

Cardiovascular Benefits of Turmeric (Curcumin) in Humans: Evidence from Clinical Trials

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Abstract

Turmeric has been used for centuries in alternative system of medicine (ASM) for treating multiple ailments owing to its organoleptic, protective and therapeutic effects. Curcumin is a major active component of turmeric which is extracted from the dry rhizome of *Curcuma longa*. A major limitation to using curcumin as a therapeutic agent is its poor bioavailability.

Although numerous animal studies have shown promising cardiovascular benefits of curcumin, very few human studies have been conducted till date addressing the cardiovascular benefits of curcumin in humans. There is variability in curcumin metabolism between humans and animals limiting the validity and extrapolation of the results of animal studies to humans. This review consolidates the available evidence from human studies which have reported the effects of curcumin on various causative factors implicated in pathophysiology of cardiovascular disease. Positive results with curcumin were seen in studies reporting anti-inflammatory activity, antioxidant activity, effect on endothelial function, metabolic syndrome and in post cardiac surgery settings, with insignificant or mixed results in other factors studied. Larger and well randomized studies need to be conducted to establish the possible therapeutic role of curcumin, if any, in primary and secondary prevention of various cardiovascular diseases.

Keywords: Cardiovascular; Turmeric (Curcumin); Human trials

Introduction

Turmeric has been used for centuries in alternative system of medicine (ASM). It has been prescribed for the treatment of common colds, coughs, jaundice, and upper respiratory disorders for centuries. It is considered to be an extraordinary plant (rhizome) because of its organoleptic, protective and therapeutic effects in ASM.

Curcumin is a major active component of turmeric which is extracted from the dry rhizome of *Curcuma longa*. Turmeric contains approximately 2 - 3% (by weight) of curcumin. A major limitation to using curcumin as a therapeutic agent is its poor bioavailability, owing to inadequate absorption in the gut and as it is rapidly broken down and quickly excreted from the body [1].

Numerous animal studies have consistently shown the antioxidant, analgesic, anti-inflammatory and beneficial metabolic effects of curcumin. In this regard, very few human studies (mostly small sized) have been conducted till date. There is variability in curcumin metabolism between humans and animals. Thus, the results of *in vitro* and animal studies cannot be extrapolated to human physiology. Hence there is a need to conduct large scale human studies to establish the cardiovascular benefits of curcumin in humans. The various mechanisms of action of curcumin (implicated for the resultant cardiovascular benefits) are beyond the scope of this review.

In this review, an attempt has been made to consolidate the available evidence base (human studies) for cardiovascular benefits of curcumin in humans.

Anti-inflammatory effects

Inflammatory response plays an important role in the pathogenesis of atherosclerosis in humans. In animal experiments and human *in-vitro* experiments, curcumin has been proved to have anti-inflammatory effects. In this context several human studies have been conducted to establish the anti-inflammatory effects of Curcumin.

A meta-analysis of 8 randomised controlled trials (RCTs) in subjects with a variety of diseases showed that curcumin significantly lowered CRP levels compared with a placebo [2]. In another meta-analysis of RCTs, curcumin significantly reduced the circulating levels of TNF- α in blood [3]. In a meta-analysis of 9 RCTs in subjects with different diseases, curcumin significantly lowered IL-6 levels compared with control group [4]. In a prospective study, Curcumin supplementation for 8 weeks significantly decreased levels of TNF- α , IL-6, transforming growth factor beta (TGF- β) and monocyte chemoattractant protein 1 (MCP-1) compared with placebo [5]. In an another randomised, double-blind, crossover trial of 30 obese subjects, curcumin treatment for 4 weeks significantly decreased levels of IL-4, IL-1 β and vascular endothelial growth factor (VEGF) without differences in IL-2, IL-6, IL-8, IL-10, IFN γ , epidermal growth factor (EGF) and MCP-1, compared with a placebo group [6].

A multicenter double-blinded placebo controlled randomized trial was conducted in ACS patients to see the effect of curcumin on the inflammatory response (marker hsCRP) among ACS patients [7]. Patients were randomized into four groups receiving three different doses of curcumin and a placebo. The results of the study showed that low-dose curcumin group (after one week of use) experienced a significant decrease in the level of hsCRP compared to placebo during the first month. Also, Curcumin in low doses proved to be most effective in reducing the hsCRP levels, rather than moderate- or high doses in this study [7].

