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REVIEW ARTICLE

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Curcumin as a potential candidate for treating hyperlipidemia: A review of cellular and metabolic mechanisms

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Curcumin is an herbal polyphenol extensively investigated for antioxidant, anti-inflammatory, and hypolipidaemic properties. In the present review, the efficacy of curcumin for improving a plasma lipid profile has been evaluated and compared with statins, a well-known class of medicines for treating hypercholesterolemia and hyperlipidaemia. Curcumin is presumably most effective in reducing triglyceride (TG), while statins are most efficient in lowering low-density lipoproteins-cholesterol (LDL-C). Additionally, various molecular and metabolic mediators of cholesterol and plasma lipid homeostasis are discussed in relation to how they are modulated by curcumin or statins. Overall, curcumin influences the same mediators of plasma lipid alteration as statins do. Almost all the pathways through which cholesterol trafficking takes place are affected by these agents. These include gastrointestinal absorption of dietary cholesterol, hepatocellular removal of plasma cholesterol, the mediators of reverse cholesterol transport, and removal of cholesterol from peripheral tissues. Moreover, the reactive oxygen species (ROS) scavenging potential of curcumin limits the risk of lipid peroxidation that triggers inflammatory responses causing cardiovascular diseases (CVD) and atherosclerosis. Taken together, curcumin could be used as a safe and well-tolerated adjunct to statins to control hyperlipidaemia more effectively than statins alone.

KEYWORDS
anti-oxidant, cholesterol, curcumin, lipoproteins, statins, triglyceride

1 | INTRODUCTION

Curcumin is a polyphenol extracted from the herbal rhizome powder of Curcuma longa known as turmeric (Goel, Kunnumakkara, & Aggarwal, 2008). It is putatively known as the foremost active ingredient responsible for a range of multifaceted biological properties, for example, antioxidant, anti-cancer, anti-inflammatory, cytoprotective, anti-depressant and hypolipidaemic features (Chattopadhyay, Biswas, Bandyopadhyay, & Banerjee, 2004; Esmaily et al., 2015; Panahi et al., 2015; Sahebkar, 2014b). For instance, the inhibitory effects of curcumin on oxidative stress, cancer progression, and inflammation have been well described (Takemoto and Liao, 2001). Furthermore, curcumin has been extensively investigated for its lipid-lowering effects. Given the aforementioned features, curcumin could be utilized as a potential candidate to control hyperlipidaemic-mediated disorders including atherosclerosis. Curcumin has been shown to be as effective in reducing plasma total cholesterol and triglycerides as statins, a well-known class of medicines prescribed for patients with hypercholesterolemia and related atherosclerotic disorders.

In the present review, a picture of total lipid metabolism is presented that is affected by curcumin and statins. In this regard, various cellular targets associated with lipid metabolism are discussed. To begin with, the efficacy of statins and curcumin are compared with regard to plasma lipid reductions. Subsequently, cellular pathways, cholesterol-cell receptors, and different apolipoproteins, nuclear receptors involved in lipid metabolism, as well as critical enzymes involved with lipid metabolism are addressed to elaborate the lipid-lowering potential of curcumin. For comparison, the same targets are also discussed for statins. Finally, the antioxidant potential of curcumin is followed in terms of lipid peroxidation, which is a precursor for triggering inflammatory responses, which, in turn, leads to progression of atherosclerosis.

1.2 | Effect of curcumin on serum lipid profile

There are controversial results about the lipid-lowering effects of curcumin and the mechanisms behind these effects have not been extensively studied (Yang et al., 2014). However, a majority of the current evidence suggests that the lipid-lowering potential of curcumin results from curcumin's ability to decrease the circulatory levels of lipid peroxides, total serum cholesterol (TC), and increase the circulating levels of high density lipoprotein-cholesterol (HDL-C) (Fan, Wo, Qian, Yin, & Gao, 2006b). Some evidence has shown that curcumin might hamper the absorption of dietary cholesterol (Baum et al., 2007; Yang et al., 2014), as it mitigated hypercholesterolemia induced in animals fed with high dietary cholesterol. In one study, curcumin was able to alleviate elevated levels of TC and triglyceride (TG) in rats fed with high-fat diet. However, no evidence was disclosed regarding the hypolipidaemic impact of curcumin on animals fed with a normal diet (Ravindranath and Chandrasekhara, 1980). Curcumin also led to a significant reduction in the plasma level of free fatty acids (FFAs), TC, and TG concentrations in high-fat diet fed hamsters, accompanied by increased levels of HDL-C (Jang et al., 2008).

Another study showed that curcumin caused a significant alteration in the serum lipid profile of healthy subjects. The level of TC and HDL-C were decreased and increased, respectively; while the serum TG level remained unchanged (Soni and Kuttan, 1992). Long-term daily intake of curcumin (for 30 days) significantly decreased the serum levels of TC, TG, and LDL-C and slightly increased the levels of HDL-C compared to the control group (Chandrakala and Tekulapally, 2014; Yousef, El-Demerdash, & Radwan, 2008).

In addition to the effects of curcumin on serum lipid profiles, it was demonstrated that curcumin feeding led to a significant reduction of hepatic cholesterol and TG concentrations in high-fat diet-fed hamsters (Jang et al., 2008). Moreover, curcumin significantly reduced hepatic total lipid levels in high-fat diet fed mice (Um, Hwang, Ahn, & Ha, 2013). Table 1 presents some experiments regarding serum lipid profile alteration of various subjects, including humans, after prolonged periods of daily oral consumption of curcumin. Given the evidence, one can certainly conclude that oral curcumin consumption indeed causes an ameliorating impact on adverse lipid profiles in subjects with hyperlipidemia. Therefore, curcumin must influence molecular targets associated with the intestinal absorption of either cholesterol and FFA's or their metabolism that will be addressed below as compared to statins; a well-known hypolipidaemic drug. The effects of curcumin on serum lipid parameters are shown in Table 1.

