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Curcumin: Phytochemical Therapy in the Treatment of Hyperlipidemia

Pehlivanović B.[a], Bečić F.[a]

[a]*Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University of Sarajevo*

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Abstract: In modern world, hyperlipidemia is the most common disorder mainly caused by lifestyle habits and the major cause of cardiovascular, coronary and atherosclerotic changes. Such disorder is characterized by abnormally elevated levels of any or all lipids or lipoproteins in the blood. A wide range of drugs are available for the treatment of hyperlipidemia, class of antihyperlipidemic drugs, but such drug-therapies are carried out with presence of various side effects. In the last decades, different *in vitro* and *in vivo* research have been conducted to confirm the therapeutic effects of various phytochemical agents that overcome the side effects caused by synthetic drugs. According to Ayurvedic recommendations and experimental studies, numerous phytochemical agents have been reported to possess different antihyperlipidemic properties. One of the most studied phytochemical agent - curcumin, herbal polyphenol and active ingredient which can be extracted from the powder rhizome of the plant *Curcuma longa*, has been reported to possess a wide range of pharmacological properties such as antimicrobial, antioxidative, antiinflammatory and anticancer property. Recent studies also suggests curcumin as potential lipid lowering candidate in treatment of hyperlipidemia. The aim of this review is to present and discuss phytochemistry, molecular mechanism of hypolipidemic activity of curcumin, demonstrating its importance as potential therapy for the treatment of hyperlipidemia.

Corresponding author:
Pehlivanović Belma
E-mail:
belma.pehlivanovic@ffsa.unsa.ba
Tel: +38761335592

INTRODUCTION

Cardiovascular diseases are defined as “modern massive illnesses” due to their leading role in mortality worldwide. It is assumed that cardiovascular diseases will be the leading cause of mortality and disabilities by the year 2020 (Jorgensen *et al*., 2013). There are many risk factors associated with cardiovascular disorders such as age, sex, hypertension, hyperlipidemia, type 2 diabetes mellitus and metabolic syndrome.

Hyperlipidemia is the major and most common cause of cardiovascular disorders and it is described as a disorder of abnormal levels of lipids and lipoproteins in the blood (Durrington, 2003). Several studies have shown that low concentrations of low-density lipoprotein cholesterol and triglycerides are associated with low risk of cardiovascular disorders (Srikanth and Deedwania, 2016; Bhatt *et al*., 2010; Stone *et al.*, 2013). Therefore, appropriate and on-time treatment of hyperlipidemia is the most important prevention of cardiovascular disorders. A wide range of drugs, a class of antihyperlipidemic drugs, is available for the treatment of hyperlipidemia.

Modern pharmaceutical science has classified antihyperlipidemic drugs into five major classes that include statins, fibric acid derivates, bile acid binding resins, nicotinic acid derivatives, and drugs that inhibit cholesterol absorption (Dipiro *et al.*, 2008). The benefits of all those classes of drugs are well documented. There are efficient and well-tolerated drugs, but however, they possess various side effects. For instance, statins can cause myopathy, rhabdomyolysis and increased serum transaminase, and such substances can also cause kidney damage (Bellosta, Paoletti and Corsini, 2004). Due to such side effects, pharmaceutical industry seeks towards producing drugs with less side effects and discovering natural substances as alternatives to existing therapies.

Phytotherapy is a growing area of complementary medicine and natural products, phytochemicals are

becoming more popular than synthetic drugs due to their small range of side effects and low negative impact on the environment (Magi and Sahk, 2003). Phytochemicals, also referred as phytonutrients, are mainly found in vegetables, fruits, spices, nuts, herbs and seeds and are classified according to their chemical structures. The total number of phytochemicals is still unknown, so far the number of identified phytochemicals is about 10,000 (Zhang *et al.*, 2015). They occur in low concentration and demonstrate wide range of pharmacological activity (Watzl and Leitzman, 2012). For some of them, pharmacological studies have proven their impact in the modulation of cholesterol synthesis and absorption of lipids, while others have been shown to reduce blood pressure and inflammation processes (Yin *et al.*, 2016).