The average levels of hsCRP depend on the population studied. People living in some countries have a higher mean hsCRP levels as cut off. In a study conducted by Kamath., *et al.* an analysis of the hsCRP levels revealed a mean hsCRP value of 1.88 mg/l in the control arms of case-control studies, which is higher than the western population where values < 1 mg/l are classified as low cardiovascular risk [8].

Further studies need to be done in humans to specifically explore and establish the role of curcumin (as an anti-inflammatory agent) in the progression of established cardiovascular diseases in humans.

Antioxidant effects

Many studies have shown the potential of curcumin to prevent lipid peroxidation, a key process in the onset and progression of cardiovascular disease (CVD) (especially atherosclerosis). Curcumin exhibits a strong antioxidant activity and is a potent scavenger of a variety of reactive oxygen species, including superoxide anion radicals, hydroxyl radicals [9] and nitrogen dioxide radicals [10]. It has also been shown to improve systemic markers of oxidative stress [11]. Human studies though sparse have shown mixed results.

A recent systematic review and meta-analysis of randomized control data showed a significant effect of curcumin supplementation on all investigated parameters of oxidative stress including plasma activities of Super oxide dismutase (SOD) and catalase, as well as serum concentrations of glutathione peroxidase (GSH) and lipid peroxides [11]. A small uncontrolled study conducted by Yang., *et al.* also showed similar results [12]. In a randomised, double-blind, placebo-controlled, crossover study, 62 overweight women with high CRP levels were treated with turmeric for 4 weeks. Results showed no changes in the parameters of oxidative stress (F2-iso-prostanol, oxidised LDL-C) when compared with either the placebo or the baseline [13].

Further human studies need to be done to explore and establish the cardiovascular benefits of curcumin as an antioxidant in patients with established cardiovascular disease.

Effects on vascular smooth muscle cell proliferation

Huang and coworkers have studied the effect of curcumin on the proliferative responses of blood mononuclear cells and vascular smooth muscle cells in humans [14]. They reported that curcumin inhibited the proliferative responses to phytohemagglutinin in a dose-dependent manner and a mixed lymphocyte reaction had an inhibitory effect on the PDGF stimulated proliferation. Since the proliferation of vascular smooth muscle cells and mononuclear cells plays an important role in the atherosclerotic process, curcumin may be useful as a new template for the development of better remedies for the prevention of atherosclerotic diseases and vascular restenosis. Large *in-vivo* human studies need to be done to explore and establish the beneficial role of curcumin as an anti-proliferative agent.

Effects on endothelial function

Curcumin has a protective effect on endothelial dysfunction [15]. The improved endothelial function with curcumin treatment is attributable to several mechanisms including hypoglycaemic and hypolipidemic effects and anti-inflammatory, anti-oxidant activities [16]. In a randomised, controlled, double-blind parallel study on healthy subjects, curcumin supplementation for 8 weeks improved endothelial function as assessed by flow-mediated dilation (FMD) compared with placebo [16].

A similar study conducted by Usharani, *et al.* on diabetics given curcumin for 8 weeks showed significantly enhanced endothelial function (measured using digital plethysmography) with lower levels of malondialdehyde (MDA), ET-1, IL-6 and TNF- α compared with the baseline. These beneficial effects of curcumin on endothelial function through anti-inflammatory and antioxidant actions were comparable to those of a statin [17].

In a double-blind, parallel, randomised study of healthy middle-aged and older adults (45 - 74 years) curcumin supplementation for 12 weeks improved resistance artery endothelial function with enhanced forearm blood flow (FBF) to brachial artery infusion of acetylcholine (FBFACH) when infused with vitamin C following curcumin compared with baseline (but not with placebo in any variable). Curcumin also increased brachial artery flow mediated dilatation [18].

