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Turmeric and its bioactive constituents trigger cell signaling mechanisms that protect against diabetes and cardiovascular diseases

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Abstract

Turmeric, the rhizome of *Curcuma longa* plant belonging to the ginger family Zingiberaceae, has a history in Ayurvedic and traditional Chinese medicine for treatment of chronic diseases, including metabolic and cardiovascular diseases (CVD). This parallels a prevalence of age- and lifestyle-related diseases, especially CVD and type 2 diabetes (T2D), and associated mortality which has occurred in recent decades. While the chemical composition of turmeric is complex, curcuminoids and essential oils are known as two major groups that display bioactive properties. Curcumin, the most predominant curcuminoid, can modulate several cell signaling pathways involved in the etiology and pathogenesis of CVD, T2D, and related morbidities. Lesser bioactivities have been reported from other curcuminoids and essential oils. This review examines the chemical compositions of turmeric, and related bioactive constituents. A focus was placed on the cellular and molecular mechanisms that underlie the protective effects of turmeric and turmeric-derived compounds against diabetes and CVD, compiled from the findings obtained with cell-based and animal models. Evidence from clinical trials is also presented to identify potential preventative and therapeutic efficacies. Clinical studies with longer intervention durations and specific endpoints for assessing health outcomes are warranted in order to fully evaluate the long-term protective efficacy of turmeric.

Keywords Curcumin · Curcuminoids · Turmeric oil · Diabetes · Cardiovascular diseases · Human clinical trials

Abbreviations

2DG	2-Deoxyglucose
ABCA-1	Adenosine triphosphate (ATP)-binding cassette transporter A1
AGE	Advanced glycation end-product
Akt	Protein kinase B
AMPK	5′ Adenosine monophosphate-activated protein kinase
ANF	Atrial natriuretic factor
Ang II	Angiotensin II
aP2	Adipocyte Protein 2 (aka. fatty acid-binding protein 4, FABP4)
ApoAI	Apolipoprotein AI
ApoE$^{-/-}$	Apolipoprotein E knockout
ATP	Adenosine triphosphate
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma-2
BDMC	Bisdemethoxycurcumin
β-MHC	Beta-myosin heavy chain
BMI	Body mass index
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CAT	Catalase
CD36	Cluster of differentiation 36
CD68	Cluster of differentiation 68
C/EBP	CCAAT/enhancer-binding protein
CHOP	C/EBP homologous protein
CK-MB	Creatine kinase-MB
CRP	C-reactive protein
CVD	Cardiovascular diseases
DMC	Demethoxycurcumin
DSPN	Diabetic sensorimotor polyneuropathy
ECM	Extracellular matrix
ER	Endoplasmic reticulum
ERK1/2	Extracellular signal-regulated kinase 1/2
FBS	Fasting blood sugar
FFAR	Free fatty acid receptor
FOXO3a	Forkhead box O3a

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G6P	Glucose 6-phosphate
GATA4	GATA-binding factor 4
GCK	Glucokinase
GLP-1	Glucagon-like peptide -1
GLUT	Glucose transporter
GPR	G-protein-coupled receptor
GR	Glutathione reductase
GSH-Px	Glutathione peroxidase
GSIS	Glucose-stimulated insulin secretion
HAT	Histone acetyltransferase
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HDL-c	High-density lipoprotein cholesterol
HFD	High-fat diet
H/R	Hypoxia/reoxygenation
hs-CRP	High-sensitivity C-reactive protein
ICAM-1	Intercellular cell adhesion molecule-1
IκB	Inhibitor of NF-κB
IL	Interleukin
i.p.	Intraperitoneal injection
IR	Insulin receptor
I/R	Ischemia/reperfusion
IRS	Insulin receptor substrate
JAK	Janus kinase
Keap1	Kelch-like ECH-associated protein 1
LC3	Microtubule-associated protein 1 light chain 3
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LDL-c	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein receptor
Lp(a)	Lipoprotein a
LXRα	Liver X receptor α
MAPK	Mitogen-activated protein kinase
MCP-1	Mast cell protease 1
MDA	Malondialdehyde
MetS	Metabolic syndrome
MI	Myocardial infarction
miR-7a/b	MicroRNA-7a/b
MMP-2	Matrix metalloproteinase-2
NAD	Nicotinamide adenine dinucleotide
NF-κB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2-related factor 2
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
oxLDL	Oxidized low-density lipoproteins
PAB	Pro-oxidant-antioxidant balance
PDK1	3-Phosphoinositide-dependent protein kinase-1
PDX-1	Pancreatic and duodenal homeobox-1
p-ERK1/2	Extracellular signal-regulated kinase 1/2
PGC-1α	Peroxisome proliferator-activated receptor-γ coactivator-1α
PGN	Peptidoglycan
PI3K	Phosphatidylinositol-3-kinase
PIP_2	Phosphatidylinositol-4,5-bisphosphate
PIP_3	Phosphatidylinositol-3,4,5-trisphosphate
p.o.	Oral administration (Latin *per os*)
PPAR-γ	Peroxisome proliferator-activated receptor-γ
RCT	Randomized clinical trials
SIRT-1	Sirtuin-1
SOD	Superoxide dismutase
SP1	Specific protein 1
SR-A	Scavenger receptor class A
SREBP	Sterol regulatory element-binding protein
STAT	Signal transducer and activator of transcription
T2D	Type 2 diabetes
TC	Total cholesterol
TG	Triglyceride
TGF-β1	Transforming growth factor beta 1
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor α
VCAM-1	Vascular cell adhesion molecule-1
VCP	Valosin-containing protein
WC	Waist circumference
%BF	Percent body fat