1.3 | Curcumin and statins and molecular targets

It has been suggested that curcumin may interfere in the gastrointestinal absorption of cholesterol from dietary materials and diminish

TABLE 1 The effect of curcumin on serum lipid profile

Dosage	Species	Treatment period	Cases status	HDL-C	LDL-C	TC	TG	References
50 mg/Kg/day	Rat	30 days	Ovariectomized	1.2%*	−2.8%*	−9.9%	−32.2%	Morrone et al. (2015)
100 mg/Kg/day				5.71%*	−11.84%*	−15.7%	−25.2%	
1890 mg/day	Human	3 months	Metabolic Syndrome	6.83%	−11.46%	−9.86%	−28,8%	Yang et al. (2014)
300 mg/day	Human	3 months	Overweight/obese type-2 diabetic patients	3.64%	−11.6%	−8.7%	−20.1%	Na et al. (2013)
0.02% w/w	Mice	18 weeks	LDLR-/-, atherogenic diet	30.76%	−11.3	−8.3%	−13.3	Shin et al. (2011)
500 mg/day	Human	7 days	Healthy subjects			−17%	−47%	Wang (2012)
6000 mg/day			Healthy subjects			−5%	−15%	
60 mg three times/day	Human	2 months	Acute coronary syndrome	7.70%	−15.40%	−0.30%	−20%	Wang (2012)
30 mg three times/day				7.70%	−3.40%	−0.20%	−10.3%	
15 mg three times/day				11.30%	−8.60%	−2.10%	−18%	
0.5 g/day		1 week		29%		12%		Baum et al. (2007)
0.05 g/100 g diet	Hamster	10 weeks	High fat diet	16.62%	−14.95%	−19.4%	−25%	Jang et al., (2008)
500 mg/day	Human	8 weeks	Metabolic syndrome	17.33	−13.06	−11.08	−8.00	Panahi et al. (2014a)
0.1% w/w of diet ad libitum	Rat	8 weeks	High fat diet	In-sig.	−68	−34	−27	Kim and Kim (2010)

cholesterol transfer from the intestine to the circulatory system (Baum et al., 2007). The molecular target studied for such a suggestion was found to be Niemen-Pick C1-like (NPC1) proteins, which are located on the gastrointestinal epithelial cells mediating cholesterol absorption. It was found that curcumin can suppress NPC1 expression in the intestine (Feng, Ohlsson, & Duan, 2010; Zhao et al., 2012). The cholesterol-lowering feature of curcumin could also be attributed to the suppression of NPC1expression in hepatocytes, as well as the up-regulation of the LDL receptor (LDL-R) on these cells (Feng et al., 2010).

As the Table 1 shows, curcumin is effective in reducing TG, LDL-C, and TC levels, but seemingly, it is ineffective in altering in HDL-C levels. This might be ascribed to the induction of scavenger receptor class B type I (SR-BI) in the liver that are responsible for "selective uptake" of HDL-C by hepatocytes. Both curcumin and statins have been shown to affect SR-BI expression.

Statins act as the competitive inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the major enzyme in cholesterol biosynthesis, leading to the overall reduction of whole body cholesterol. Competitive inhibitors of the reductase promote LDL receptor up-regulation on hepatocytes, which results in enhanced catabolism of plasma LDL and reduced plasma concentrations of cholesterol. Table 2 refers to various investigations demonstrating the lipid lowering features of two statins, rosuvastatin (Asztalos et al., 2002; Olsson, Pears, McKellar, Mizan, & Raza, 2001) and atorvastatin (Liao and Laufs, 2005; Schachter, 2005). The former is the newest, while the latter is one of the most prevalent statins currently prescribed, respectively.

TABLE 2 The effects of rosuvastatin and atorvastatin on serum lipid profile

Statin	Dosage	Species	Status	Treatment period	HDL-C	LDL-C	TC	TG	References
Ros*	10 mg/kg	Human	Metabolic syndrome	5 weeks	5.5	−49	−34	−23	Ooi et al. (2008)
	40 mg/kg				11	−57	−49	−41.5	
Ros	5 mg/kg	Human	Hypercholesterolemia (LDL-C 160 to <250 mg/dl)	12 weeks	6	−46	−35	−15	Olsson et al. (2002)
	10 mg/kg			12 weeks	8	−50	−40	−19	
Ator[a]	10 mg	Human	Hypercholesterolemia (LDL-C 160 to| <250 mg/dl)	12 weeks	6	−39	−32	−16	
Ator	5 mg/kg	New Zealand White Rabbit	Chow-fed (normal fed)	3 weeks	−4	–	−45	−13	Rashid, Uffelman, Barrett, and Lewis (2002)
Ator	First 4 weeks: 20 mg/kg/day	Human	Coronary heart disease (CHD)	12 weeks	6	−36	−30	−13	Asztalos et al. (2002)
	Second 4 weeks: 40 mg/day)				7	−45	−38	−27	
	Third 4 weeks 80 mg/day				5	−50	−41	−35	
Ros	10 mg/kg/day	Human	Hypercholesterolemia	6 weeks	14	−50	−35	−10	Olsson et al. (2001)
	20 mg/kg/day				10	−57	−40	−23	
					10	−63	−45.5	−28	
					13	−65	−47	−23	
Ros	5 mg/kg/day	Human	Hypercholesterolemia	12 weeks	6	−42	−30	−12	Wong et al. (2008)
	10 mg/kg/day				7	−49	−34	−18	
Ros	10 mg/kg/day	Human	Hypercholesterolemia Patients (with LDL-C levels ≥ 130 mg/dl) and with low fat diet.	2 months	Non sig.	−44.5	−31	−10	Koh et al. (2013)
Ros	20 mg/day	Human	acute ischemic stroke	14 days	−2.69	−51.46	−36.2	12.7	Heo et al. (2016)

[a]Ros and Ator are for rosuvastatin and atorvastatin, respectively.

