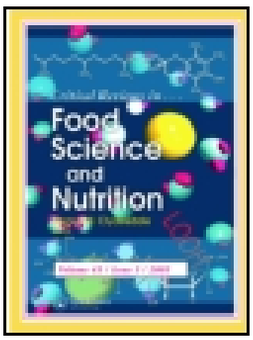

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SYSTEMATIC REVIEW ARTICLE

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Curcumin against advanced glycation end products (AGEs) and AGEs-induced detrimental agents

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ABSTRACT

Objectives: This study was aimed to review and collate effects of curcumin on generation of advanced glycation end products (AGEs) and AGEs induced detrimental agents.

Methods: Pubmed, Googlescholar, ScienceDirect, and Scopus databases were searched. Searching was not limited to specific publication period. Only English language original articles (in vitro, experimental and human) which had examined the effect of curcumin on AGEs formation and AGEs induced apoptosis, oxidative stress or inflammatory responses were included. To review effect of curcumin on AGEs formation, search terms were as following: "curcumin" (title) and AGEs or pentosidine or methylglyoxal or carboxymethyllysine or glucosylation (title/abstract). Totally 104 articles were searched which 19 were selected for review. To review effect of curcumin on AGEs induced harmful agents, key words were as following: "curcumin" (title) and AGEs (title/abstract) and apoptosis or oxidative stress or DNA damage or cell injury or inflammatory or cell death or cell proliferation (title/abstract). Totally 126 articles were searched which 18 were found appropriate for review.

Results: Regarding curcumin and AGEs formation, ten eligible articles (1 human trial, 5 animal models and 4 in vitro) and with regarding curcumin and AGEs-induced complications, 17 articles (5 on apoptosis, 9 on oxidative stress, and 3 on inflammatory responses) were selected. Except one, all studies indicated that curcumin is able to prevent AGEs formation and AGEs-induced disturbances with different potential mechanisms.

Conclusion: Curcumin can inhibit AGEs formation and AGEs-induced disturbances. More RCT researches are suggested to evaluate beneficial effect of curcumin regarding AGEs in different age-related chronic diseases, with specific attention to AGEs memberships.

Abbreviations: AGEs: advanced glycation end products; AGE-R1: Advanced glycation end product receptor 1; AKT: Protein kinase B; CAT: catalase; CML: carboxymethyl lysine; DCM: diabetic cardiomyopathy; ERK: extracellular signal-regulated kinase; GCL: glutamate-cysteine ligase; GSH: glutathione; HSCs: hepatic stellate cells; HUVECs: human umbilical vein endothelial cells; ICAM-1: intercellular adhesion molecule-1; IKB: inhibitor of kappa B; JAK2: Janus kinase 2; MAPK: Mitogen-activated protein kinase; MCP-1: monocyte chemotactic protein- 1; MD: Mediterranean diet; MDA: malondialdehyde; MGO: methylglyoxal; MMP-13: matrix metalloproteinase-13; NF-KB: nuclear factor-kappa B; Nrf2: Nuclear factor 2; PARP: poly(ADP-ribose) polymerase; PPARγ: peroxisome proliferator-activated receptor-gamma; RCT: randomized controlled trial; ROS: reactive oxygen species; SOD: superoxide dismutase; sRAGE: soluble receptor for AGE; TGF-β1: transforming growth factor-β1; TNF-α: tumor necrosis factor-α

KEYWORDS
Curcumin; AGEs; methylglyoxal; apoptosis; oxidative stress; inflammatory response

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Introduction

Advanced glycation end products (AGEs) are damaging compound that are generated when proteins or lipids become nonenzymatically glycated due to encountering with sugars (American Heart Association, 2016). These compounds are generated exogenously in foods via high-temperature processing and endogenously under hyperglycemic condition in the body. Two classes of plasma membrane receptors, including receptor for AGEs (RAGE) and AGE receptor-1 (AGE-R1), intervenes impacts of AGEs. RAGE is related with enhanced oxidative stress, cell growth, and inflammation (Schmidt et al. 2000), while AGE-R1 is contributed in detoxification and elimination of AGEs (Lu et al. 2004). AGEs are able to prevent expression of AGE-R1 and stimulate expression of RAGE (Lin (a) et al. 2012; Lin (b) et al. 2012).