Introduction

Curcuma longa Linn. (Syn. *Curcuma domestica* Valeton) belongs to the ginger family Zingiberaceae, a perennial plant that grows in tropical and humid climates and originates from the Indian Subcontinent and Southeast Asia [1, 2]. The term *longa* refers to the elongated shape of the rhizome, where turmeric is derived from the rhizome of the plant having a characteristic orange-yellow color. The term for turmeric varies among languages, but most often it refers to "yellow colour" or "bright colour" [3]. The Latin word *curcuma* is believed to be derived from the Arabic root *kurkum* meaning "saffron," in reference to similar coloring properties [4]. Turmeric is also known as "Indian saffron."

The history of using turmeric dates back to more than 4000 years during the Vedic age of India, where it was initially used as a dye and a culinary spice, due to its bright yellow color and aromatic flavor [2, 3]. Turmeric also has a spiritual significance, where with the Hindu religion, turmeric was connected with South East Asian countries by 700 AD, migrating later to West and East African countries during 800 to 1200 AD [2, 3]. Turmeric has become a commonly cultivated seed in many of these countries and regions. Along with the history of use, turmeric has had an important role in folk medicine, especially Ayurveda and traditional Chinese medicine where it was used as a remedy for various diseases that range from simple ailments to more complex chronic illnesses, such as digestive (e.g., abdominal

pain and bloating, dyspepsia), cardiovascular (e.g., heart burning, heart pain), respiratory (e.g., runny nose, sinusitis, asthma), and hepatic disorders [1, 5–8]. On the other hand, turmeric although arriving in Europe in the 13th century by Arab traders currently remains a minor spice in Western countries. Until more recently, turmeric has been recognized, and since gained popularity as a dietary supplement and a nutraceutical thus becoming one of the most successful natural health products sold in the US since 2013 [9]. Recent studies that have also shown therapeutic potential of turmeric against coronavirus disease 2019 (COVID-19) [10] and the potential to modulate cytokine storm in COVID-19 patients [11] have produced formidable renewed interest in this herb.

Notwithstanding the long history of using turmeric in traditional medicine to treat various diseases, the mechanism or scientific basis for its bioactivity has remained unclear, until more recently when pharmacological assessments demonstrated safe use for modern medicine [3]. Curcuminoids and essential oils (mainly terpenoids) are two major components present in turmeric, the former being responsible for the orange-yellow color of the herb and the latter accounting for the aromatic flavor [12]. These components also possess a wide range of bioactivities (Table 1), for which evidence has been substantiated at all levels of inquiry that range from in vitro and in vivo experiments to human clinical studies [12, 13]. Curcumin, a principal and abundant curcuminoid in turmeric, has been extensively studied for bioactivity in pharmaceutical studies [14]. Albeit a majority of preclinical and clinical studies have focused on the efficacy of turmeric extracts and isolated curcumin, relatively less information exists on bioactivity of other curcuminoids and essential oils present from turmeric for potential use in modern-day medicinal and nutraceutical industries [12].

Table 1 Major bioactivities of turmeric and its bioactive constituents that relate to specific health disorders

Health disorder	Reported bioactivity	References
Oxidative stress	Antioxidant	[15–18]
Inflammation and inflammatory diseases	Anti-inflammatory Immunomodulatory	[19–21]
Allergy	Anti-allergic	[22–24]
Cardiovascular diseases	Hypolipidemic Atheroprotective Cardioprotective	[25–28]
Diabetes	Hypoglycemic Antiglycation Antidiabetic	[29–32]
Cancer	Antitumor Pro-apoptotic Antimetastatic Anticancer	[33–36]
Neurodegenerative diseases	Neuroprotective	[37–39]
Depression	Antidepressant	[40–42]
Liver diseases	Hepatoprotective	[43–45]

Among the various bioactivities possessed by turmeric and its bioactive components listed in Table 1 [15–45], the antidiabetic and cardioprotective effects have attracted pronounced attention from numerous researchers with a common interest in understanding the role of turmeric and related bioactives in the protection against cardiovascular diseases (CVD), that currently exists as a leading cause of mortality worldwide. Diabetes is also one of the top 10 causes of death and is often associated with onset of CVD [46]. Although a number of therapeutic strategies for diabetes and CVD have been developed and tested, there are limited applications because of the high costs, low accessibility, and complications [14].