The statins appear to induce greater serum reductions in TC and LDL-C levels than TG. Comparing the results with those of Table 1, curcumin seems to be more efficient in reducing TG rather than TC and LDL-C.

Similar to curcumin, the statins promote slight or non-significant increases of HDL-C that could be attributed to SR-BI up-regulation in the liver. It infers that SR-BI promotes "selective uptake" of cholesterol from HDL-C by hepatocytes. As a result, the levels of HDL-C and HDL proteins, such as apolipoprotein A1 (apo A1), remain almost constant upon treatment with curcumin and statins (Cuchel and Rader, 2006). ATP-binding cassette transporter (ABCA1), also known as the cholesterol efflux regulatory protein (CERP), mediates the efflux of cholesterol and lipids from liver, small intestine, and adipose tissues to lipid-poor apolipoproteins, that is, apo-A1 and E, which brings about the formation of HDL. Although curcumin and statins were determined to be effective in inducing both apo-A1 and ABCA1 up-regulation (Dong et al., 2011; Wassmann et al., 2002; Wong, Quinn, Gelissen, Jessup, Brown, 2008; Zhao et al., 2012), a remarkable elevation in HDL-C concentration was not found following administration of statins or curcumin.

Overall, statins show an affinity of 8,000 times greater than the natural HMG-CoA substrate for binding with HMG-CoA-reductase. They are more capable of reducing plasma cholesterol concentration than curcumin, but some adverse effects have been reported for statins such as myopathy, which necessitates screening alternative medicines with more minor side-effects like curcumin (Calderon, Cubeddu, Goldberg, & Schiff, 2010; Simic and Reiner, 2015).

As it can be deduced from the comparison of the materials listed in Tables 1 and 2, curcumin exerts a remarkable lowering effect on TG and cholesterol, which can be used for the treatment of hypertriglyceridemia and hypercholesterolemia. Furthermore, it appears that high concentrations of curcumin are well tolerated, as there has not been any dose-limiting toxicity observed (Sharma et al., 2004). Accordingly, curcumin might be suited for treating hyperlipidemia and associated disorders like atherosclerosis as co-therapy with statins in order to attain optimum therapeutic responses. Curcumin may synergistically reduce total serum lipid in patients and reduce the effective doses of statins needed as well as their adverse effects. Considering such justifications, it is plausible that curcumin be investigated with scrutiny in terms of mechanisms involved in curcumin's hypolipidaemic properties.

1.4 | Curcumin effects on the component involved in reverse cholesterol transport

Cholesterol is a necessary component of all animal cell membranes and plays a key role in maintaining the membrane's integrity. However, the peripheral tissues cannot utilize excess cholesterol; therefore, excess cholesterol needs to be removed from cells. The extra amount of cholesterol is transferred from the peripheral tissues to liver and intestinal tissues via a process called the "reverse cholesterol transport" (Ohashi, Mu, Wang, Yao, & Chen, 2005). Such a cellular cholesterol efflux is mediated via a multiple component mechanism, which begins with the efflux of cellular cholesterol to lipid-poor apolipoproteins through the engagement of ATP-binding cassette transporters ABCA1 and ABCG1/4, followed by HDL-C formation, and finally, HDL-C removal by SR-BI in the liver (Rosenson et al., 2012; Truong, Aubin, Falstrault, Brodeur, & Brissette, 2010). ABCA1, by facilitating export of intracellular cholesterol and phospholipids to the extracellular lipid poor apo-A1, has the leading role in cholesterol efflux to the liver and the intestine (Peschel et al., 2007).

It was reported that curcumin can promote cellular cholesterol efflux through the PPARγ-LXR-ABCA1 pathway (see next section) (Dong et al., 2011; Wassmann et al., 2002; Wong et al., 2008; Zhao et al., 2012). Peroxisome proliferators-activated receptors (PPARs) are a series of ligand-activated transcription factors with three different isoforms of PPARα, PPARδ, and PPARγ. Ligand activation of PPARγ leads to the primary induction of the ligand X receptors (LXR α), another family of transcription factors mediating cholesterol and fatty acid homeostasis, and to coupled induction of ABCA1. They all foster reverse cholesterol transport. Moreover, it was reported that curcumin can up-regulate caveolin-1, which forms a cholesterol transport complex along with other elements in the cell membrane. The complex directly binds to free cholesterol (FC) and transports additional cholesterol to the cholesterol acceptors such as HDL particles (Yuan et al., 2008).