AGEs alter structure and function of nearly all type of molecule and cell in the body and are contributed to aging and have pathogenetic role in the development of age-related chronic diseases including diabetes (Yamagishi et al. 2012; Yap et al. 2012), atherosclerosis (Del Turco and Basta 2012), cardiovascular diseases (Semba et al. 2009; Prasad et al. 2012), nonalcoholic steatohepatitis (Gaens et al. 2012), chronic renal disease (Kalousová et al. 2006) and neurological disorders (Li et al. 2012; Wetzels et al. 2017). The AGEs are also involved in diverse microvascular and macrovascular problems (Yamagishi et al. 2015); stimulate production of reactive oxygen species

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(ROS) and enhance oxidative stress (Lin et al. 2012; Liu et al. 2012); increase inflammation (Yang et al. 2013), expression of adhesion molecules (Vlassara et al. 1995), synthesis of extracellular matrix components (Berrou et al. 2009), apoptosis (Liu et al. 2012), and cell proliferation (Peterszegi et al. 2006) form cross-links with circulating proteins (Zieman and Kass 2004); and involved in tumor growth and metastasis (Nankali et al. 2016; Abe et al. 2004).

Curcumin is a natural phenol and the main curcuminoid which belongs to curcuma longa (known as turmeric). Recent in vitro and in vivo evidence indicates multiple biological functions for curcumin. It possesses antioxidant (Meng et al. 2013), anti-inflammatory (Meng et al. 2013), anti-apoptosis (Awad and El-Sharif 2011), anticancer and anti-proliferative effects (Wilken et al. 2011). Numerous evidences have suggested protective effects of curcumin against several chronic diseases such as diabetes (Zhang et al. 2013). Increasing in vitro, animal models and human studies have investigated anti-glycation effect of curcumin. However, in our knowledge, there is no review study to summarize the effects of curcumin on AGEs. Therefore, the aim of this study was to collate effects of curcumin on AGEs and AGEs-induced problems.

Search strategy

Searched databases were Pubmed, Googlescholar, ScienceDirect, and Scopus, updated until July, 2017. There was no time limitation for publications. All English language original articles (in vitro, experimental and human studies) which had examined the effect of curcumin on AGEs formation and AGEs induced apoptosis, oxidative stress or inflammatory responses were included. To review the effects of curcumin on AGEs generation, keywords were as follows: "curcumin" in title and "AGEs" or "methylglyoxal (MGO)" or "pentosidin", or "carboxymethyllysine" or "glucosylation" in title / abstract. To review effect of curcumin on AGEs induced detrimental agents, key words were as follows: curcumin (in title) and AGEs and apoptosis, oxidative stress, DNA damage, cell injury, inflammatory, cell death, and cell proliferation, in title / abstract. References of each article were reviewed to find any relevant articles that could have not been comprised by the algorithm. Extracted articles were entered into endnote file and sorted to prevent duplicated references. In this review, the PICO (Patient/Population; Intervention; Comparator; Outcome) question was as follows: in human or in an animal model or cell culture (P), does a curcumin supplementation (I) compared to a group without curcumin supplementation (C), influence AGEs formation or AGE-induced apoptosis, oxidative stress and inflammation biomarkers (O)?

Analysis of the data

Regarding curcumin and AGEs formation, totally, 104 articles were retrieved by the search strategy. After removing repeated articles, a total of 69 references were maintained which among them 19 articles were selected for review following critical analysis of title and summary of articles. Abstract, results section, tables and figures of each article were reviewed independently for eligibility and data extraction. Finally, 10 articles were included in the analysis (Fig. 1). Review articles and any irrelevant articles were excluded.

Regarding curcumin and AGEs induced harmful agents (apoptosis, oxidative stress or inflammatory responses), totally 126 articles were searched which 62 references were maintained, after removing duplicated references. Of them, 18 were selected for review following critical analysis of title and summary of articles (Fig. 1). Abstract, results section, tables and figures of each article were reviewed independently for eligibility and data extraction. After excluding one non-eligible article, 17 references remained for analysis.

Curcumin and AGEs generation

Characteristic of studies on curcumin and AGEs formation have been summarized in Table 1. After grave appraise of the chosen articles, ten studies were found appropriate in this area which categorized into three groups: in vitro (n = 4), animal (n = 5) and human (n = 1) studies.

In vitro studies

Hu et al. (2012) have investigated the effects of curcumin on MGO-trapping capacity and protein expression of carboxymethyllysine (CML), a member of AGEs, in human umbilical vein endothelial cells (HUVECs). The authors have reported that exogenous MGO significantly enhances CML expression in HUVECs, while, pre-treatment of HUVECs with curcumin significantly decreases the levels of intracellular MGO induced by exogenous MGO and modifies the exogenous MGO-induced CML formation in a dose-dependent manner.

Sun et al. (2016) examined the effect of curcumin on the formation of AGEs in HUVECs using two different methods. First, they incubated MGO and human serum albumin (HAS) in the presence or absence of curcumin in various concentrations and assessed the reaction kinetics. The authors found that curcumin inhibited significantly the formation of MGO-induced AGEs in a dose-dependent manner.