This review provides an overview on the complex chemical composition of turmeric and its bioactive constituents that are involved in metabolic health benefits. Furthermore, we review mechanistic preclinical (in vitro and in vivo) evidence on the antidiabetic and cardioprotective effects attributed to turmeric constituents. A comprehensive discussion on the cellular and molecular mechanisms that corroborates the beneficial outcomes observed from human clinical trials is given.

Chemical composition of turmeric

Proximate analysis (Fig. 1) of turmeric reveals that the herb contains 6–13% moisture, with 60–70% carbohydrate, 6–8% protein, 5–10% fat, 3–7% minerals (potassium, sodium, calcium, iron, phosphorus), and trace amounts of vitamins [47–49]. Essential oils obtained by steam distillation represent 3–7% of the turmeric rhizome and mainly consist of terpenoids, including sesquiterpenoids (e.g., α-phellandrene, zingiberene), monoterpenoids (e.g., sabinene, cineol), and norsesquiterpenoids [12, 49]. There is also 3–5% curcuminoids, which comprises more than 50 structurally related compounds; the three principal ones being curcumin, demethoxycurcumin, and bisdemethoxycurcumin [47]. In general, turmeric composition varies according to the soil conditions used in cultivation, with Indian turmeric being regarded as having superior quality and high curcumin content [3]. Curcuminoids and essential oils are classified as secondary metabolites produced by *Curcuma* plants, with well-defined bioactivity [50].

Curcuminoids

Curcuminoids are bioactive phenolic compounds and consist of more than 100 individual curcuminoids that have been isolated and identified from genus *Curcuma*, about 50 of which are present in *C. longa* (turmeric). Turmeric contains

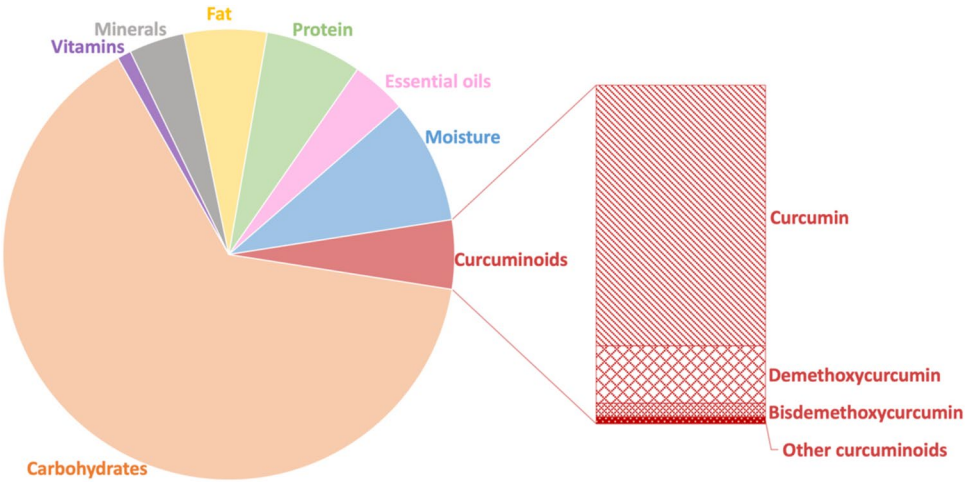


Fig. 1 Composition of turmeric (*C. longa*) rhizome [47–49]

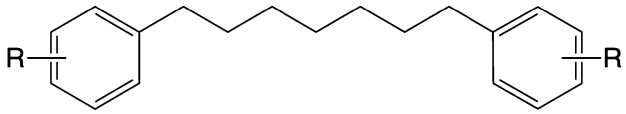


Fig. 2 Skeleton structure of diphenylheptanoids

three major curcuminoids: curcumin (CUR; 77%), demethoxycurcumin (DMC; 17%), and bisdemethoxycurcumin (BMC; 3–6%) [12, 47].

Strictly speaking, curcuminoids only refer to linear diphenylheptanoids with a skeleton structure that has two aromatic rings linked by a heptane chain (Fig. 2) [51]. By this definition, there are 15 curcuminoids isolated and identified in turmeric (*C. longa*).

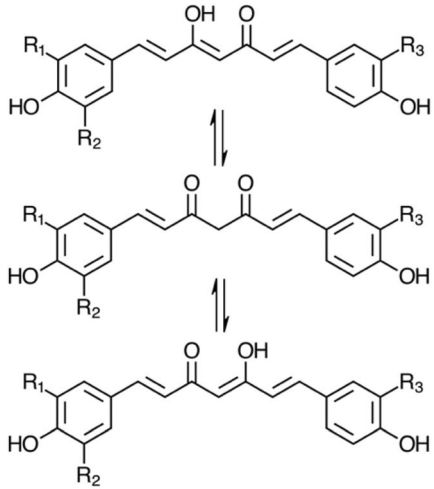
The definition of curcuminoids has expanded to include any orange-yellow-colored compounds present in turmeric that are structurally related to the principal constituent curcumin [51]. Specifically, there must be two aryl groups (aromatic rings) linked by an aliphatic chain, which is usually a heptane (7C) chain (Compounds **1**–**15**), or a pentane (5C) chain (Compounds **16**–**18**). Alternatively, a cyclic chain structure exists (Compounds **19**–**21**). Cyclization of the heptane chain leads to the formation of a furanone ring, as shown in curcumalongin A and B (Compounds **20**, **21**), or a pyrone ring present in cyclcocurcumin (Compound **22**). These are generally not common and found only in *C. longa*. The structures and names of these compounds are presented in Table 2 [52–56]. More recently, uncommon structures of curcuminoids that are conjugated with monoterpenes or sesquiterpenes have been isolated from turmeric and have been termed terpecurcuminoids or terpenoid-conjugated curcuminoids [57].