Akazawa, *et al.* investigated the effects of curcumin ingestion and aerobic exercise training on flow-mediated dilation as an indicator of endothelial function in postmenopausal women. The curcumin group ingested curcumin orally for 8 weeks. Flow-mediated dilation increased significantly and equally in the curcumin and exercise groups, whereas no changes were observed in the control group [19]. Curcumin ingestion had similar benefit (on endothelial function) as did aerobic exercise. This study suggested that curcumin can potentially improve the age-related decline in endothelial function.

Further human studies need to be done to explore and establish the benefits of curcumin on endothelial dysfunction in patients with established cardiovascular disease.

Effects on lipid homeostasis

The results of the studies done on effects of curcumin in lipid homeostasis are mixed. Among the studies done in that regard, seven RCTs had shown positive lipid profile changes, while ten of them showed no effect of curcumin on lipid profile [20]. Therefore, evidence of beneficial role of curcumin on lipid homeostasis is still lacking. A further meta-analysis of RCTs also showed no effect of curcumin on lipid profiles [21].

According to a 2017 position paper from an International Lipid Expert Panel [22], the lipid lowering effect of curcumin in human intervention studies is inconsistent, but several recent interventions report favourable effects on lipid profiles [23,24].

A randomized double blind interventional study was done in ACS patients to evaluate the effects of escalating doses of curcumin administration on various lipid levels in ACS patients with no significant difference in cardiac medications. The results showed a trend that the lower the dose of curcumin, the higher the effect of reduction on total cholesterol level and LDL cholesterol level. Similarly, lower doses of curcumin had higher effects of increase in HDL cholesterol level. However, for triglyceride (TGL) the pattern was not the same and the group of moderate-dose curcumin showed the minimal effect of increase, followed by the low-dose curcumin and finally the high-dose curcumin that showed the highest effect of increase in TGL levels [25].

With the available data from human studies no definitive recommendations can be made for curcumin as a lipid lowering agent for primary or secondary prevention of CVD.

Effects on blood pressure

In a study conducted by Santos-Parker, *et al.* [26] in diabetic subjects, ingestion of curcumin reportedly had no difference in blood pressure between placebo and curcumin-treated groups. No statistically significant differences were observed in the mean systolic and diastolic blood pressure between the two groups (curcumin and placebo) after 10 weeks of intervention. The possible reason is curcumin has no hypotensive effect on normal healthy subjects.

Effects on coronary artery disease

Atherosclerosis is considered a chronic and progressive disease arising from the inflammatory processes and oxidative stress within the vessel wall. The benefit of curcumin in the progression of atherosclerosis has been described in some animal studies.

A randomised double-blind trial involving diabetic subjects reported a decrease in CVD risk with 6 months of curcumin dietary supplementation, exemplified through a lower pulse wave velocity and improved metabolic profile [27].

In-vitro studies have shown that curcumin can prevent macrophages by inhibiting AMP kinase activator mediated signaling pathways in the human THP-1 cell line from being transformed into foam cells leading to the prevention of progression of atherosclerosis [28].

In a trial done to investigate efficiency of curcumin on some cardiovascular risk factors in patients with coronary artery disease (CAD), serum levels of triglycerides, LDL-cholesterol and VLDL-cholesterol were significantly decreased in the curcumin group compared to baseline, without significant changes in total cholesterol, HDL-cholesterol, blood glucose and hs-CRP levels. Although curcumin improved some of lipid profile components, it did not show appreciable effect on inflammatory markers in patients with CAD [29].

A randomized placebo controlled trial conducted by Panahi, *et al.* showed that curcumin supplementation (for 12 weeks) reduced the risk of developing acute cardiovascular events in diabetic patients complicated by dyslipidaemia [30].

It would have been more interesting if the above studies had also studied other biomarkers associated with CVD risk, like vitamin D to assess the CVD risk. In a study conducted by Kimball, *et al.* an optimal 25 (OH) D concentrations (≥ 100 nmol/L) was associated with significant reductions in CVD risk parameters [31].

Larger and longer duration human studies (with various CVD risk groups included) need to be conducted to document the effects of curcumin on the progression of atherosclerosis (for both primary and secondary prevention of CVD).

Effects on weight control

In a systematic review of 8 RCTs, three studies showed a favourable effect on weight control while the remaining five studies showed no effects of curcumin on weight control [32]. Given the findings from limited numbers of RCTs, curcumin at usual doses is unlikely to contribute to weight control.

