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Review

Curcumin as a natural remedy for atherosclerosis: a pharmacological review

Laxman Singh [1], Shikha Sharma [2], SuowenXu [3,*], Devesh Tewari [2,*], Jian Fang [4,*]

[1] Centre of Biodiversity Conservation & Management, G.B.Pant National Institute of Himalayan Environment, Kosi-Katarmal, Almora, Uttarakhand, India; laxmansingh_13@yahoo.com

[2] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara-144411, Punjab, India; shikhasharma22012@gmail.com (S.S.); dtewari3@gmail.com (D.T,)

[3] Department of Endocrinology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, 230037, China; sxu1984@ustc.edu.cn (S.X)

[4] Department of Pharmacy, Huadu District People's Hospital, Southern Medical University, Guangzhou, China; lifegz@qq.com(J.F)

* Correspondence: lifegz@qq.com;sxu1984@ustc.edu.cn; dtewari3@gmail.com

Abstract: Curcumin (diferuloyl methane), a natural polyphenolic compound, is prevalent in *Curcuma longa* L. rhizomes, showing strong anti-oxidant, anti-inflammatory, anticancer and anti-atherosclerotic properties. Atherosclerosis is an umbrella term for a series of degenerative and hyperplasic lesions such as thickening or sclerosis in large and medium-sized artery walls that decrease vascular-wall elasticity and lumen diameter. The atherosclerotic cerebro-cardiovascular disease has become a major concern for human health in recent years. Curcumin concoction has been shown in studies to modulate several important signalling pathways related to cellular growth, proliferation, cholesterol homeostasis, inflammation, and transcriptions, among other things. Here, we provide an overview of Curcumin's underlying mechanism of action and protective effects against atherosclerosis.

Keywords: Curcumin; atherosclerosis; pharmacology; therapeutics

1. Introduction

Atherosclerosis is a common cause of cerebro-cardiovascular disease and is an age-related chronic large-artery disease that tends to occur in adult and aged patients [1]. The pathogenesis of atherosclerosis is extremely multifaceted. Numerous investigations have highlighted hyperlipidemia, diabetes, smoking, and hypertension, etc. to endorse oxidative stress causing damage to vascular endothelial cells, infiltration of low-density lipoprotein into the sub-endothelial spaces, monocyte chemotaxis and aggregation below the endothelium, and platelet activation leading to chronic inflammatory responses in vascular walls [2–5]. Atherosclerosis is the pathological basis for many cerebro-cardiovascular diseases and acute cerebro-cardiovascular events such as myocardial infarction and ischemic stroke, making it a serious public health concern. [6,7]. Anti-arteriosclerotic traditional Chinese medicines are widely used in Chinese clinical practice with a good safety profile and lasting efficacy [8,9]. Studies have found that many traditional Chinese medicines such as turmeric and ginseng have anti-atherosclerotic effects [10,11].

Turmeric prepared from the dried rhizome of Curcuma longa (family-Zingiberaceae) was enriched with numerous proven bioactivities and therapeutic applications. The roots of turmeric contain curcumin that has been used as a traditional drug to increase blood circulation and remove stasis [12]. Curcumin has lipid-lowering, anti-oxidative, anti-inflammatory, and anti-infective effects [13–15]. There is growing evidence that curcumin can regulate different signalling molecules to restrain the progression and development of atherosclerosis [16]. Similarly, it is also known to regulate inflammatory responses by inhibiting nuclear factor kappa B (NF-κB) expression in atherosclerotic plaques of aortic walls in domestic rabbits and alleviate the severity of atherosclerosis [16].