Curcuminoids are readily soluble in polar organic solvents, such as dimethyl sulfoxide (DMSO), acetone, methanol, and ethanol, but are poorly soluble in water, lipids, and hydrocarbons, like cyclohexane and hexane [47, 58]. The 1,3-diketone group in curcumin and some curcuminoids (Compounds **1**–**8**) exhibit keto–enol tautomerism, and therefore exist in keto and enol tautomeric forms (Fig. 3). The diketo form predominates in crystal curcumin or in acidic and neutral solutions, whereas the keto–enol form is exclusively present in alkaline conditions [47–49]. Water solubility increases under alkaline conditions when curcuminoids assume ionic forms upon dissociation of enolic and phenolic protons [47].

Curcuminoids are subject to chemical degradation in aqueous-organic solutions, especially under alkaline pH, or in dilute solutions of curcuminoids. Binding to macromolecules, such as albumins, lipids, and liposomes, will increase curcuminoid stability [59, 60]. Although the degradation mechanism is not fully understood, it is generally believed that hydrolysis of the α,β-unsaturated β-diketone moiety, which is a common structure in curcuminoids, is involved in the reaction. Major degradation products of curcuminoids that have been identified include vanillin, vanillic acid, ferulic acid, ferulic aldehyde, and others [60].

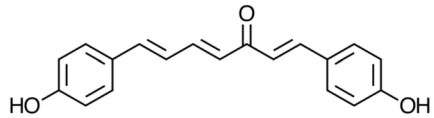
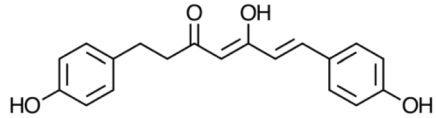
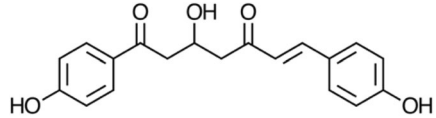
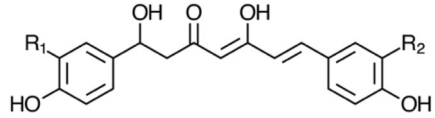
An even more significant and rapid degradation of curcuminoids occurs when exposed to photooxidation, as is the case when curcuminoids are exposed to sunlight. Photochemical degradations of curcuminoids occur in both solid form and in solution [58, 60]. The products of photodegradation are almost identical to those that are produced from chemical degradation, thereby indicating similar decomposition pathways. Photodegradation is initiated by photoexcitation resulting in the formation of triplet excited states of curcuminoids, which subsequently act as principal photosensitizers of singlet oxygen. The curcuminoids in turn undergo self-photosensitization, a reaction that is not dependent on the presence of oxygen [60, 61]. To prevent photodegradation of curcuminoids from ultraviolet light sources, commercial products are typically packaged in brown or amber containers for shelf-storage.

Table 2 Unconjugated curcuminoids present in the rhizome of *C. longa*

No.	Compound name	Structure	Reference
1	Curcumin		[52]
2	Demethoxycurcumin (DMC)		
3	Bisdemethoxycurcumin (BDMC)		
4	(*1E,6E*)-1-(3,4-dihydroxyphenyl)-7-(4- hydroxyphenyl)-1,6-heptadiene-3,5-dione		[53]
5	(1*E*,6*E*)-1,7-Bis(3,4-dihydroxyphenyl)-1, 6-heptadiene-3,5-dione (Didemethyl curcumin)		[54]
6	(1*E*,6*E*)-1-(3,4-dihydroxyphenyl)-7- (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione (Monodemethylcurcumin)		[53, 55]
7	Curcumalongin C		[54]
8	(1*E*,6*E*)-1-(4-hydroxy-3,5-dimethoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)- 1,6-heptadiene-3,5-dione (5′-methoxycurcumin)		[55]

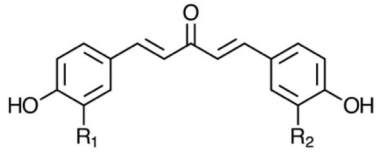
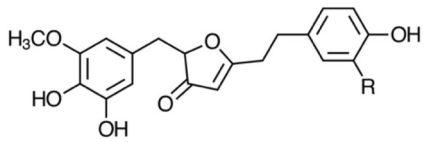
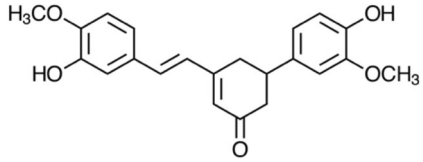
	R_1	R_2	R_3
1	OCH_3	H	OCH_3
2	OCH_3	H	H
3	H	H	H
4	OH	H	H
5	OH	H	OH
6	OCH_3	H	OH
7	OCH_3	OH	OCH_3
8	OCH_3	OCH_3	OCH_3