Li et al. (2006) have investigated inhibitory effects of curcumin derivatives on non-enzymatic glucosylation in vitro. The researchers incubated bovine serum albumin (BSA) with D-fructose in carbonate buffer in the presence or absence of the curcumin derivative extracts for ten days. They concluded that all of the curcumin derivatives were able to inhibit the formation of AGEs. Among them curcumin had the most strong dissuasive activity.

Liu et al. (2016) evaluated curcumin anti-glycative abilities, inhibitory effects on total AGEs formation, and its MGO trapping ability. They showed that curcumin extracts had anti-AGEs effects, inhibited MGO induced AGEs formation and scavenged MGO by 99.0.

Animal studies

Fleenor et al. (2013) have studied effects of dietary curcumin supplementation on AGEs addressing aorta arterial AGEs expression in old and young mice. The authors have demonstrated that old mice had higher arterial AGEs expression

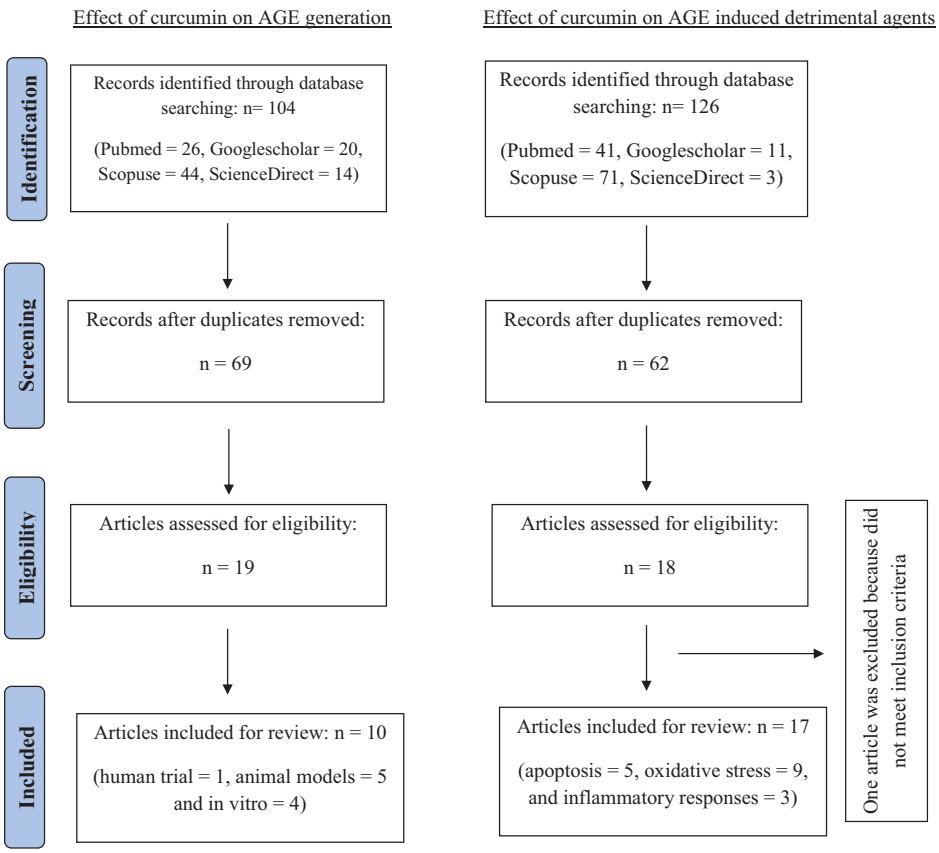

Figure 1. Flowchart for articles selection.

compared with young animals. However, dietary supplementation of curcumin entirely normalized arterial AGEs in old mice.

Sajithlal et al. (1998) have investigated effect of curcumin on the advanced glycation in diabetic rats. In the study, diabetic rats were given curcumin orally for 8 weeks. The level of AGEs was studied in tail tendons and skin. Diabetic rats had higher levels of AGEs compared to control animals. Curcumin treatment prevented accelerated accumulation of AGE in diabetic animals.

Suryanarayana et al. (2003) studied dietary curcumin effect on galactose-induced cataractogenesis and AGEs formation in rats. In this study, animals in two of experimental groups received 30% galactose plus 0.002% and 0.01% curcumin, respectively, for 4 weeks and reported that curcumin at the 0.002% level had antioxidant and antiglycating effects. Feeding of curcumin at the both levels inhibited carbonyl formation and AGE-fluorescence.

Yu et al. (2012) investigated the effects of curcumin on modulating diabetic cardiomyopathy (DCM) on experimental diabetic rat. Diabetic rats were treated orally with curcumin at a dose of 100 or 200 mg/ kg/ d for 16 weeks. Elevated AGEs accumulation and RAGE (receptor for AGEs) expression was observed in rats with DCM. They noticed that curcumin diminished AGEs accumulation in the heart of diabetic rats.