The mechanistic function of curcumin against atherosclerosis is due to its anti-inflammatory and anti-oxidative effects, inhibition of vascular smooth muscle cell (VSMC) proliferation and migration. Firstly, inflammation is involved in the entire process of atherosclerosis progression [17]. According to previous research, curcumin affects inflammatory cells and factors such as inflammation-related enzymes to exert its anti-inflammatory effects. [18,19]. Likewise, it blocks NF-κB signalling to diminish the production of vascular cell-adhesion molecules and inhibit interactions between leukocytes and endothelial cells [20]. Secondly, oxidative stress is a prominent marker molecule that initiates the development of atherosclerosis [21]. Oxidized low-density lipoprotein (oxLDL) is the central link in atherosclerosis [22]. Curcumin decreases the sensitivity of low-density lipoprotein (LDL) towards being oxidized, and thus decreases the amount of oxidized product to interact with the oxidized low-density lipoprotein receptor 1 (LOX-1) [23]. Curcumin can also down regulate inducible nitric oxide synthase activity to inhibit nitro-/oxidative-stress [24]. Thirdly, VSMC proliferation and migration to the intima causes intimal thickening in atherosclerosis. Specifically, neointimal responses associated with artery damage cause proliferation, migration, and collagen synthesis in VSMCs that may increase the susceptibility of blood vessels towards atherosclerosis [25]. Curcumin can increase PPAR-γ activity to inhibit the proliferation of VSMCs [26].

Additionally, epidemiological studies highlight that human cytomegalovirus (HCMV) infection is intimately coupled with the progression and development of atherosclerosis [27]. HCMV gene product can enter and damage vascular endothelial cells and alter their proliferation [28]. Oral administration of curcumin in ApoE-/-mice inhibits HCMV-protein expression and improves the cellular microenvironment in the host, thereby effectively preventing the development of atherosclerotic lesions [29].

2. Atheroprotective effects of curcumin in vitro

The potential of curcumin in counteracting force against various ailments has been widely studied, including atherosclerosis. Atherosclerosis is a chronic inflammatory disease resulting from arterial wall injuries; sustained due to dyslipidemia, diabetes, hypertension, etc. that leads to macrophage and VSMC-derived foam cell formation, endothelial cell dysfunction, and immune cell activation and platelet activation and thrombus formation [30, 31, 32, 33]. Several studies have demonstrated curcumin's potent therapeutic potential in preventing foam cell formation, modulating macrophage polarization, tuning cholesterol efflux, and regulating pro-inflammatory response [16, 34, 35, 36, 37, 38]. The anti-atherosclerotic property of curcumin is through suppressing macrophage polarization (M1 to M2) [39] or by inducing M2 polarization via IL-4 and/or IL-13 secretion in macrophages [40]. Similarly, convincing evidence suggests that curcumin when in action against macrophages treated with oxLDL, upregulates the expres-

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sion of thrombospondin-4 (THBS-4) [36] and modulates chemoattractant protein-1 (MCP-1) responsible for anti-inflammatory response [41]. The molecular targets of curcumin exerting anti-atherosclerotic effects involve upregulation of miR-126, which, in a way, further inhibits signal transduction and PI3K/AKT and JAK2/STAT5 activation [42]. Other targets include NF-κB inhibition in the M1 macrophage phenotype or by IκBα activation and, lastly, promoting M2 phenotype via PPAR-γ activation. Further, curcumin inhibits TLR4toll like receptor-4 (TLR4), MAPK and NF-κB signalling in macrophages and VSMCs [43] (Table 1).

Table 1. Evidence highlighting the potent potential of curcumin against atherosclerosis is confirmed by *in vitro* studies.

Experimental model	Curcumin concentration used	Outcomes and possible mechanisms of action	References
U937 monocytes cell-culture	0.01–1 μM	-Inhibits lipid peroxidation and inflammatory cytokine production at high glucose concentration	[44]
HMEC-1 cells	0.1–10 μM	- Reduce cell migration, viability, and repress MMP-2, MMP-9, and VEGF expression -Upregulates miR-126 expression and inhibits PI3K/AKT and JAK2/STAT5 signal transduction	[42]
ANA-1 mouse macrophage cell line	5–25 μM	-Curcumin at all concentration significantly decreased THBS-4 expression as induced by oxLDL	[36]
RAW 264.7 murine macrophages.		-Inhibits cell formation and CD36 expression level via p38 MAPK phosphorylation inhibition	[34]
H9c2 rat cardiac myoblasts	5–40 μM	- Activates p38-MAPK and JNKs, signalling pathways - Promote apoptosis by chromatin condensation	[36]
Human monocytic THP-1 cell line	7.5 – 30 μM	- Inhibits M1 macrophage polarization, cytokine production (IL-6, IL-12B, TNF-α) and decrease in TLR-4 expression - Inhibits ERK, JNK, p38 and NF-Kb phosphorylation, exerting anti-inflammatory and anti-atherosclerosis activity	[43]
Human THP-1 cell line	. 5 – 20 μM	- Reduce influx of oxLDL in THP-1 cells - Suppress CD36 and aP2expression	[9]
RAW264.7 macrophage	6.25 and 12.5 μM/L	- Increase cholesterol via Apo-A1 and HDL in M1 cells - Reduced ox-LDL induced cytokine production as well as M1 cell apoptosis-Upregulates CD36 and ABCA1 expression in M1 macrophages	[37]
Ba/F3 cells	10- 20 μM	- Inhibit TLR4 dimerization at the receptor level	[45]