Table 2 (continued)

No.	Compound name	Structure	Reference
9	(1*E*,4*E*,6*E*)-1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one		[55]
10	(4*Z*,6*E*)-5-hydroxy-1,7-bis-(4-hydroxyphenyl)-4,6-heptadien-3-one		[53]
11	(6*E*)-3-hydroxy-1,7-bis (4-hydroxyphenyl)-6-heptene-1,5-dione		[53]
12	(4*Z*,6*E*)-1,5-dihydroxy-1,7-bis-(4-hydroxyphenyl)-4,6-heptadien-3-one		[53]
13	(4*Z*,6*E*)-1,5-dihydroxy-1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)- 4,6-heptadien-3-one		
14	(4*Z*,6*E*)-1,5-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)- 4,6-heptadien-3-one		
15	(4*Z*,6*E*)-1,5-dihydroxy-1,7-bis(4-hydroxy-3- methoxyphenyl)-4,6-heptadien-3-one		

	R_1	R_2
12	H	H
13	H	OCH_3
14	OCH_3	H
15	OCH_3	OCH_3

Table 2 (continued)

No.	Compound name	Structure	Reference
17	1,5-Bis(4-hydroxyphenyl)-1,4-pentadiene-3-one		[52]
		R_1 R_2 16 H H 17 OCH_3 H 18 OCH_3 OCH_3	
18	(1*E*,4*E*)-1-(4-hydroxy-3-methoxyphenyl)-5-(4-hydroxyphenyl)-1,4-pentadien-3-one		
19	(1*E*,4*E*)-1,5-bis(4-hydroxy-3- methoxyphenyl)-penta-1,4-dien-3-one		
20	Curcumalongin A		[54]
		R 19 H 20 OCH_3	
21	Curcumalongin B		
22	Cyclocurcumin		[56]

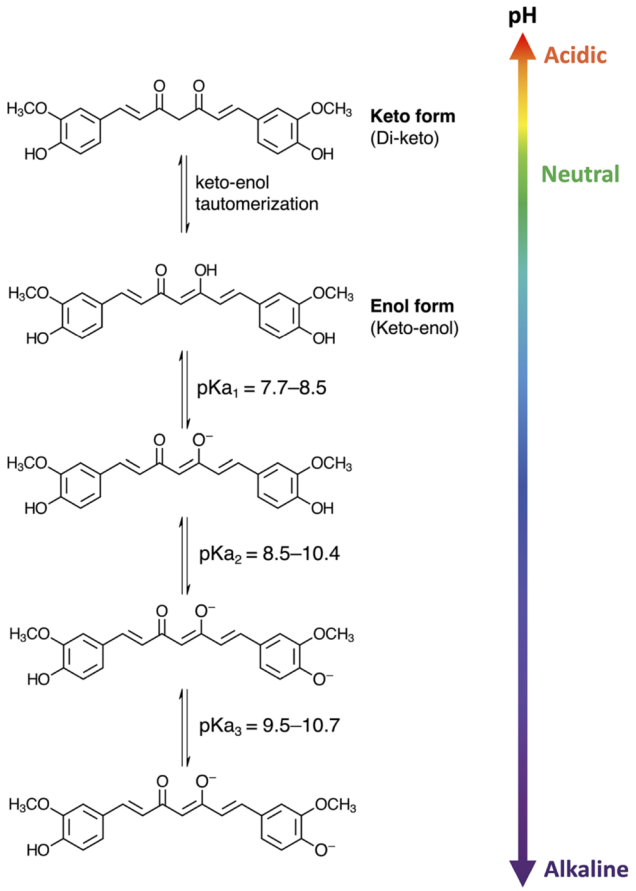


Fig. 3 Different forms of curcumin depending on pH conditions

Besides degradation, bioavailability of phytochemicals is also an important factor limiting pharmaceutical applications. The efficacy of curcumin toward antioxidant, anti-inflammatory, and anti-angiogenic activities is governed by factors that limits bioavailability, or accelerates metabolism and elimination. Low bioavailability of curcumin, due to its poor water solubility, has received considerable attention to find ways to enhance bioavailability using novel encapsulation delivery strategies that include liposomes, polymeric micelles, micro-emulsions, and nano-particle technologies [62–64]. Moreover, improved gastrointestinal absorption and bioavailability of curcumin has been observed using other plant bioactive components, such as piperine [65], and genistein [66] as adjuvants to increase permeability of curcumin, whereas tea catechins, namely, epigallocatechin-3-gallate-EGCG, are known to counteract certain curcumin activities [67].