Hassan et al. (2013) investigated the protective effect of curcumin–induced hemeoxygenase-1 against hypertension associated with diabetes. In this study, experimental diabetic rats received daily injection of curcumin (5 mg/kg) for 6 weeks. Diabetic animals had a significantly higher level of serum AGEs than controls. However, curcumin was not able to reduce serum levels of AGEs.

Human studies

There was only one study on humans which has investigated effect of curcumin in combination with Boswellia serrata (BSE) gum resin. Chilelli et al. (2016) in a RCT study researched effect of curcumin and BSE gum resin on glycoxidation in chronically exercising master athletes. In this study, 47 healthy male athletes were participated. Twenty two subjects were given a Mediterranean diet (MD) alone (group 1), and 25 subjects a MD plus curcumin and BSE (group 2), for three months. Total AGE and soluble receptor for AGE (sRAGE) were assessed. The authors have reported that total AGE had significant decrease in the curcumin/BSE group.

Possible mechanisms on how curcumin abolishes AGEs' generation

As shown in Fig. 2, curcumin inhibits AGEs' generation through two possible pathways as follows:

a. MGO-trapping capacity of curcumin

Previous in vivo studies have demonstrated that increased levels of MGO leads to carbonyl stress and subsequent formation of AGEs (Desai and Wu 2008). MGO-derivatized CML is the most plentiful AGEs (Huang et al. 2008). Hu et al. (2012) have indicated that curcumin is effectively able to trap MGO in the cell free system as well as HUVECs and suggested that MGO-trapping capacity of curcumin leads to reduced CML expression.

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Table 1. Summary table of curcumin effects on AGEs formation.

	Author/date	Source	Curcumin Dosage	Model	Results
In vitro	Hu et al./2012 (28)	Taiwan	0.48, 0.73, 1.45 mM	HUVECs treated with curcumin for 24 h and MGO-trapping capacity of curcumin and CML expression was studied.	Pre-treatment of HUVECs with curcumin modified the exogenous MGO-induced CML formation in a dose-dependent manner.
	Sun et al./2016 (29)	China	10^{-7}, 10^{-6} and 10^{-5} M	HUVECs treated with MGO in the presence or absence of curcumin and formation of MGO-induced AGEs was studied.	Curcumin inhibited the MGO-induced AGEs formation in a dose-dependent manner.
	Li et al./2006 (30)	China	50 μmol/L	Bovine serum albumin was incubated with D-fructose in the presence and absence of curcumin derivatives for 10 days	All of the curcumin derivatives inhibited the formation of AGEs.
	Liu et al./2016 (31)	USA	100 mg/mL	Curcumin anti-glycative abilities, inhibitory effects on AGEs formation, and its MGO trapping ability were evaluated.	Curcumin extracts: — had anti-AGEs effects — inhibited MGO induced AGEs formation — scavenged MGO.
Animals	Fleenor et al./ 2013 (32)	USA	0.2%	Young and old male mice were given normal or curcumin supplemented chow for 4 weeks	Curcumin ameliorated aorta arterial AGEs in old mice.
	Sajithlal et al./ 1998 (33)	India	200 mg/kg body wt	Diabetic rats were given curcumin orally for 8 weeks. Tail tendons and skin AGEs level was studied.	Curcumin prevented accumulation of AGE in diabetic animals.
	Suryanarayana et al./ 2003 (34)	India	0.002% and 0.01%	Rats were given dietary curcumin for 4 weeks and galactose-induced AGEs formation was investigated.	— Curcumin had antioxidant and antiglycating effects. — Curcumin inhibited carbonyl formation and AGE-fluorescence.
	Yu et al./2012 (35)	China	100 or 200 mg/ kg/ d	Diabetic rats were treated orally with curcumin for 16 weeks.	— AGEs accumulation and RAGE expression elevated in rats with DCM. — Curcumin diminished AGEs level in the heart of diabetic rats.
	Hassan et al./ 2013 (36)	Saudi Arabia	5 mg/kg	Diabetic rats received daily injection of curcumin for 6 weeks.	Diabetic animals had higher levels of serum AGEs than controls. Curcumin did not reduce serum levels of AGEs.
Human	Chilelli et al./ 2016 (37)	Italy	10 mg	Male athletes were given a MD alone or a MD plus curcumin and BSE, for 12 weeks.	Total AGE decreased in the curcumin/BSE group.

AGEs, advanced glycation end products; HUVECs, human umbilical vein endothelial cells; CML, carboxymethyl)lysine; DCM, diabetic cardiomyopathy; MD, Mediterranean diet; sRAGE, soluble receptor for AGE.