		- Inhibits activation of MyD88 and TRIF-dependent pathways, thereby blocks NF-kB and IRF3 signalling	
RAW264.7 macrophages	6.25- 25 μM	-Inhibit M1 phenotype markers expression (i.e. iNOS, IL-1b, IL-6, and MCP-1) and up regulates IKBα expression	[46]
Raw264.7macrophage cell line	6.25- 50 μM	- Upregulates the expression of M2 markers such as MMR, Arg-1, and PPAR-, as well as macrophage M2 polarization via IL-4 and/or IL-13 secretion.	[40]
Murine macrophage RAW 264.7 cells	6.25, and 25 nM	- Repress titanium (Ti) particle-induced inflammation via modulating macrophage M1 to M2 polarization	[34]
RAW 264.7 cells	8-128 μM	- Inhibits lipid accumulation and MCP 1, TNF α, IL 6 production	[47]
Mouse peritoneal macrophages	10-50 μM	- Curcumin significantly reduced TLR4 expression and inhibited NF-Kb activation	[16]
Human THP1 cells	20 - 40 μM	- Curcumin inhibit HIF-1α induced apoptosis and inflammation of macrophages via ERK signalling pathways	[48]
Bovine aortic endothelial cells (BAECs)	5 μM- 15μM.	- When stimulated with TGF-β, curcumin inhibits the expression of ET-1mRNA in BAECs, which may influence the formation of atherosclerotic plaques	[49]
Raw 264.7 cells	0.1 -30 μM	- Repress IL-1β, IL-6, and TNF-α production	[50]
Human monocyte cell line THP-1	0 - 50 μM	- Curcumin attenuates MMP-9 and EMMPRIN expression via down regulation of NF-kB and p38 MAPK signaling	[51]
Human monocytic cell line THP-1	0 to 100 μM	-Curcumin inhibits MMP-9 and EMMPRIN expression via AMPK and PKC pathway down-regulation	[52]
Human monocytic cell line THP-1	10–20 μM	- Inhibit the PKC-δ/NADPH oxidase/ROS signaling and suppress matrix invasion	[53]
Human monocytic THP-1 cells	0–50 μM	- Suppress TLR4/MyD88/NF-kB and P2X7R signaling, and inhibit inflammasome expression	[54]
THP1-derived macrophage foam cells	0- 80 μM	- Promote cholesterol efflux via increased ABCA1 expression via AMPK-SIRT1-LXRa signalling	[38]
Human monocytic cell line THP-1	5.0 μg/mL	-Hydroxyl acylated curcumin under	[55]