Turmeric oil (essential oils)

Turmeric oil (TO) is a group of essential oils which mainly consists of more than 250 diverse terpenoids, identified from *Curcuma* species [68]. TO represents another major group of bioactive compounds in turmeric. Table 3 summarizes the major and most commonly reported terpenoids isolated from turmeric (*C. longa*) [69–88], which have been categorized into sesquiterpenoids (Compounds **22**–**81**), monoterpenoids (Compounds **82**–**86**), norsesquiterpenoids (Compounds **87**–**89**), and norditerpenes (Compound **90**) [12].

Monoterpenes, with a molecular formula $C_{10}H_{16}$, consist of two isoprene units existing in either linear (acyclic) or ring structure (mono- or bi-cyclic) forms. Monoterpenoid derivatives are produced through modification, such as oxygenation or demethylation [51]. Sesquiterpenes, with a molecular formula $C_{15}H_{24}$, and associated sesquiterpenoid derivatives consist of three isoprenoid units. As is the case with monoterpenes and monoterpenoids, sesquiterpenes and sesquiterpenoids also exist in either acyclic or cyclic form [68]. Sesquiterpenoids are the dominant group of terpenoids in the turmeric rhizome and are further sub-categorized into several types; the major three being bisabolane, guaiane, and germacrane types, and the minor ones being carane, elemane, spironolactone types, and others [12]. Turmerones (α, β, and aromatic) that fall into the bisabolane-type sesquiterpene category are the predominant constituents that contribute to approximately 50% of the total TO [68]. A broad spectrum of biological activities has been reported in all the sesquiterpenoid classes.

Terpecurcuminoids (terpenoid-conjugated curcuminoids)

Terpecurcuminoids are a minor group of bioactive compounds recovered from turmeric and are distinguished by having a curcuminoid moiety that is conjugated with a terpenoid moiety [89–93]. Out of the 29 identified terpecurcuminoids (Compounds **91**–**119**), 20 compounds have a curcumin moiety, while others possess DMC, BDMC, and curcuminoid derivatives; bisabolene-type sesquiterpenoids are the most common terpenoid moiety, existing in 24 terpecurcuminoids (Table 4). The curcuminoid and terpenoid moieties in 17 of these compounds are conjugated via one or two C–C bonds, while in 12 compounds they are conjugated via C–O–C bonds [92, 93].

The terpecurcuminoids show cytotoxicity against various human cancer cell lines (e.g., human breast cancer cell lines MDA-MB-231 and MCF-7, human liver cancer cell line HepG2, and human lung cancer cell line A549), and some have exhibited greater cytotoxic potency compared to curcumin, thereby suggesting a promising anti-cancer activity of these compounds that requires more investigation on clinical efficacies [89, 90].

Table 3 Terpenoids present in the rhizome of *C. longa*

No.	Compound	Reference
Sesquiterpenoids		
Bisabolane-type sesquiterpenes		
22	α-turmerone	[69]
23	β-turmerone	[69]
24	Aromatic (*ar*)-turmerone	[70]
25	*ar*-dihydroturmerone	[71]
26	β-sesquiphellandrene	[72]
27	*ar*-curcumene	[73]
28	Curlone	[74]
29–32	Curculonone A–D	[75]
33	β-atlantone	[75]
34–35	(*Z*)/(*E*)-α-atlantone	[76]
36	(6S,7*R*)-bisabolone	[76]
37	(6*R*,7*R*)-bisabolone	[77]
38	β-bisabolene	[72]
39	α-zingiberene	[72]
40	2-methoxy-5-hydroxybisabola-3,10-diene-9-one	[78]
41	2,8-epoxy-5-hydroxybisabola-3,10-diene-9-one	[78]
42	4-methylene-5-hydroxybisabola-2,10-diene-9-one	[78]
43	Bisacurone	[79]
44–46	Bisacurone A–C	[78]
47	(6*S*)-2-hydroxy-6-(4-hydroxy-3-methylphenyl)-2-methylheptan-4-one	[80]
48	(6*S*)-6-(4-hydroxy-3-methylphenyl)-2-methoxy-2-methylheptan-4-one	[80]
Bisabolane-type sesquiterpenoids		
49–50	(5α/5β)-hydroxyl-1β-bisabolon-9-one	[81]
51–52	Turmeronol A–B	[82]
53	(*6S*)-2-methyl-6-(4-hydroxyphenyl)-2-hepten-4-one	[83]
54–57	Turmerone A–D	[84]
58	Turmerone Q	[85]
59	Bisabola-3,10-diene-2-one	[79]
60	2,5-dihydroxybisabola-3,10-diene	[79]
61	4,5-dihydroxybisabola-2,10-diene	[79]
62	*ar*-tumerol (bisacumol)	[79]
63, 64	Longpene C, D	[86]
65	Intermedin B	[86]
Guaiane-type sesquiterpenoids		
66	Curcumenol	[79]
67	Procurcumadiol	[79]
68	Procurcumenol	[79]
69	Isoprocurcumenol	[79]
70	Epiprocurcumenol	[79]
71	Zedoarondiol	[79]
72	1,10-dehydro-10-deoxy-9-oxozedoarondiol	[75]
Germacrane-type sesquiterpenoids		
73	Dehydrocurdione	[79]
74	Germacrone-13-al	[79]
75	(4*S*,5*S*)-germacrone-4,5-epoxide	[79]
Carane-type sesquiterpenoid		
76	Curcumenone	[79]