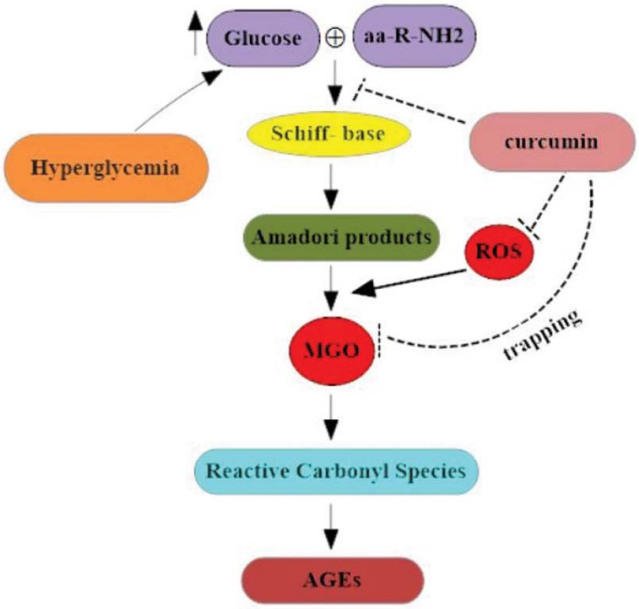

Figure 2. A simplified mechanistic model of curcumin in inhibition of AGE formation.

Sun et al. (2016) have also suggested that curcumin inhibits the formation of AGEs through its MGO-trapping characteristic.

b. Antioxidant capacity of curcumin

Importance of oxygen radicals in the advanced glycation and accumulation of AGEs has been indicated previously. Anti-oxidative conditions and scavengers of free radicals have been reported to prevent the AGEs formation (Sajithlal et al. 1998). Li et al. (2006) have indicated that curcuminoids react with proteins more easily and quickly than sugars, thus inhibiting protein glucosylation. Moreover, the authors have concluded that the inhibition of AGE formation by curcumin attributes to antioxidant capacity of curcumin and clearance of free radicals from environment. Sajithlal et al. (1998) also presented antioxidative property of curcumin as inhibitory factor for AGE formation.

Curcumin and AGEs induced detrimental agents

Totally, seventeen researches were found on curcumin and AGEs induced complications which were categorized into three groups: apoptosis (n = 5), oxidative stress (n = 9) and inflammatory responses (n = 3). Characteristic of the studies have been shown in Table 2.

1. Apoptosis

Liu et al. (2012) in an in vitro study treated rat mesangial cell line HBZY-1 with AGEs in the presence or absence of curcuminoids including curcumin, demethoxycurcumin. In this study, acridine orange/ethidium bromide fluorescence staining and flow Cytometry methods were used to evaluate the effect of curcumin and demethoxycurcumin on the apoptosis of AGEs-induced HBZY-1 cells. Results of both the methods indicated that exposure of the cells to AGEs markedly increased apoptosis, while, curcumin and demethoxycurcumin lowerd AGEs-induced apoptosis in a dose-dependent manner.

The apoptotic effect of MGO and then protective effect of curcumin in mononuclear cells (Chan and Wu 2006) and human hepatoma G2 Cells (Chan et al. 2005) were assessed. Curcumin inhibited MGO- induced apoptosis, dose-dependently.

Hsuuw et al. (2005) incubated mouse embryonic stem cells ESC-B5 with MGO and assessed apoptotic biochemical events. They showed that treatment of the cells with curcumin inhibit the MGO-induced apoptotic biochemical changes. Also, curcumin prevented the MGO-induced apoptosis of mouse blastocysts isolated from pregnant mice.

Du et al. (2000) investigated effect of curcumin on MGO induced apoptosis in Jurkat cells and showed that curcumin reduced MGO-induced caspase-3 activation, PARP cleavage, and apoptosis.

2. Oxidative stress

Lin (b) et al. (2012) treated serum-deprived hepatic stellate cells (HSCs) with AGEs in the presence or absence of curcumin for 24 h. The authors have reported that AGEs increased levels of ROS and lipid peroxidation, dose-dependently. Administration of curcumin reduced AGEs-induced oxidative stress and lipid peroxidation in a dose-dependent manner.

Sun et al. (2016) incubated HUVECs with MGO in presence or absence of curcumin. They found that intracellular ROS levels significantly decreased in presence of curcumin.

Fleenor et al. (2013) have studied effect of dietary curcumin supplementation on arterial oxidative stress in old and young mice. Old mice had greater arterial oxidative stress biomarkers. Curcumin supplementation reduced all oxidative stress parameter and enhanced manganese superoxide dismutase (SOD) expression in old mice.