With respect to HDL particles, it was shown that curcumin could also induce Apo-A1 expression, which mediates cholesterol transfer from cells to HDL particles (Jang et al., 2008; Ramırez-Boscá et al., 2000; Shin, Ha, McGregor, & Choi, 2011; Tian, Wang, Yu, Liu, & Li, 2012; Zhao et al., 2012). On the other hand, curcumin was found to increase the expression of SR-BI in the liver (Zhao et al., 2012) and modulating the removal of HDL-C by hepatocytes. Taken together, the aforementioned molecular modulation by curcumin expedites reverse cholesterol transport.

Although curcumin induces HMG-CoA reductase expression (Peschel, Koerting, & Nass, 2007), it was found that curcumin decreased the enzymatic activity of HMG-CoA reductase (Shao et al., 2012; Shin et al., 2011). In this regard, statins (Bjarnadottir et al., 2013) also manifested a similar effect as curcumin and it seems that the up-regulation of HMG-CoA reductase is a compensatory response to cholesterol reduction induced by curcumin or statins.

More than 60% of LDL clearance is mediated by the LDL-receptors or LDL-R (Brown and Goldstein, 1986). Curcumin was shown to be effective in inducing various LDL-R located on hepatocytes that leads to notable reductions of LDL-C in the circulation (Fan et al., 2006a,b; Peschel et al., 2007; Shao et al., 2012). Moreover, curcumin down-regulates the expression of apoB100 as the major apo-lipoprotein of LDL (Jang et al., 2008; Ramırez-Boscá et al., 2000; Shin et al., 2011).

Taken together, curcumin and statins were effective in increasing HDL-C and decreasing LDL-C levels in the circulatory system through the modulation of the aforementioned molecular targets. The functional similarity between curcumin and statins is related to the molecular components involved in "reverse cholesterol transport" and cholesterol metabolism as shown in Fig. 1.

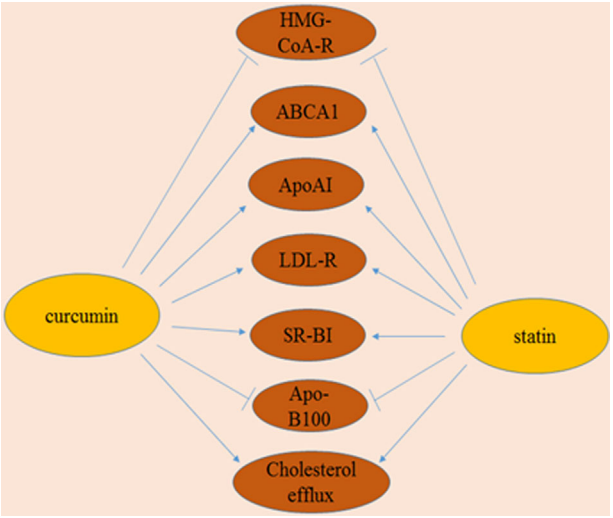

FIGURE 1 The similarity of functional hypolipidaemic features of curcumin and statins. They suppress the enzymatic activity of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol synthesis pathway They induce the expression of ABCA1, Apo A1, and SR-BI that are involved in reverse cholesterol transport via HDL-C particles. Further, they inhibit ApoB100 expression on the one hand, and induce LDL-receptors (LDL-R) expression on the other hand, resulting in a reduction in plasma LDL-C

1.5 | Curcumin modulates varying nuclear receptors implicated in serum lipid modulation

There are several nuclear receptors involved in cholesterol and FFA's homeostasis that have been determined to be modulated following curcumin treatment. These include the induction of LXRs, PPARs and sterol regulating element binding proteins (SREBPs), which regulate the expression of several genes involved in lipid metabolism (Table 3 and Fig. 2).

LXRs function as whole-body cholesterol sensors (Beaven and Tontonoz, 2006; Schmitz & Langmann, 2005) and these are best known for up-regulation of genes involved in cholesterol efflux from peripheral tissues such as ABCA1 (Wong, Quinn, & Brown, 2006). The two isoforms of LXR, that is, LXRα and LXRβ form heterodimers with the 9-cis retinoic acid receptor are also termed retinoid X receptors (RXR). Elevation of the cellular cholesterol content is usually accompanied by the over production of oxysterols, the oxygenated derivatives of cholesterol. Oxysterols are LXR agonists and their binding to LXRs leads to the activation of such nuclear receptors, whose target genes are engaged in the modulation of cholesterol and lipid metabolism (Niemi, 2010).

It has been stated that statins might affect LXRα activity via a two different mechanisms with counter-effect: (i) Statins could suppress LXR activity by the reduction of oxysterols (ligands for LXRα) and (ii) Statins could induce LXR via suppression of prenylation of multiple cellular proteins. Obviously, statins decrease the cellular cholesterol content and oxysterols (Maejima et al., 2004). To elaborate more, it has been proven that statins inhibit HMG CoA reductase activity, and as a consequence, decrease mevalonate, the precursor with 5 carbons, and the downstream products of the pathway, that is, isoprenoid units including farnesyl pyrophosphate (Fpp; having 15 carbons) and geranylgeranyl pyrophosphate (GGpp; having 20 carbons) as well as cholesterol . Prenilation (lipidation) of GTP-binding proteins such as Ras, Rac, and Rho family, leads to their translocation from the cytosolic compartment to the membrane, and subsequently their activation (Martin et al., 2001), where they can act as molecular switches, transducing a spectrum of extra-cellular signals, promoting cell survival, growth, and attenuating apoptosis (Jasińska, Owczarek, & Orszulak-Michalak, 2007). Statins via the reduction of RhoA activity, cause decreased phosphorylation and subsequently enhance activity of PPARγ as the modulator of the expression of LXR. Furthermore, GGPP can directly antagonize LXR activity. Therefore, mevalonate metabolites possess remarkable roles in the regulation of cellular cholesterol homeostasis (Argmann et al., 2005).