Table 3 (continued)

No.	Compound	Reference
Elemane-type sesquiterpenoid		
77	Curzerenone	[86]
Spironolactone-type sesquiterpenoid		
78	6α-hydroxycurcumanolide A	[75]
Other sesquiterpenoids		
79	Bicycloturmeronol	[87]
80	Longpene B	[86]
Novel sesquiterpene with new skeleton		
81	(6*S*)-2-methyl-6-(4-hydroxy-3-methylphenyl)-2-hepten-4-one	[83]
Monoterpenoids		
Linear monoterpene		
82	(*Z*)-β-ocimene	[88]
Monocyclic monoterpene		
83	2-(2,5-dihydroxy-4-methylcyclohex-3-enyl)-propanoic acid	[78]
84	p-cymene	[77]
Monocyclic monoterpenoid		
85	1,8-cineole	[77]
Bicyclic monoterpenoid		
86	α-pinene	[77]
Norsesquiterpenoids		
87	4-hydroxybisabola-2,10-diene-9-one	[79]
88	4-methoxy-5-hydroxybisabola-2, 10-diene-9-one	[79]
89	(6*R*)-[(1*R*)-1,5-dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-one	[75]
Norditerpene		
90	Longpene A	[86]

Table 4 Terpecurcuminoids in the rhizome of *C. longa*

No	Compound	Curcuminoid moiety	Terpenoid moiety	Reference
C–C conjugation				
91	Bisabocurcumin	Curcumin	Bisabolane-type sesquiterpenoid	[92]
92, 93	Terpercurcumin H, I			[89]
94–100	Terpercurcumin L–P, R, T			[90]
101	Terpercurcumin Q	Curcumin	Other sesquiterpenoid	[90]
102	Terpercurcumin X	Tetrahydrocurcumin	Bisabolane-type sesquiterpenoid	[91]
103	Terpercurcumin Y	Cyclocurcumin	Bisabolane-type sesquiterpenoid	[91]
104, 105	Terpercurcumin J, K	Dihydro-BDMC	Other sesquiterpenoid	[90]
106, 107	Terpercurcumin V, W	Curcumin	Monocyclic monoterpenoid	[90]
C–O–C conjugation				
108	Bisabolocurcumin ether	Curcumin	Bisabolane-type sesquiterpenoid	[93]
109–114	Terpercurcumin A–F			[89]
115	Demethoxybisabolo-curcumin ether	DMC	Bisabolane-type sesquiterpenoid	[93]
116	Terpercurcumin G			[89]
117	Terpercurcumin U			[91]
118	Didemethoxybisabolo-curcumin ether	BDMC	Bisabolane-type sesquiterpenoid	[93]
119	Terpercurcumin S			[91]

Table 5 In vitro studies on antidiabetic and cardioprotective effects of turmeric and turmeric-derived bioactive compounds

Disease/bioactivity	Model	Treatment	Dose	Main outcomes	Reference
Diabetes					
High glucose-induced insulin resistance	Rat insulinoma cell line INS-1	Curcumin	5–15 μM	⬆ Expression of: insulin, GSIS, GCK, PDX-1, GLUT2; ⬆ Phosphorylation of: IR, IRS1, PI3K, Akt	[32]
High glucose-induced oxidative stress and pancreatic β-cell apoptosis	Min-6 mouse pancreatic β-cells	Curcumin	1–10 μM	⬇ ROS, MDA, ⬆ SOD levels; ⬇ CHOP, ⬆ PGC-1α; ⬇ p-ERK1/2	[30]
Leptin-stimulated increase in intracellular glucose	Rat hepatic stellar cells (HSCs) and immortalized human hepatocytes	Curcumin	20 μM	⬇ Glucose level; ⬇ GLUT4 translocation to membrane; ⬇ Phosphorylation of: IRS-1, PI3K, Akt; ⬆ Glucokinase activity; ⬆ G6P levels	[94]
Akt signaling pathway and glucose uptake	3T3-L1 adipocytes	Curcumin	10–75 μM (dose response); 50 μM (time response)	[Dose-dependent] ⬇ Akt protein levels; ⬇ GLUT4 plasma membrane expression; ⬇ Glucose uptake; ⬆ LC3-II protein; ⬆ LC3-II/LC3-I ratio	[95]
Glucose uptake in GLUT1-expressing cells	L929 mouse fibroblast cells, HK2 human kidney cells, immortalized human corneal-limbal epithelial (HCLE) cells	Curcumin	25–200 μM	[Dose-dependent] ⬇ 2DG uptake (all three cell types); ⬇ Cytochalasin B binding (L929 cells)	[96]
Glucagon-like peptide-1 secretion	GLUTag L cells	Curcumin	25 μM	⬆ GLP-1 secretion (the effect diminished by GW1100)	[31]
Human adipocyte differentiation and peroxisome proliferator-activated receptor gamma (PPAR-γ) ligand-binding activity	Human preadipocytes	Turmeric extract (ethanol), curcumin, DMC, BDMC, *ar*-turmerone	Turmeric extract: 2–20 μg mL^{-1} Others: 2–5 μg mL^{-1}	[Dose-dependent] ⬆ adipocyte differentiation (turmeric extract); ⬆ PPAR-γ ligand-binding activity (all treatments)	[101]
Human adipocyte differentiation and PPAR-γ ligand-binding activity	Human preadipocytes	Turmeric extracts (ethanol: E-ext; hexane: H-ext; ethanol extraction from hexane extraction residue: HE-ext), curcumin, DMC, BDMC, *ar*-turmerone	[Adipocyte differentiation] E-ext: 2–20 mg L^{-1} [GAL4-PPAR-γ chimera assay] Turmeric ext: 5–10 mg L^{-1} Others: 2–5 mg L^{-1}	[Dose-dependent] ⬆ adipocyte differentiation (E-ext); ⬆ PPAR-γ ligand-binding activity (all treatments)	[102]