Evidence from epidemiological studies indicates a positive correlation between reduction in the incidence of cardiovascular disorders and consumptions of plant-based food rich with phytochemicals (Dauchet *et al.*, 2005). Recent findings show that phytochemicals possessing hypolipidemic properties may be the first choice in the treatment and prevention of hyperlipidemia (Sikder *et al.*, 2014). One of the most studied phytochemicals in the past decades is curcumin - natural product that can be extracted from the rhizome of the plant turmeric, *Curcuma longa* L. (Zingiberaceae). Boiled and dried plant's rhizome is mainly used as medicinal agent with a very specific yellow colour of the powder. In addition to its medical properties and because of such colour, powder is very often used as a coloring agents. The main components of turmeric are curcumin (60%), desmethoxycurcumin, monodemethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin. The main bioactive ingredient is curcumin with a wide range of pharmacological effects such as cell cycle arest, induction of apoptosis, and anti-inflammatory activity.

This phytochemical has been used as a traditional medicinal agent in Ayurvedic medicine for ~6000 years and its pharmacokinetic, pharmacodynamic and clinical pharmacological properties have been extensively studied (Aggarwal, Kumar and Bharti, 2003). Different scientific findings indicate that curcumin possesses a wide range of pharmacological properties. These studies indicated that curcumin acts as an antioxidant, anti-inflammatory and anti-atherosclerotic; inhibits scarring, cataract, and gallstone formation, promotes wound healing and muscle regeneration; prevents liver injuries and kidney toxicity; and exerts medicinal benefits against cardiovascular diseases, diabetes, Alzheimer's and multiple sclerosis. Additional studies on cardioprotective and anticancer properties of curcumin have been performed (Beevers and Huand, 2011). Srivastava *et al.* reported on the first evidences of curcumin against cardiovascular disorders. They studied the effects of curcumin on the induction of myocardial ischemia by the ligation of the left coronary artery. Their findings demonstrated promising results in the protection and prevention of the ischemia-induced elevation of malonaldialdehyde and lactate dehydrogenase release (Srivastava *et al.*, 1985). Numerous phytochemical candidates have been studied for the treatment of hyperlipidemia and prevention of cardiovascular diseases, but curcumin has demonstrated the highest antihyperlipidemic effects based on preclinical and clinical trials conducted with promising results.

Chemistry of Curcumin

Curcumin or diferuloylmethane is a symmetric, hydrophobic natural product with IUPAC name (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione. It was isolated in 1815 and its chemical configuration was described in 1973 by Whiting and Roughley. The chemical structure of curcumin is shown in Figure 1. It consists of two phenolic rings, each substituted with a methoxy ether functionality in the *ortho*-position. The two phenolic rings are connected via an aliphatic unsaturated heptane linker in *para*-position that also contains α, β diketone functionality on carbon-3 and -5.

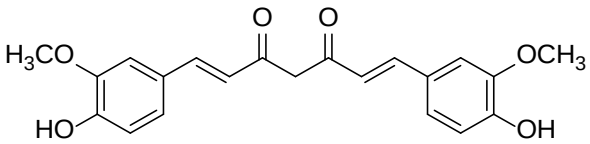

Figure 1: Chemical structure of curcumin.

Curcumin is an orange-yellow crystalline substance that is soluble in ketone, ethanol, dimethylsulfoxide, alkalis, acetic acid and chloroform and is insoluble in water. The absorption in the visible region of curcumin ranges from a maximum 410 to 430 nm, while the UV region has maximum absorption at 265 nm. Different studies have described tautomerization of curcumin and obtained results have demonstrated the ability of diketone functionality to undergo reversible tautomerization between enol and keto forms in pH-dependent manners (Payton *et al.*, 2007).

It has been showed that curcumin undergoes degradation in aqueous-organic solutions and that such degradation increases with increasing pH, thus limiting its use. However, when attached to lipids, surfactants, albumins, polymers and other macromolecular systems its degradations decreases (Priyadarsini, 2009).

The biosynthetic route of curcumin has proven to be very difficult to determine and there are two proposed mechanisms for curcumin biosynthesis. The first mechanism is explained as a chain reaction between cinnamic acid and 5 malonyl-CoA molecules that arylated into curcumin. While the second mechanism involves two cinammate units being bonded together by malonyl-CoA (Kita *et al*, 2008).