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		low-intensity ultrasound increased apoptosis and necrotic effect on THP-1 macrophages, indicating son dynamic therapy for atherosclerosis	
VSMCs	5-30 μM	- Suppress oxLDL induced MCP-1 expression via p38 MAPK and NF-kB signaling	[56]
H9c2 embryonic rat heart derived cells	5–15 μM	-Enhance DOX-induced cells apoptosis via Bcl-2 repression and increasing expression of caspase-8 & 9	[55]
VSMCs	5- 30 μM	- Inhibits overexpression of MCP-1, TNF-α, NO and ROS production - Suppresses TLR4 activation and inhibits ERK1/2 and p38 MAPK phosphorylation	[58]
Raw264.7 cells	0–40 μM	-Inhibit MCP-1 production via the JNK and NK-κB signalling - Enhance cholesterol efflux via activating the LXR-α – ABCA1/SR-BI pathway	[59]
3T3-L1 fibroblast cells	0–30 μM	-Using Wnt/β-catenin signalling inhibits MAPK phosphorylation that leads to 3T3-L1 cells differentiation into adipocytes	[60]
VSMCs	1.25 - 5 μM	- Inhibits CRP protein production by modulating ROS-ERK1/2 signalling	[61]
Endothelial cells	10^{-5}mol/L	-Inhibit CD40 expression and inflammatory activity via miR-590-3p-dependent pathway	[62]
Cultured porcine coronary artery rings	5 μmol/L	-Blocks superoxide anion production mediated by eNOS down-regulation and reverses endothelial dysfunction	[63]
HUVEC cells	1, 10, 100 μM	-Reduce E and P-selectins expression and monocytes adhesion as induced by PM10 (3 μg/cm^2) and TiO2-NPs (10 μg/cm^2) -Attenuate oxidative stress activation as a result of PM10 particles and TiO2-NPs on endothelial cells	[64]
HUVEC cells	25 μM	- Inhibits COX-2 expression and prostaglandin production - Inhibits phosphorylation of PKC, p38 MAPK, and cAMP response triggering COX-2 expression	[65]
HUVEC cells	1- 25 μM	-Suppressed the expression profile of ROS species, LOX-1 receptor and adhesion molecules (VCAM-1 and ICAM-1) -Inhibits IκBα degradation and nuclear NFκB translocation	[66]

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HUVEC cells	2.5 - 100 μM	- TLR2 and TLR4 receptors that bind HMGB1 and cause an inflammatory response are downregulated. -Inhibits adhesion molecules and E-selectin expression that reconcile monocyte adhesion and endothelial migration	[67]
HUVEC cells	3 - 30 μM	-Inhibits NF-kB activation via TNF-α -Suppress intracellular ROS production, monocyte adhesion, JNK, p38 and STAT-3 phosphorylation -Attenuates expression profile of ICAM-1, MCP 1, and IL 8 at both mRNA and protein level	[68]
VSMCs	20 - 40 μM	-Diminish phosphorylation of p-RhoA/p-MEK1/2 and NF-κB signaling	[69]
VSMCs	-	Activates miR-22/SP1 signalling pathway and prevents Proliferation and migration of VSMCs	[70]
VSMCs	12.5 - 50 μM	Inhibits cholesterol accumulation via activating caveolin-1 expression that in turn negatively regulates SREBP-1 and prevents nuclear translocation	[71]
HUVEC cells	0.5 – 2 μM	-Inhibited HCMV replication and proliferation -Reduced intracellular ROS production, and diminished inflammatory cytokine production -Down-regulates HMGB1-TLR-NF-κB signalling	[29]
VSMCs	10 - 20 μM	Reduces NO production by inhibiting IL-6 and TNF-expression -Upregulate PPAR-γ activity and attenuates VSMCs proliferation	[34]
VSMCs	20 μM	Inhibits cell migration by negatively regulating NLRP3 expression via NFκB-mediated response and reduces IL-1β concentration	[26]

HMEC-1- Human micro-vascular endothelial; **PARP**- poly(ADP-ribose) polymerase; **MMR**- Macrophage mannose receptor; **Arg-1**- Arginase-1; **HIF-1α**- Hypoxia- inducible factor 1α; **TGF- β**- Transforming growth factor beta; **AMPK**- AMP-activated protein kinase; **PKC**- Protein Kinase C; **DOX-** Doxorubicin; **ET-1**- Endothelin-1; **TGF- β**- Transforming growth factor β; **PAR- γ-** Proliferator-activated receptor **γ;LXR- α** - Liver X receptor **α; SR-BI**- Scavenger receptor class B type I; **JAKs**- Janus activated kinases; **iNOS**- Inducible nitric oxide synthase; **MyD88**- Myeloid differentiation factor 88; **P2X7R**- Purinergic 2X7 receptor; **PKC**- Protein kinase C. **AD** – aldosterone, **CRP**- C-reactive protein, **HUVEC-** human umbilical vein endothelial cells , **LOX-1**- Lectin-like oxidized