Effects in metabolic syndrome

Curcumin has been shown to attenuate several aspects of metabolic syndrome (MS) by improving insulin sensitivity, suppressing adipogenesis, inflammation and oxidative stress. In addition, there is evidence that curcumin modulates the expression of genes and the activity of enzymes involved in lipoprotein metabolism that lead to a reduction in plasma triglycerides and cholesterol and elevate HDL-C concentrations [33].

In a randomized double-blind placebo-controlled trial, curcumin supplementation significantly decreased serum concentrations of pro-inflammatory cytokines in subjects with MS [34]. From the same study, the authors also reported improvement in the markers of oxidative stress. The authors concluded that short-term supplementation with curcumin significantly improves oxidative and inflammatory status in patients with MS. A study conducted by Panahi, *et al.* reported similar findings in their study in subjects with MS [5].

Effect on left ventricular function

In vitro studies have shown that curcumin possesses anti p300 activity, a histone acetyltransferase (HAT), which is increased in common types of heart failure (HF) where pathological cardiomyocyte overgrowth occurs in response to hemodynamic overload [35]. Human studies assessing the effects of curcumin on Left ventricular (LV) hypertrophy and LV function are sparse and few.

In a study conducted by Morimoto, *et al.* in hypertensive patients who received daily curcumin for 24 weeks there was improvement in diastolic function, fractional shortening and regression of LV hypertrophy (LVH). However, systolic and diastolic blood pressures did not change during this period. They concluded that curcumin regresses LVH and appears to improve LV systolic function as well as diastolic function independent of blood pressure in hypertensive patients [36].

Numerous other RCTs need to be conducted in humans to study the effect of curcumin on the LV function (systolic and diastolic) in various patient subsets (post MI LV dysfunction, dilated cardiomyopathy, HCM, LVH etc).

After cardiac surgery

A study was carried out on patients who underwent coronary artery bypass grafting (CABG) surgery, to evaluate the effect of curcuminoids in preventing myocardial infarction (MI) after CABG surgery. The results demonstrated that the in-hospital MI was decreased from 30% to 13% in placebo and curcuminoids treated group, respectively. In addition, in the curcumin-treated group, CRP, N-terminal pro-B-type natriuretic peptide (NT pro BNP) and MDA levels were also lowered [37].

In another clinical trial, curcumin pretreatment (45 mg/day, for 14 days) led to positive effects in children undergone corrective surgery for tetralogy of Fallot. Several parameters such as glutathione levels, monoaldehyde, caspase-3 expression, NF- κ B translocation, and activity of JNK were evaluated. The study revealed that there was substantial decrease of activated JNK protein from the pre-ischemia to the phase of reperfusion. Curcumin also suppressed the expression of caspase-3 in ischemia phase, and ameliorated myocardial performance, body temperature and oxygen saturation at 6-h stage. The authors recommended the plausible use of curcumin as a standard procedure before tetralogy of Fallot correction [38].

The benefits of curcumin demonstrated in the above studies are probably attributable to the anti-inflammatory and anti-oxidant properties of curcumin.

Need for Further Studies

In addition to the above stated cardiovascular diseases (CVDs), there is a need to conduct human studies in some of the CVDs (with beneficial effects being documented in some animal studies) with no published human data. Some of them include:

- Aortic diseases (aortic aneurysm (AA), post op recovery in AA surgery)
- Pulmonary arterial hypertension (especially PAH)
- Arrhythmias (particularly atrial arrhythmias)
- Heart Failure (particularly HF_{rEF}).

Conclusion

Although curcumin exhibits pleotropic beneficial effects and appears to have a significant potential in the treatment of multiple human diseases that are a result of inflammation and oxidative stress, the results of animal studies have not been reproducible in the human studies conducted so far, for cardiovascular benefits. Nevertheless, Curcumin stands out to be a potential therapeutic agent for cardiovascular diseases by virtue of its anti-inflammatory and anti-oxidant properties. Large scale, randomized controlled clinical trials need to be conducted to unravel and establish the cardiovascular benefits of curcumin as a therapeutic agent in real life clinical practice.

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