With respect to the nuclear receptors in Table 3, it was shown that curcumin, like statins, can activate PPARγ (Narala et al., 2009; Wong et al., 2008), yet the mechanism/s is not concisely clear (Narala et al., 2009). Curcumin might serve as either a direct ligand for PPARγ or, indirectly, induce the production of intracellular ligands of PPARγ (Dong et al., 2011). Both PPARγ and LXR are known to compete together to form heterodimers with RXR. Each of these heterodimerizations governs an array of gene expression involved in lipid and cholesterol homeostasis.

As with statins, the curcumin-cholesterol lowering potential can be attributed to the modulation of many enzymes and proteins rather than a single target gene. Curcumin feeding can lead to the up-regulation of cholesterol 7α-hydroxylase or cytochrome P450 7A1 (CYP7A1), the first and rate-limiting enzyme in the pathway of bile acid biosynthesis. In this regard, curcumin must somehow interfere in PPARɣ, LXR, and RXR cross-talk directing the expression of downstream target genes, as with CYP7A1, towards cholesterol biodegradation. Trans-intestinal cholesterol efflux and fecal excretion of bile acids is the leading mechanism for cholesterol elimination from the body. The up-regulation of CYP7A1 is an example of the biomolecular targets by which curcumin can result in the reduction of plasma cholesterol concentrations (Kim and Kim, 2010).

SREBP-2 is another nuclear receptor that is completely implicated in sterol metabolism (Table 3). Reduction of the cellular cholesterol load leads to proteolytic activation of SREBP-2 (Sato, 2010). Up-regulation of genes involved in cholesterol biosynthesis and uptake have been considered as the leading roles of SREBP-2 (Wong et al., 2006). Thus, it is expected that a reduction of cellular cholesterol content by curcumin and statins activates SREBP-2 as a compensatory mechanism for cholesterol reduction, and subsequently its target genes such as HMG-CoA reductase.

1.5 | Biomolecular modulating impacts of curcumin with respect to TG and FFAs

The TG-reducing function of curcumin could be related to the involvement of multiple factors that play key roles in TG and fatty acid homeostasis. These include PPARα, PPARγ, cholesteryl ester transfer protein (CETP), and lipoprotein lipase (LPL) (Yang et al., 2014). Curcumin could induce PPARα, a nuclear receptor with widespread

TABLE 3 Roles of different nuclear receptor

Factors	Role of the factor	References
PPAR γ	A nuclear receptor (disease targets of type 2diabetes) that is mainly expressed in adipose tissue and it is an essential component of "adipocyte differentiation program." In macrophages, it modulates differentiation and cytokine production. PPAR-γ has a central role in insulin sensitivity of adipose tissue and glucose metabolism. Its activity is governed by the binding of small lipophilic ligands such as polyunsaturated fatty acids, derived from nutrition or metabolism and 15-deoxy-$\Delta^{12,14}$ -prostaglandin J2 (15d-PGJ2). Synthetic ligands such as thiazolidinediones (TZDs) also activate PPAR γ. Upon activiation, PPAR γ forms heterodimers with the RXR, resulting in the up-regulation of ABCA1, ABCG1, LXRα, CD36 and cytochrome P450 oxidase or sterol 27-hydroxylase (Cyp27), These modulations encourage reverse cholesterol transport and their biodegradation to bile acids. It inhibits the production of inflammatory cytokines such as NF-kβ and matrix metalloproteinases (MMPs) in macrophages.	Kugimiya, Takagi, & Uesugi (2007); Rowe et al. (2003); Schmitz and Langmann (2005); Schultz et al. (2000); Tian, Zhang, Wang, & Li (2013) Wong et al. (2008)
PPAR-α	(Disease targets hypertriglyceridemia), primarily expressed in liver, promotes energy production through β-oxidation of fatty acids and therefore preventslipid accumulation in the cell. It also down-regulates SREBP-1c through suppression of LXR/RXR formation. Fibrates are its agonist. They are medicines for lowering triglyceride levels. It upregulates Apo-AI, Apo-AII and mitochondrial HMG-CoA reductase, down-regulates the Apo-CIII (inhibitor of lipoprotein lipase), and inhibits Acyl-CoA cholesterol acyltransferase (ACAT), which catalyzes cholesterol esters from acetyl CoA and cholesterol in endoplasmic reticulum . It interferes with the transcription factors of nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1).	Bloch (1945); Horie et al. (2010); Peschel et al. (2007); Um et al. (2013); Wong et al. (2008); Yoshikawa et al. (2003)
LXR	LXR-α shows tissue-specific expression with prominent activity in macrophages and liver and medium expression levels in intestine, adipose tissue, and kidney. In contrast, LXRβ is ubiquitously expressed. Oxysterols, the oxidized derivatives of cholesterol, are their ligands and they act as a major sensor of dietary cholesterol that promotes reverse cholesterol transport and bile acid production. Various enzymes and proteins associated with cholesterol and lipid metabolisms are modulated by LXRs, including varying members of ATP-binding cassette transporters such as ABCA1, ABCG1, ABCG5, ABCG8, the cholesterol ester transfer protein (CETP) that mediates triglyceride and cholesterol ester exchange between VLDL/LDL and HDL, cytochrome P450 7A1 (CYP7A1), an enzyme involved in bile acid generation, sterol regulatory element binding protein-1c (SREBP-1_C), and LXRα. The most likely endogenous ligand for LXR in macrophages is 27-hydroxycholesterol that is produced by CYP27.	Kugimiya et al. (2007); Rowe et al. (2003); Schmitz and Langmann (2005); Schultz et al. (2000); Tian et al. (2013); Wong et al. (2008)
SREBP-1	Primarily activates the fatty acid, triglyceride, and phospholipid synthetic pathways: SREBP-1c (the major SREBP-1 isoform in liver) activates transcription of the major genes coding for enzymes responsible for fatty acid synthesis including acetyl CoA carboxylase, fatty acid synthase, stearoyl CoA desaturase-1, glycerol-3-phosphate acyl-transferase as well as for members of the class B scavenger receptors of CD36 and SR-BI.	Peschel et al. (2007); Um et al. (2013); Wong et al. (2008)
SREBP-2	The prominent isoform supporting cholesterol synthesis and uptake: facilitates transcription of HMG-CoA reductase, LDL-R, ABCA1 synthesis in liver, but inhibits ABCA1 synthesis.	Horie et al. (2010); Peschel et al. (2007); Schmitz and Langmann (2005); Sato (2010); Wong et al. (2008)