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LDL receptor-1, **TEM**- Trans-endothelial migration, **HMGB1**- High mobility group box-1 , **MEK** ½-mitogen-activated protein kinase kinase ½, **JNK**- c-Jun N-terminal Kinase

TLR4, an important signalling receptor, has been actively reported in the pathogenesis of plaque formation and atherosclerosis development [72]. Furthermore, TLR4 activates a variety of signal transduction molecules as well as transcription factor activation. The important one being NF-κB and MAPK activation, that triggers nuclear transduction that simultaneously propels gene expression profile of inflammatory reaction. Amplified expression profile increases ROS production and inflammatory molecules, which cause the initiation of atherogenesis, finally destabilising atherosclerotic plaques [16]. Reports on curcumin supplementation foster negative regulation not only on TLR receptor but also on nuclear transduction molecules and inflammatory cytokines (TNF-α, IL-1β, VCAM-1, ICAM 1, etc.) are presented [73] (Figure. 1).

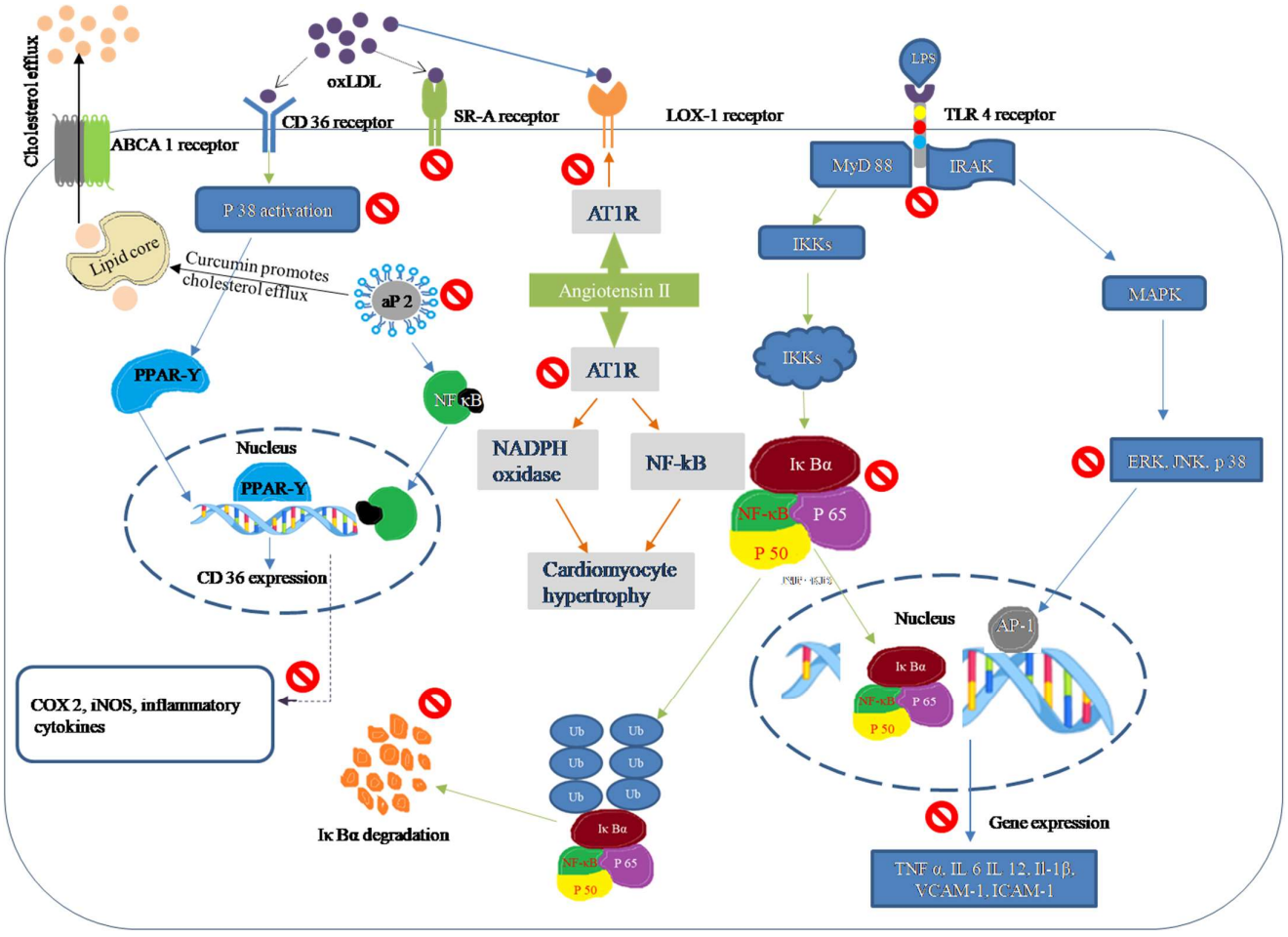

Figure 1. Pharmacological effects and mechanism of action of curcumin in atherosclerosis

Likewise, curcumin stalls ligand-induced and ligand-independent dimerization at the receptor level. LPS-induces activation of both MyD88-and TRIF-dependent signalling via TLR4 receptor. Upon curcumin supplementation and inhibition of TLR4 receptor, further molecular docking between receptor and NF-kB and IRF3 stimulation is examined [45]. In a similar fashion, curcumin inhibited the NOD-like receptor (NLR) family,

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the pyrin domain containing 3 (NLRP3) inflammasome via suppressing TLR4/MyD88/NF-kB, phosphorylation level of IkB-α and purinergic 2X7 receptor (P2X7R) pathways in Phorbol 12-myristate 13-acetate (PMA)-induced macrophages [54]. NLRP3 inflammasome is composed of a multiprotein complex having caspase and caspase 1 protein complex for apoptosis [74]. On NLRP3 complex stimulation, caspase-1 is activated that cleaves off the pro-forms of interleukin (IL)-1β and IL-18 into their mature forms. Once in fully mature form, IL-1β (a primary pro-inflammatory cytokine) mediates the development of atherosclerosis. Curcumin also inhibits cell migration in VSMCs by negatively regulating NLRP3 expression via an NF-B-mediated response and decreasing IL-1 concentration [54], halting atherosclerosis progression.