Molecular Mechanisms Of Curcumin

Since curcumin exhibits a wide range of pharmacological effects, it was very difficult and challenging for researchers to discover the primary molecular targets of the compound and mechanisms of action. Evidence indicates that curcumin affects multiple molecular targets and highly complex molecular mechanisms that depend on its capacity of interacting and regulating these targets.

So far, it has been described that curcumin targets transcription factors, kinases, inflammatory cytokines, enzymes, adhesion molecule, proteases, cell surface receptors, transporters and apoptotic factors (Aggarwal,

Kumar and Bharti, 2003). A variety of curcumin molecular targets is presented in Figure 2.

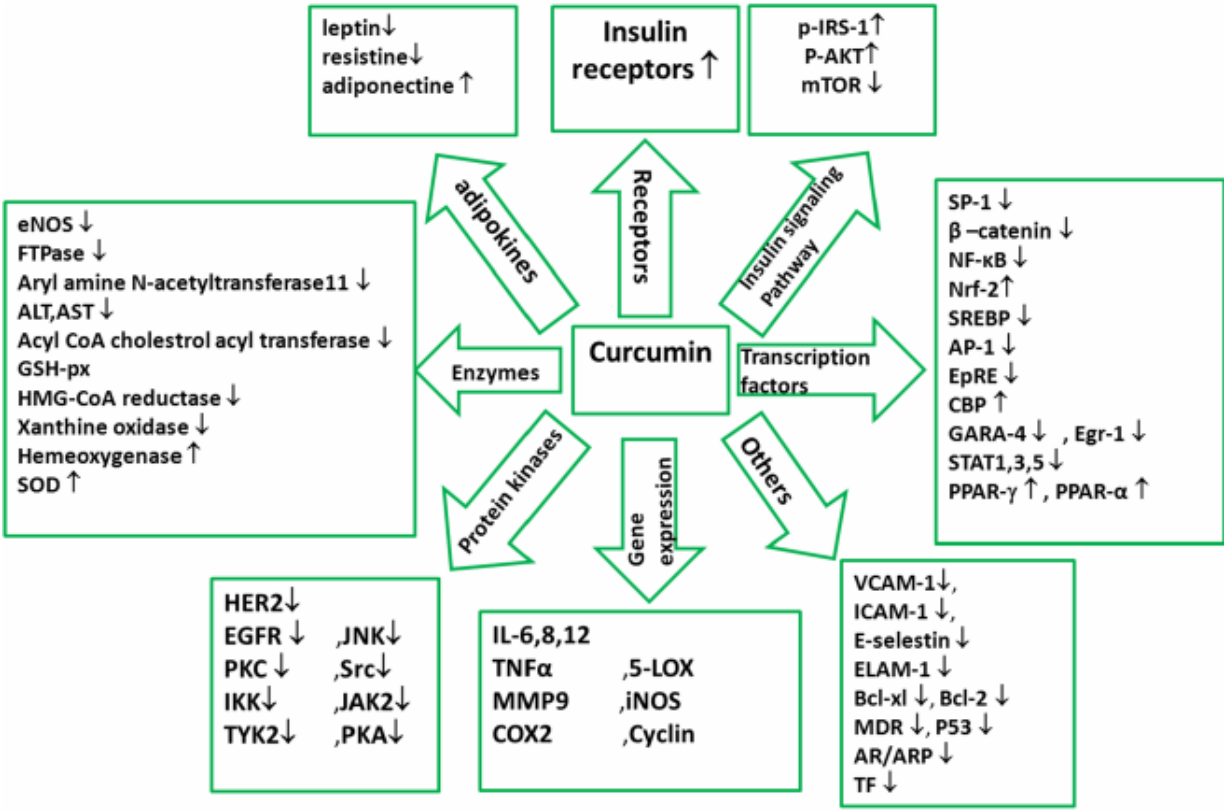

Figure 2: Different molecular targets effected by curcumin.