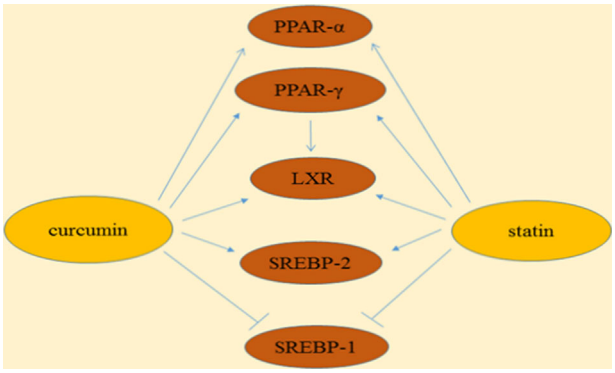

FIGURE 2 Curcumin and statins could modulate the expression of multiple principal nuclear receptors involved in fatty acid and cholesterol metabolism (see also Table 3). These include various isoforms of PPAR, LXR and SREBP, which mediates the modulation of many regulators and enzymes responsible for fatty acid and cholesterol metabolism (see also Table 3). Curcumin and statins could activate PPARα, which is the leading nuclear receptor in regulating fatty acids β oxidation. They could induce PPAR-γ as the main nuclear receptor in glucose hemostasis and insulin resistance. Moreover, curcumin and statins induce SREBP-2 activity, the master regulators of sterol metabolism, through the reduction of the cellular cholesterol content. On the other hand, curcumin and statins inhibit SREBP-1, the leading nuclear receptor promoting fatty acid synthesis

effects on genes related to mitochondrial fatty acid β-oxidation (Table 3) (Shin et al., 2011). On the other hand, it was shown that dietary curcumin significantly reduced the level of SREBP-1c, which acts as the main nuclear receptor involved in fatty acid biosynthesis (Heo et al., 2016; Shao et al., 2012), and inhibited nuclear translocation of SREBP-1 (Yuan et al., 2008). Conclusively, curcumin may shift the plasma TG and fatty acid status toward metabolism, rather than biosynthesis.

The activity of a few enzymes engaged in lipid metabolism has been investigated and whihc corroborates curcumin's function in affecting lipid metabolism. Curcumin can stimulate AMP-activated protein kinase (AMPK), which discourages the fatty acid synthetic pathway (Heo et al., 2016; Kim and Kim, 2010). Induced-AMPK suppresses acetyl CoA carboxylase (ACC) activity, the first enzyme in the pathway in the synthesis of fatty acids, which produces malonyl-CoA. Malonyl-CoA allosterically inhibits carnitine palmitoyl transferase-1 (CPT-1) which transfers long-chain fatty acyl CoA into the mitochondria for β-oxidation. Therefore, the reduced level of malonyl-CoA by curcumin is accompanied by CPT-1 activation and subsequently β-oxidation. (Ejaz, Wu, Kwan, & Meydani, 2009; Heo et al., 2016). Thus, dietary curcumin could possibly tailor fatty acid metabolism via concomitant induction of β-oxidation and a reduction in the biosynthesis of fatty acids. In this regard, statins behave similarly. They induce transcriptional activity of PPARα (Jasiñska et al., 2007; Takemoto and Liao, 2001) and subsequently induce the same effects as curcumin on the metabolism of fatty acids and TG.

Taken together, curcumin can lower the overall plasma lipids, including cholesterol and FFAs, which could coincide with decreased levels of lipid peroxides and oxidized LDL (ox-LDL). Therefore, curcumin can reduce the mentioned risk factors of inflammation, atherosclerosis, and cardiovascular disease (CVD). In this regard, the induced- PPARɣ potential of curcumin could impose the fatty acid translocase/cluster of differentiation 36 (FAT/CD36) up-regulation of the class B scavenger receptors family, where they can bind to and remove ox-LDL and lipid peroxides that form in the circulation. Furthermore, the direct anti-oxidant potential of curcumin may also be a contributory factor in curcumin's cardio-protective capabilities.