Likewise, curcumin supplementation in VSMCs markedly reduces inflammatory responses induced by LPS via TLR4 activation. This stimulation significantly increases phosphorylation of IκBα, NF-κB (p65) and MAPKs [58]. Concurrently, this increases the inflammatory cytokine expression profile of TLR4, MCP-1, iNOS, TNF-α, and NO production. In addition, Meng et al. (2013) [58] established curcumin supplementation inhibits TLR4 activation ERK1/2 and p38 MAPK phosphorylation and prevents NF-κB nuclear translocation that mediates ROS production. Thus, inhibition of the expression profile may reduce atherosclerotic plaque formation, and reduce plaque infiltration and progression. More recently, Zhang et al. [61] have shown that curcumin inhibited aldosterone-induced production of CRP in VSMCs by reducing ROS production via limiting aberrant activation of the ERK1/2 signal pathway.

LDL is another important pathological stimuli that contribute to atherosclerotic lesions. ROS modifies LDL, thereby producing Ox-LDL. An increase in Ox-LDL concentration in plasma has long been accredited as a key factor resulting in atherosclerosis development. Ox-LDL, instead of binding to LDL receptor, binds to scavenger receptors (SRs). The major SRs receptor is a differentiation 36 (CD36) cluster that recognizes ox-LDL [75]. ox-LDL on binding with CD36 receptor activates PPAR-Ɣ[76]. PPAR-Ɣ, once activated, dimerizes with the retinoid X receptor (RXR) and triggers PPAR-response element (PPRE) containing a gene which ultimately increases CD36 expression, resulting in more ox-LDL influx [77]. Cholesterol accumulation in macrophages results in foam cell formation and fatty streak development. Other channels/receptors used by macrophages to influx ox-LDL-related receptors include: SR-AI/II, SRBI, CD36, LOX-1, and TLRs. In contrast to this, various efflux transporters play an active role via ATP-binding cassette (ABC) transporters ABCA1, ABCG1, and SR-BI to overturn cholesterol transport from macrophages [78]. Fatty acid-binding protein (FABP)-4 or adipocyte protein 2 (aP2) coordinates cholesterol trafficking (efflux) but is also known to activate an inflammatory response. Lack of aP2 protein complex changes the cholesterol composition in macrophages, which concurrently amplify CD36 expression and enhance oxLDL influx [79]. This creates a diseased state whereby macrophages induce the release of IL-1β, TNFα, ROS, and metalloproteases coupled with the development of inflammation, cell migration, and plaque formation (Figure. 1). Hence, reducing or total inhibition of aP2 and CD36 expression might offer protective and remedial promise to atherosclerosis development.