Transcription factors play a significant role in many metabolic processes and they can be induced or inhibited by many substances. Factors such as nuclear factor-κB (NF-κB), activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, hypoxia-inducible factor-1 (HIF-1), Notch-1, early growth response-1 (Egr-1) and β-catenin are being inhibited by curcumin via different molecular mechanisms.

On the other hand, transcription factors such as peroxisome proliferator-activated receptor-gamma (PPAR-γ), NF-E2-related factor (Nrf2), aryl hydrocarbon receptor (AhR), electrophile response element (EpRE) and aryl hydrocarbon receptor (AhR) are affected and activated by curcumin. Many of these transcription factors are involved in very important life processes such as cell survival, cell proliferation, inflammation and angiogenesis. As curcumin targets many of those factors, it has been suggested that all those processes can be modulated by its influence (Sharma, Gescher and Steward, 2005; Shishodia, Sethi and Aggarwal, 2005).

Besides the transcription factors, a significant role in the normal process of growth and differentiation is given to growth factors. Different growth factors are described as one of the molecular targets of curcumin that can be modulated and activated by curcumin, thereby exhibiting antiproliferative, anti-invasive an antiangiogenic effects.

It has been shown that curcumin inhibits lung adenocarcinoma PC-14 and pancreatic adenocarcinoma p34 cells proliferation by modulating extracellular receptor kinase (Soung and Chung, 2011).

Curcumin also has the ability of scavenging a variety of reactive oxygen species (ROS) that includes superoxide anion, singlet oxygen, nitric oxide and peroxynitrite. This ability provides curcumin a significant role in protection of lipids and DNA from oxidative degradation. All three forms of curcumin possess this ability, but the pure curcumin is a more potent scavenger than demethoxycurcumin or bisdemethoxycurcumin (Subramanian *et al.*, 1994; Kunchandy and Rao, 1990).

Evidence indicates that curcumin is involved in the lipid peroxidation process, which is the main trigger for the development of many cardiovascular disorders. Different *in vivo* and *ex vivo* studies confirmed the ability of curcumin to lower plasma lipid peroxides and reduce LDL vulnerability to the oxidation process. Further studies have also demonstrated antithrombotic effects of curcumin (Rao, 1994).

Molecular Mechanisms Of Hypolipidemic Activity Of Curcumin

In recent years, there has been a growing interest in the potential pharmacological effects of curcumin in the treatment of hyperlipidemia and prevention of cardiovascular diseases. It has been demonstrated that curcumin can be as effective in reducing total cholesterol and triglycerides as statins, drugs prescribed to patients with hyperlipidemia and atherosclerotic disorders.

Several *in vivo* studies were conducted on different animal models and majority of evidence demonstrate that the lipid-lowering potential of curcumin is due to the ability of curcumin to decrease the circulatory levels of lipid peroxidase, total serum cholesterol (TC), and increase the circulating levels of high density lipoprotein-cholesterol (HDL-C) (Fan *et al.*, 2006).

Animal study conducted on high-fat diet-fed hamsters has demonstrated that the feeding with curcumin leads to a significant reduction of hepatic cholesterol and

triglycerides (Um *et al.*, 2013). Therefore, it was assumed that curcumin interacts with molecular targets associated with the intestinal absorption of cholesterol and free fatty acids metabolism. Due to such evidence, it can be concluded that orally applied curcumin actually causes ameliorating impact on lipid profiles in subjects with hyperlipidemia.

Zhao *et al.* described that molecular mechanisms of lipid-lowering activity of curcumin are based on gastrointestinal intake of cholesterol from dietary substances and reduction of cholesterol transfer to the circulatory system. For such suggestion, Niemen-Pick C1-like proteins, which are located on the gastrointestinal epithelial cells, were studied as molecular targets and it has been proven that curcumin can suppress its expression (Zhao *et al.*, 2012).

Wassmann *et al*. suggested that curcumin can induce cholesterol efflux through the system of transcription factors such as peroxime proliferators-activated receptors (PPARs). These transcription factors are a series of ligand-activated factors which occur in three different isoforms of PPARα, PPARδ, and PPARγ. When PPARγ is activated by a certain ligand, it induces ligand X receptors (LXR-α) and these processes lead to reverse cholesterol transport (Wassmann *et al.*, 2002).