Liu et al. (2012), in an in vitro study, treated rat mesangial cell with AGEs in the presence or absence of curcuminoids including curcumin, demethoxycurcumin. The authors reported that exposure of the cells to AGEs significantly increases ROS generation, whereas, curcuminoids decreases dramatically intracellular ROS generation within 48 h in a concentration-dependent manner. In organisms, SOD activity and malondialdehyde (MDA) level are two main factors in the oxidative balance system. Curcumin and demethoxycurcumin were able to enhance AGEs-decreased SOD activity and lower AGEs-increased MDA level.

Yang et al. (2013) exposed rabbit chondrocytes with AGEs and then treated with different doses of curcumin. The authors indicated that AGEs reduced the activity of catalase (CAT), SOD and improved MDA level, in concentration-dependent manner. In comparison to AGEs treatment group, curcumin treatment increased the activity of CAT and SOD, and reduced MDA level, dose-dependently. Pretreatment with curcumin decreased AGE-induced ROS production, dose-dependently.

Chan and Wu (2006) and Chan et al. (2005) have revealed that MGO treatment increased the intracellular ROS content in human mononuclear cells and human hepatoma G2 Cells. While, administration of curcumin prevented MGO-induced oxidative stress and DNA damage, dose-dependently.

Lip et al. (2013) assessed protective ability of antioxidants against glyoxal and MGO in rat hepatocytes. Incubation of the

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Table 2. Summary table of curcumin effects on AGEs induced detrimental agents.

	Author/date	Source	Curcumin Dosage	Model	Results
Apoptosis	Liu et al./2012 (16)	China	$10^{-11} - 10^{-9}$ M	Rat mesangial cell line HBZY-1 was treated with 200 μg/mL AGEs in the presence or absence of curcumin.	– AGEs increased apoptosis – curcumin lowerd AGEs-induced apoptosis in a dose-dependent manner
	Hsuuw et al./ 2005 (42)	Taiwan	2.5–20 μM	Mouse embryonic stem cells ESC-B5 were incubated with MGO in the presence or absence of curcumin.	– Curcumin inhibited the MGO-induced cell death and apoptosis. – Curcumin prevented the MGO-induced apoptosis of mouse blastocysts isolated from pregnant mice.
	Chan et al./ 2006 (40)		2.5–20 μmol/L	Mononuclear cells were incubated by 50 μM MGO in the presence or absence of curcumin.	Curcumin inhibited MGO- induced apoptosis, dose-dependently.
	Chan et al./ 2005 (41)		2.5–10 μM	Human hepatoma G2 Cells were incubated by 200 μM MGO in the presence or absence of curcumin.	Curcumin inhibited MGO- induced apoptosis, dose-dependently.
	Du et al./2000 (43)	Japan	20 μM	Jurkat cells were incubated with or without curcumin for 2 h and treated with 0.25 mM MGO for 1 h.	Curcumin reduced MGO-induced apoptosis.
Oxidative stress	Lin et al./2012 (5)	USA	10, 20, 30 μM	Serum-deprived HSCs were treated with AGEs in the presence or absence of curcumin for 24 h.	– AGEs increased levels of ROS and lipid peroxidation dose-dependently. – Curcumin reduced AGEs-induced oxidative stress and lipid peroxidation in a dose-dependently.
	Sun et al./ 2016 (29)	China	10^{-7}, 10^{-6}, 10^{-5} M	HUVECs were incubated with MGO in the presence or absence of curcumin.	– Intracellular ROS levels decreased in presence of curcumin.
	Fleenor et al./ 2013 (32)	USA	0.2%	Young and old male mice were given normal or curcumin supplemented chow for 4 weeks.	– Old mice had higher arterial ROS biomarkers. – Curcumin reduced all ROS parameter and enhanced SOD expression in old mice.
	Liu et al./2012 (16)	China	$10^{-11} \sim 10^{-9}$ M	Rat mesangial cell line HBZY-1 was treated with 200 μg/mL AGEs in the presence or absence of curcumin.	– AGEs increased ROS generation. – Curcuminoids decreased intracellular ROS level, dose-dependently. – Curcuminoids enhanced SOD activity and lowered MDA level.
	Yang et al./ 2012 (17)	China	10, 25, 50 μmol/l	Rabbit chondrocytes were exposed to AGEs and then treated with different doses of curcumin.	– AGEs reduced the activity of CAT, SOD and increased MDA level, dose-dependently. – Curcumin treatment increased the activity of CAT and SOD, and reduced MDA level, dose-dependently. – Curcumin decreased AGE-induced ROS production, dose-dependently.
	Chan et al./ 2006 (40)	Taiwan	2.5–20 μmol/L	Human Mononuclear cells were incubated by 50 μM MGO in the presence or absence of curcumin.	– MGO increased the intracellular ROS content. – Curcumin prevented MGO-induced oxidative stress and DNA damage, dose-dependently.
	Chan et al./ 2005 (41)	Taiwan	2.5–10 μM	Human hepatoma G2 Cells were incubated by 200 μM MGO in the presence or absence of curcumin.	Curcumin attenuated MGO-induced ROS formation.
	Lip et al./2013 (44)	Canada	4 μM	Rat hepatocytes were incubated with glyoxal (5 mM) and MGO (15 mM,) and then treated with curcumin.	– Hepatotoxicity and ROS formation at 2 h of treatment increased. – Curcumin reduced ROS formation and had hepatoprotection effect.
	Hsuuw et al./ 2005 (42)	Taiwan	2.5–20 μM	Mouse embryonic stem cells ESC-B5 were incubated with MGO and then treated with curcumin.	Curcumin prevented MGO-induced increase of ROS.
Inflammatory responses	Sun et al./ 2016 (29)	China	10^{-7}, 10^{-6}, 10^{-5} M	HUVECs were incubated with MGO in the presence or absence of curcumin.	Expression of TGF-β1and ICAM-1 decreased in presence of curcumin.
	Yang et al./ 2012 (17)	China	10, 25, 50 μmol/l	Rabbit chondrocytes were exposed to AGEs and then treated with different doses of curcumin.	– AGEs increased level of TNF-α and MMP-13 mRNA. – Curcumin decreased the expression and protein levels of TNF-α and MMP-13.
	Margina et al./ 2013 (45)	Romania	2.5–20 μM	Jurkat T lymphoblasts and HUVECs exposed to high glucose levels or AGE in the presence or absence of curcumin and incubated for 4 h.	– Production of MCP-1 was greater when cells were exposed to AGE. – Curcumin inhibit MCP-1 production in a dose-dependent manner.