Several lines of experimental evidence have highlighted curcumin's potent anti-atherogenic effects over the years (Table 1). Zhou et al. (2014) [36] demonstrated curcumin reduced the expression profile of oxLDL-induced Thrombospondins-4 (THBS-4). THBS-4 was reported to influence important cellular responses like cell migration, proliferation and adhesion, leading to atherogenesis progression [80] . Curcumin further in-

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hibits p38 MAPK activation; reduces PPAR-Y and CD36 expression in oxLDL-treated macrophage, resulting in decreased foam cell formation [76]. In human umbilical vein endothelial cells (HUVECs), curcumin inhibits ROS production, inhibits LOX-1 and NF-κB expression, inhibits adhesion (VCAM-1 and ICAM-1) molecules and promotes NO production [66]. Recent studies also suggest that curcumin could reduce oxidative stress, ER stress and inflammatory response induced by acrolein (a toxin from tobacco smoke) and cytomegalovirus (CMV) infection in human endothelial cells [29,65]. The anti-inflammatory mechanism of curcumin is through inhibiting COX-2 expression and prostaglandin production via reducing phosphorylation of PKC, p38 MAPK, and cAMP response element-binding protein as well as HMGB1-TLRS-NF-κB signalling pathway [29,65]. The broad anti-inflammatory effects of curcumin underline its reported effects on improving flow-mediated dilation in human subjects [81].

Atheroprotective effects of curcumin *in vivo*

Numerous lines of experimental evidence *in vivo* models advocate the high relevance of curcumin in reducing the cardiovascular risk associated with atherosclerosis. Ramı´rez-Tortosa et al. (1999) [10] studied ethanolic rhizome extract on LDL oxidation and plasma lipids concentration in rabbits. Atherosclerosis was induced by feeding with a diet that contains 95.7% standard chow, 3% lard and 1.3% cholesterol. Two groups received extracted doses of 1.66 (group A) and 3.2 (group B) mg/kg body weight of the three groups, while the third group served as control. Lipid peroxidation in high extract dosage (group B) was highest i.e. 10.48 ± 2.66 mg/dl, then low extract dosage (group A) (9.20 ± 2.10) and control (8.47± 1.14 mg/dl). Total plasma cholesterol was significantly lower in group A (1495± 174 mg/dl) and group B (1489 ± 227mg/dl) when compared to the control (2589± 160 mg/dl). Moreover, group A had lower levels of cholesterol (1495± 174 mg/dl), phospholipids (938 ± 155 mg/dl) and triglycerides (190±12 mg/dl) in LDL than group B of extract featuring phospholipids (1084± 61 mg/dl), and triglycerides (198±23 mg/dl). The results highlight *C. longa* extract administration in decreasing lipid peroxidation. In conclusion, usage of this extract was thought to provide some relief against atherosclerosis development.

Similarly, Li et al. (2015) [82] established a heart disease model that studied the permeability, protein expression and therapeutic potential of curcumin extract in treating male Wistar rat coronary heart disease (CHD). Atherosclerosis was induced by feeding with a diet enriched with high-fat content for 12 weeks along with vitamin D3 injection intraperitoneally. Once atherosclerosis was developed, curcumin (100 mg/kg·d) was provided for four weeks of experimentation. Upon completion, the heart was finally dissected, and the coronary artery was obtained. Using the immunofluorescence method, pathological changes in endarterium permeability were compared between blank control, treatment and model control group. Fluorochrome permeability was highest in the model control group, then the treated group, and least in blank control.