Furthermore, it has been shown that curcumin regulates the activity of cavelion-1, a protein that is able to form cholesterol transport complex with different elements in the cell membrane. Such complex became attached to free cholesterol and regulates transport of additional cholesterol to the HDL particles (Yuan *et al.*, 2008).

Recent findings suggest that curcumin is involved in the modulation of different enzymes and proteins, not just single target gene, as previously suggested. Intake of curcumin regulates enzymes cholesterol 7α-hydroxylase or cytochrome P450 7A1 (CYP7A1), leading to a reaction with PPARɣ, LXR, and RXR and biodegradation of cholesterol. Many molecular targets have been described as the primary targets of curcumin activity, which leads to reduction in plasma cholesterol concentration and modulation of enzyme CYP7A1 has so far shown the most significant reduction in cholesterol concentrations (Kim and Kim, 2010).

Peschel *et al.* have shown that curcumin induces HMG-CoA reductase expression, an enzyme involved in cholesterol synthesis (Peschel *et al.*, 2007), while Shao *et al.* suggested that curcumin decreased the enzyme activity of HMG-CoA reductase (Shao *et al.*, 2012).

Many enzymes involved in lipid metabolism undergo modifications by curcumin. Such an enzyme is AMP-activated protein kinase (AMPK) stimulated by curcumin to interrupt fatty acid synthetic pathway (Kim and Kim, 2010). Shao *et al.* have described that curcumin reduces the level of malonyl-CoA by stimulating carnitine palmitoyl transferase-1 (CPT-1) and involves in β-oxidation. Malonyl-CoA is formed during fatty acids synthesis, and inhibits CPT-1 used to transfer fatty acyl CoA into mitochondria for β-oxidation. These processes lead to interruption of fatty acids pathway synthesis (Shao *et al.*, 2012).

CONCLUSION

The overall assessment demonstrates that curcumin is a potential candidate for the treatment of different cardiovascular diseases due to its diverse and complex multi molecular targets. The interest in pharmacological properties and the use of curcumin is rapidly growing.

The pharmaceutical industry seeks more efficient solutions and focuses on natural products such as curcumin itself. Phytotherapy is becoming more popular due to demonstrated evidence on efficiency and safety of natural products. Curcumin can play a significant role in the treatment of hyperlipidemia due to its ability to reduce total cholesterol and triglycerides. Furthermore, curcumin can improve lipid profiles by different molecular mechanisms and secure its role as one of the protective cardiovascular agents. Current clinical trials will provide a deeper understanding of the therapeutic potential of curcumin in the treatment and prevention of hyperlipidemia and will help to place this fascinating molecule at the fore front of novel therapeutics.

DISCLOSURE:

The authors have no disclosures or other conflicts of interest to this paper.

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Summary/Sažetak

Povećana vrijednost lipida (hiperlipidemija) predstavljaju jedan od osnovnih faktora rizika u nastanku različitih kardiovaskularnih oboljenja. Medikamentozna terapija hiperlipidemija obuhvata veliki izbor lijekova iz grupe hipolipemika, koji su dokazano farmakološki efikasni lijekovi. Međutim, svaka medikamentozna terapija sa sobom nosi rizik od nastanka neželjenih dejstava usljed primjene određene količine lijekova. Posljednih godina, a s ciljem da se uklone ili smanje neželjena dejstva sintetičkih lijekova, prednost se daje ispitivanju prirodnih supstance ili fitonutritienata koji čine osnov fitoterapije utemeljene na dokazima. Kurkumin, aktivna supstanca iz biljke *Curcuma longa* L. je od davnina poznat po svojim ljekovitim svojstvima, te do danas privlači pažnju istraživača. Dokazano je da kurkumin ispoljava različita farmakološka djelovanja, uključujući i antihiperlipidemijsko djelovanje. Cilj ovog rada je opisati osnovna fitohemijska svojstva kurkumina, prikazati njegove osnovne molekularne mehanizme hipolipidemijske aktivnosti, te naglasiti opravdanost upotrebe kurkumina kao zamjenske ili dopunske terapije hiperlipidemija.