AGEs, advanced glycation end products; HUVECs, human umbilical vein endothelial cells; HSCs, hepatic stellate cells; SOD, superoxide dismutase; MDA, malondialdehyde; CAT, catalase; TGF-β1, transforming growth factor-β1; ICAM-1, intercellular adhesion molecule-1; TNF-α, tumor necrosis factor-α; MMP-13, matrix metalloproteinase-13; MCP-1, monocyte chemotactic protein- 1; MGO, methylglyoxal; ROS, reactive oxygen species.

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cells with glyoxal and MGO were led to significant increase in hepatotoxicity and ROS formation at 2 h of treatment. Significant hepatoprotection and reduced ROS formation was observed when the cells treated by polyphenols including curcumin.

Hsuuw et al. (2005) incubated mouse embryonic stem cells ESC-B with MGO and then treated with curcumin. They demonstrated that curcumin prevents MGO-induced increase of ROS.

Inflammatory responses

Sun et al. (2016) incubated HUVECs with MGO in the presence or absence of curcumin. They demonstrated that expression of transforming growth factor-β1 and intercellular adhesion molecule-1 significantly decreased in presence of curcumin.

Yang et al. (2013) treated rabbit chondrocytes with AGEs and then exposured with various levels of cucumin. The authors reported that AGEs treated chondrocytes had increased level of TNF-α and MMP-13 mRNA, whereas, curcumin treatment could decrease the expression and protein levels of TNF-α and MMP-13.

Margina et al. (2013) assessed in vitro pro-inflammatory factors such as monocyte chemotactic protein- 1 (MCP-1) release by Jurkat T lymphoblasts and HUVECs (endothelial cells), exposed to high glucose levels or AGE in the presence or absence of curcumin. Production of MCP-1 was greater when cells were exposed to AGE. Curcumin inhibit MCP-1 production in a dose-dependent manner.

Possible mechanisms on how curcumin abolishes AGEs-induced effects

As shown in Fig. 3, curcumin extirpates AGEs-induced destructive agents through three possible pathways as follows:

a. MGO-trapping capacity of curcumin

Numerous evidences suggest a role for MGO in development of oxidative damage and pro-inflammatory responses (Akhand et al. 2001; Miyazawa et al. 2010; Chu et al. 2016). Therefore, the trapping of MGO has been represented as an effective strategy to suppress AGEs-induced damages (Hu et al. 2012; Sun et al. 2016). Sun et al. (2016) have attributed the protective effect of curcumin on pro-inflammatory responses and oxidative stress related damages and dysfunctions in endothelial cells to MGO- trapping capability of curcumin.

b. Modulatory capacity of curcumin on expression of AGEs receptors

As mentioned earlier, function of AGEs is mediated through two types of cellular membrane receptors including RAGE and AGE-R1. Activation of first group receptors is accompanied by detrimental effects of AGEs, while the second group of receptors is associated with detoxification and clearance of AGEs (Schmidt et al. 2000; Lu et al. 2004). Previous evidences indicated that AGEs prevent expression of AGE-R1 and motivate expression of RAGE in HSC (Lin (a & b) et al. 2012). Whereas, curcumin is able to suppress expression of RAGE and induce the AGE-R1 expression, which subsequently leads to inhibition of the AGEs effects, through different pathways:

Lin et al. have reported that curcumin induces gene expression of AGE-R1 and suppress gene expression of RAGE via inhibition of extracellular signal-regulated kinase activity and induction of gene expression and the activity of peroxisome proliferator-activated receptor-gamma (PPARγ) (Lin (a & b) et al. 2012).