Similarly, changes in MMP-9 and CD40Lwas detected using Western blotting assay, wherein MMP-9 and CD40L were significantly higher than treated and control. Similar findings were obtained for the expression profile of serum TNF-α and CRP using ELISA. The results highlight rat CHD might be due to upregulation of MMP-9, CD40L, TNF-α and CRP protein and its permeability, which in the treated group was counter checked/inhibited by curcumin placebo.

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Likewise, Zhang et al. (2017) [16] studied the pathogenesis of atherosclerosis via suppressing TLR4 using curcumin in ApoE$^{-/-}$mice. The treated mice were kept on curcumin extract (0.1% w/w) for 16 weeks. The result highlights a significant reduction in TLR4 expression, IL-1β, TNF-α, VCAM-1, ICAM-1, and NF-κB activity. In addition, it inhibited macrophage infiltration, atherosclerotic plaques and lesions development in aortic tissues.

In addition, Hasan and coworkers [9] studied the effect of Curcumin supplementation (500; 1000; 1500 mg/kg diet) on atherosclerosis in Ldlr$^{-/-}$mice for 16 weeks. The finding highlight Curcumin dose-dependently reduced uptake of oxLDL in THP-1 cells and modulated lipid metabolism. At medium doses of 500-1000 mg/kg diet, curcumin effectively reduced fatty streak formation and inhibited inflammatory cytokine production. In addition, a high dose (1500mg/kg diet) of curcumin, suppressed the progression of steatohepatitis, reduced tissue fibrosis, and preserved glycogen levels in the liver. s a result of the findings, curcumin at a medium dosage was most effective in suppressing aP2 and CD36 expression and preventing atherosclerosis. Human cytomegalovirus (CMV) infection is an important risk factor for atherosclerosis, and curcumin has demonstrated protective effects against HCMV-infection. In a recent model of atherosclerosis in ApoE$^{-/-}$mice infected with mouse CMV, curcumin inhibited the replication and proliferation of CMV, reduced lipid profile (TC, TG, and LDL), and aortic lesion area [29], indicating that the anti-atherosclerotic effects of curcumin is also related to its anti-infectious effects.

More recently, oral administration of curcumin has been reported to reduce fatty streaks and aortic lesions in cholesterol-fed rabbits. Mechanistic studies revealed that curcumin increased antioxidant capacity, lowered the serum levels of TC, TG, and LDL, and reduced the levels of pro-inflammatory markers (CRP, ICAM1, and VCAM1). The lipid-modulatory effects of curcumin are possibly related to decreased expression of PCSK9. In cholesterol-fed rabbits, curcumin also exerts anti-atherosclerotic effects via increasing miR-126, thereby reducing the activation of PI3K/AKT and JAK2/STAT5 [42]. Therefore, curcumin could prevent atherosclerosis via inhibiting oxidative stress, systemic inflammation, and hypoglycemic effects [83].

Conclusion and perspectives

In conclusion, substantial experimental evidence suggests that curcumin prevents endothelial dysfunction and foam cell formation and modulates macrophage polarization and counteracts inflammatory response, supporting its potential role in anti-atherosclerosis activity. The anti-atherosclerosis property of curcumin is through suppressing inflammatory response by skewing macrophage polarization from M1 to M2 or by inducing M2 polarization through regulating TLR4/MAPK/NF-κB pathways in macrophages and secretion of interleukins (IL-4 and/or IL-13). Similarly, curcumin concurrently regulated the expression and activity of lipid transporter expression (CD36, CD38, ABCA1, aP2 etc.) for cholesterol uptake and efflux, thus maintaining cell homeostasis. In addition, Curcumin reduces ox-LDL level and oxLDL elicited pro-atherogenic events by reducing MCP-1/THBS-4 expression via the p38 MAPK and NF-kB pathways [51]. Likewise, curcumin suppresses TLR4 expression and macrophage infiltration in aorta tissue and protects against atherosclerosis plaque formation [16]. Additional studies are required to improve or add meaningful insights into our understandingof the mechanism of the action of curcumin against atherosclerosis in mice and human patients. In addition, the development of novel drug delivery systems, such as the creation of curcumin nanomicelles [84,85], is critical for improving curcumin oral bioavailability [86].

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