1.6 | The antioxidant, anti-inflammatory, and cardioprotective effects of curcumin

The aforementioned explanations offered for the anti-inflammatory and cardioprotective potential of curcumin attributed its properties to the coincident reduction of total plasma lipids and peroxidized lipids. However, the anti-atherogenic effects of curcumin arise from multiple mechanisms, including direct curcumin's antioxidant potential for scavenging various reactive oxygen species (ROS) (Shin et al., 2011). The putative linkage of free-radicals-to-blood lipid peroxidation, such as ox-LDL, is the major cause in the pathogenesis of atherosclerosis and cardiovascular diseases (Ramırez-Boscá et al., 2000). The cardio-protective properties of curcumin are primarily attributed directly to its inhibitory effects on inflammation and oxidative stress (Sahebkar, 2014a).

Oxidative stress arises from the excessive formation of ROS, which are endogenously formed as byproducts of metabolic reactions (Xu, Fu, & Chen, 2003). Curcumin has been shown to be effective in eliminating a variety of ROS including superoxide anion radicals, hydroxyl radicals, and nitrogen dioxide radicals (Maheshwari, Singh, Gaddipati, & Srimal, 2006). It is assumed that the unique conjugated structure of curcumin acts as a radical-trapping structure as well as a chain-breaking antioxidant (Chattopadhyay et al., 2004). Therefore, curcumin keeps the effective forms of antioxidant enzymes like superoxide dismutase, glutathione *S*-transferase, glutathione peroxidase, and catalase (Azza, El-Wakf, Elhabiby, & El-kholy, 2011; Chattopadhyay et al., 2004). Furthermore, curcumin inhibits xanthine-oxygenase activity; an important cardiovascular source of ROS (Elahi, Kong, & Matata, 2009; Haglund and Bergqvist, 1999).

The role of ROS in inflammatory processes is well studied (Anto, Kuttan, Babu, Rajasekharan, Kuttan, 1998). For instance, experimental studies have demonstrated that ox-LDL stimulates the release of leukocyte chemo-attractants from vascular endothelial cells that trigger vascular inflammation (Panahi et al., 2014b). Thus, there is a strong correlation between the anti-inflammatory and antioxidant activities of curcumin (Anto et al., 1998). Accordingly, curcumin could be generally regarded as a promising candidate for treating a number of inflammatory diseases (Aggarwal and Sung, 2009) and, in this regard, curcumin might interfere in inflammation processes via a combination of mechanisms (Rao, 2007).

Arachidonic acid-derived mediators, which have important roles in inflammation, aresynthesized through pathways where cyclooxygenase (COX) and lipoxygenase (LOX) enzymes are the rate-limiting enzymes (Rao, 2007). It has been shown that curcumin inhibited both

COX and LOX activity (Abe et al., 1999; Huang et al., 1991). The roles of LOX and COX isoforms, especially COX-2, have been well-documented in inflammation (Rao, 2007). Additionally, curcumin was demonstrated to inhibit induced ROS production by 12-O-tetradecanoylphorbol-13-acetate (TPA)- (Abe, Hashimoto, & Horie, 1999; Huang et al., 1991) and suppress high mobility group box 1 (HMGB1) mediated pro-inflammatory responses (Kim, Lee, & Bae, 2011). HMGB1 is a chromatin-modifying protein that is secreted from activated macrophages as a cytokine mediator of inflammation.

Nuclear factor-kappa B (NF-kB) is the preliminary transcription factor governing the signaling pathway in response to cellular stimuli including ROS, tumor necrosis factor-alpha (TNF-α), interleukin 1b (IL-1b), and bacterial lipopolysaccharides (LPS) (Panahi, Khalili, Hosseini, Abbasinazari, & Sahebkar, 2014a). NF-kβ is considered a critical mediator of the pro-inflammatory gene activation in endothelial cells and atherosclerosis (Jasińska et al., 2007). In this regard, curcumin was found to be effective in preventing ROS production and development of ROS-activated transcription factors, including NF-kB and activator protein-1 (AP-1), which is another transcription factor involved in inflammatory responses. The reduced production of pro-inflammatory cytokines, including TNFα, IL-1b, IL-8, monocyte inflammatory protein-1 (MIP-1a), monocyte chemotactic protein-1 (MCP-1), and C reactive protein (CRP) following curcumin treatment are some of down-stream signaling manifestations that could be attributed to the curcumin-mediated inactivation of NF-kB and AP-1 (Abe et al., 1999; Dhillon et al., 2008; Mirzabeigi et al., 2015).

The nuclear receptor NF-kB is kept sequestered in cytoplasm via attachment to the "Inhibitor of NF-kB" (IKB). Extracellular stimuli, such as pro-inflammatory cytokines, ROS, and mitogens lead to the activation of the IKB kinase complex (IKK), which phosphorylates IKB and this targets IKB for ubiquitination and degradation. It was shown that curcumin can promote phosphorylation of IkB-α by IKK and prevent NF-kB from entering into the nucleus (Aggarwal and Harikumar, 2009), where it can trigger the expression of pro-inflammatory cytokines. TNFα, IL-1b, and interferon γ (IFN-γ) are among the cytokines that could induce the synthesis of nitric oxide ($NO^{\cdot}$) by inducible nitric oxide synthase (iNOS). Moreover, it has been shown that curcumin can reduce sodium nitroprussid-induced $NO^{\cdot}$ generation by competing with oxygen and reduce the level of nitrite that emerges from the reaction between oxygen and $NO^{\cdot}$ (Rao, 1997).