Lin (b) et al. (2012) in another study have shown that curcumin through increasing glutamate-cysteine ligase activity and by elevating glutathione synthesis leads to the

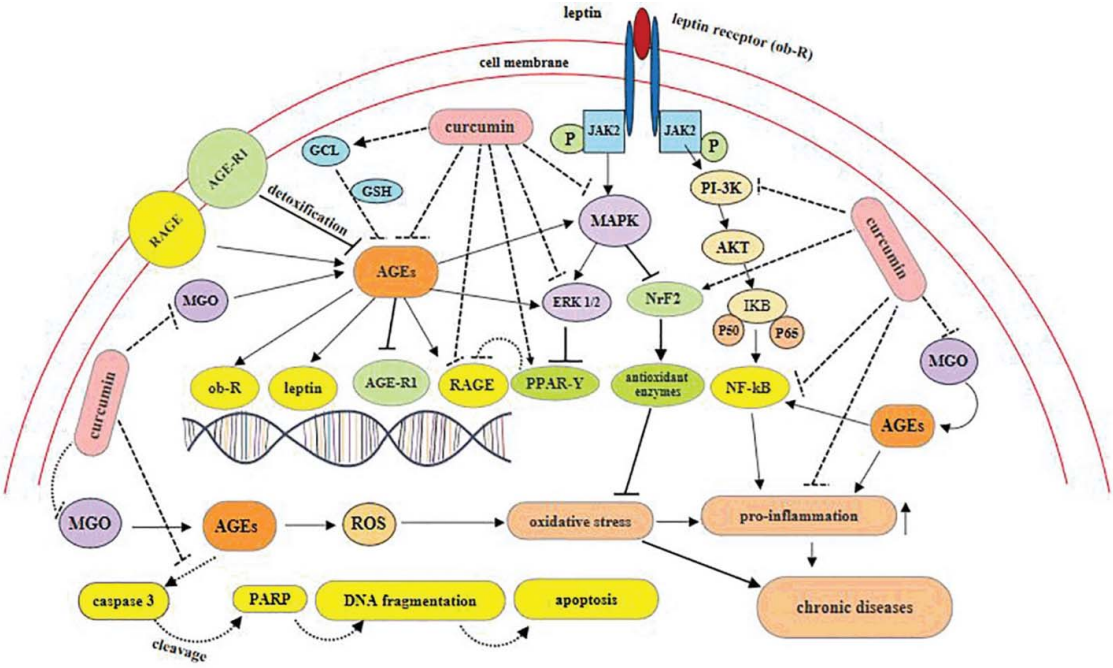

Figure 3. A simplified mechanistic model of curcumin in the neutralization of AGEs-induced damaging agents.

inhibition of RAGE gene expression which subsequently attenuates the stimulant effects of AGEs on the cellular levels of oxidative stress.

Tang and Chen (2014) have reported that AGEs activate leptin signaling through supporting gene expression of leptin and its receptor. Then, leptin modifies gene expression of RAGE and AGE-R1, as AGEs. Curcumin abolish AGEs induced oxidative stress by disturbing leptin signaling, triggering transcription factor Nrf2, and enhancement of cellular glutathione.

c. *Interfering with NF-κB pathway*

It has been reported that AGEs and its receptor RAGE motivate the activation of nuclear factor-κB dependent pathways and elevate oxidative stress, consequently leading to pro-inflammatory responses (Rasheed et al. 2011). Yang et al. (2013) in a study on rabbit chondrocytes have showed that curcumin abrogates AGE-induced inflammatory response by preventing NF-κB activation and oxidative stress.

Limitations and future outlooks

Human studies were limited. There was only one human study that had evaluated anti-AGEs effects of curcumin in combination with boswellia serrate on athletes. More RCT studies are suggested to assess net effect of curcumin on AGEs generation and effects in different age-related chronic diseases. In addition, almost in all reviewed studies, total AGEs had been assessed rather than members of AGEs which need to take account it for future studies.

Conclusion

Taken all together, the results of in vitro, animal and human studies provide significant evidence that curcumin is a potential protective agent against AGEs formation and AGEs-induced disturbances with various potential mechanisms.

Conflict of interests

The authors declare that they have no financial or non-financial conflict of interests.

Authors' contributions

Both authors conducted the search, and participated in manuscript writing. Both authors read and approved the final manuscript.

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