of the combination among patients at risk of developing diabetes, hypertension and hyperlipidemia with no definitive indication for pharmacological management.

Methodology

Study setting and sample selection

Patients were recruited from a small community, Hijrat Colony, an urban—slum located at Mai-Kolachi, Karachi,