ROS are produced from multiple metabolic pathways and they can readily initiate the peroxidation of membrane lipids (Shin et al., 2011) of cells and LDL (giving rise to ox-LDL formation) (Panahi et al., 2014b). The aldehyde groups of these lipid peroxides bind to the ε-amino groups of lysine residues of ApoB100, as the major Apo lipoprotein of LDL. The reaction prompts the uptake of modified LDLs by macrophages, which leads to the formation of fat-laden macrophages or foam cells, which are the indicators of plaque build-up or atherosclerosis (Miura et al., 1995). In this regard, curcumin was found to be effective in reducing the formation of ox-LDL, foam cells, and atherosclerosis. Moreover, curcumin might reduce cholesterol accumulation in foam cells by inducing proteasomal degradation of scavenger receptor type A (SR-A), which acts as the major ligand for ox-LDLs, as well as by inducing the ABCA1 expression in an LXRα-dependent manner (Lin et al., 2015). Both the anti-oxidant and related anti-inflammatory potency of curcumin is cited as the counter-causes

TABLE 4 The anti-inflammatory and anti-oxidant roles of curcumin and statins

Anti-inflammatory effects of curcumin	References	Anti-oxidant effects of curcumin	References
Inhibition of the pro-inflammatory transcription factors; NF-kB and AP-1 Reduction of the pro-inflammatory cytokines; TNFα, IL-1b, IL-6, IL-8, MIP-1a, MCP-1, CRP and PGE2 Inhibition of the enzymes such as COX- 2, 5 and 5-lipoxygenase Inhibition of mitogen-activated protein kinases (MAPK) and pathways involved in synthesis of nitric oxide synthase enzymes	Aggarwal & Sung (2009); Panahi et al. (2014a,b); Panahi, Saadat, Beiraghdar, & Sahebkar (2014c); Panahi, Sahebkar, Parvin, & Saadat (2012); Rao (2007); Xu et al. (2003); Vera-Ramirez et al. (2013)	Elimination of free-radical; thus maintaining the activities of antioxidant enzymes: superoxide dismutase, catalase, glutathione peroxidase, glutathione *S*-transferase, Inhibition of "xanthine-oxygenase" as the source of ROS in the cardiovascular systems. Inhibition of prostaglandin E2 (PGE2) production, Suppression of oxidative DNA adduct (M1G) formation.	Azza et al. (2011); Chattopadhyay et al. (2004); Panahi et al. (2014a); Sharma et al. (2004)
Anti-inflammatory effects of statins	References	Anti-oxidant effects of statins	References
Reduction of MCP-1 and IL-8, COX2, TNFα, IL6, IL-1β, CRP, GM-CSF, INFγ, Inhibition of NF-kβ, PAI-1. Down-regulation of the iNOS in macrophage and up-regulation of eNOS. Attenuation of P-selectin, down-regulation of CD40, ICAM-1.	Bonetti et al. (2003); Jasińska et al. (2007); Basraon et al. (2012); Kostapanos, Milionis, and Elisaf (2008); Liao and Laufs (2005); Morikawa et al. (2002); Stalker et al. (2001); Usui et al. (2003); Wong et al. (2008)	Reduction of NAD(P)H oxidase activity, by preventing isoprenylation of the small GTP-binding protein Rac, which is essential for NADPH activation Induction of the catalase activity Up-regulation of the heme-oxygenase-1, paraoxonase-1 activity, Up-regulation of glutathione synthesis. Down-regulation of the iNOS	Bonetti et al. (2003); Cerda, Hirata, & Hirata (2012); Erdös et al. (2006); Wassmann et al. (2002)

of atherosclerosis progression following curcumin treatment (Hansson, 2005; Libby, Ridker, & Hansson, 2009).

Similarly, statins were shown to exert both anti-oxidant (Wassmann et al., 2002) and anti-inflammatory responses (Basraon et al., 2012; Jasińska et al., 2007; Usui et al., 2003). Thus, in addition to their cholesterol-lowering role, statins prevent atherosclerosis progression through the same mechanisms as curcumin (Table 4).

It seems that trapping free radicals is the leading mechanism for anti-oxidant and anti-inflammatory properties of curcumin (Aggarwal, Surh, & Shishodia, 2007; Chattopadhyay et al., 2004). Statins may exert a variety of anti-inflammatory effects (Bonetti, Lerman, Napoli, & Lerman, 2003); however, it is mostly mediated via the suppression of adherent molecules on the vessel and leukocytes that promotes the recruitment of inflammatory cells to the atherosclerotic prone locations (Bonetti et al., 2003; Liao and Laufs, 2005; Stalker, Lefer, & Scalia, 2001). Regarding the efficient anti-oxidant, anti-inflammatory, and cholesterol lowering potentials of curcumin, it seems that curcumin, similar to statins, has a strong potential for the prevention of atherosclerosis.

2 | CONCLUSION

In summary, curcumin can play a significant role in improving the lipid profile and it seems that curcumin may act as a protective agent against atherosclerosis through the reduction of lipid peroxidation. The efficient anti-oxidant properties of curcumin, which give rise to the elimination of free radicals, prevent the progression of inflammatory responses. As a result, dietary curcumin could hamper the development of chronic diseases such as atherosclerosis Overall, curcumin could be considered a multifaceted agent as it alters the expression of many transcription factors and enzymes involved in cholesterol and lipid homeostasis as well as those that trigger lipid peroxidation and inflammation. Curcumin, for the most part, is as efficient as statins in the alteration of the lipid profile. In this regard, statins and curcumin target almost similar critical nuclear receptors and enzymes addressed in the current review. Nevertheless, statins are more effective in terms of lipid-lowering than curcumin. Given the side effects of statins, the synergistic effect of curcumin and statins could be used to more effectively treat patients with hyperlipidaemia.

DISCLOSURES

The authors have no discloures or other conflicts of interest to report.

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