Table 5 (continued)

Disease/bioactivity	Model	Treatment	Dose	Main outcomes	Reference
Sterol regulatory element-binding protein (SREBP) pathway	Luciferase-expressing cancer cells Huh-7/SRE-Luc, rat heptaocytes CRL-1601	Curcumin	0.1–40 µM (Huh-7/SRE-Luc) 10 µM (CRL-1601)	[Dose-dependent] ⬇ Luciferase activity (in Huh-7/SRE-Luc cells); ⬇ Intracellular cholesterol, TG; ⬇ Expression of mRNA: SREBP-1, SREBP-2; ⬇ Expression of endogenous nuclear: SREBP-1, SREBP-2; (in CRL-1601 cells)	[107]
Inhibition of α-amylase and α-glucosidase	Chemical assays: α-amylase inhibition, α-glucosidase inhibition	Turmeric oil from fresh (FTO) and dried (DTO) rhizomes; *ar*-tumerone	0.1–100 µg mL^{-1}	Inhibition of: α-amylase, α-glucosidase, (*ar*-tumerone > DTO > FTO > acarbose)	[99]
In vitro antidiabetic potential	Chemical assays: α-amylase inhibition, α-glucosidase inhibition, antiglycation activity	Turmeric rhizome extracts using ethyl acetate (EtOAc Ex), methanol (MeOH Ex), and water (Water Ex)	0–600 µg mL^{-1}	Inhibition of: α-amylase (EtOAc Ex > MeOH Ex > acarbose > Water Ex), α-glucosidase (EtOAc Ex > MeOH Ex > Water Ex > acarbose) Antiglycation activity: (EtOAc Ex > MeOH Ex > Water Ex)	[97]
Inactivation of human pancreatic α-amylase (HPA)	Chemical assays (α-amylase inhibition, α-glucosidase inhibition)	BDMC	2–15 µg mL^{-1}	Inhibition of HPA (IC_{50} = 0.025 mM; Acarbose IC_{50} = 0.015 mM)	[98]
CVD					
Monocyte adhesion to TNF-α-stimulated endothelial cells	Primary human umbilical vein endothelial cells (HUVECs), human monocytic cell line U937	Curcumin	0.1–1 µM	[Dose-dependent] ⬇ Monocyte adhesion to HUVECs; ⬇ VCAM-1 gene expression	[123]
Cholesterol accumulation in foam cells	Mouse macrophage cell line J774.A1	Curcumin	5–40 µM	[Dose-dependent] ⬇ oxLDL-induced intracellular cholesterol accumulation; ⬇ Dil-oxLDL binding; ⬇ SR-A expression; ⬆ SR-A turnover; ⬆ SR-A–ubiquitin–VCP complex formation; ⬆ ApoAI-mediated cholesterol efflux; ⬆ ABCA1 expression (Curcumin's effect on ABCA1 abolished by LXRα inhibition.)	[28]

Table 5 (continued)

Disease/bioactivity	Model	Treatment	Dose	Main outcomes	Reference
Lipid accumulation in monocyte/macrophage	Human acute monocytic leukemia THP-1 cells	Curcumin	1–20 μM	[Dose-dependent] In THP-1 and THP-1 differentiated macrophages: ⬆ Lipid accumulation; ⬆ CD36 and aP2 protein expression; ⬆ FOXO3a phosphorylation	[125]
TLR4 expression and NF-κB activation	Mouse peritoneal macrophages (MPMs)	Curcumin	10–25 μM	[Dose-dependent] ⬇ TLR4 mRNA level; ⬇ NF-κB activation	[27]
Hypoxia-induced cardiomyocyte apoptosis	Mouse cardiac myocytes (MCMs)	Curcumin	10 μM	⬆ miR-7a/b expression; ⬇ SP1 expression and cell apoptosis (the effect diminished by miR-7a/b inhibitors)	[129]
TLR2 and MCP-1 expression	Neonatal rat cardiomyocyte	Curcumin	10 μM	⬇ TLR2 and MCP-1 (otherwise by TNF-α, PGN and H/R)	[130]
p300-HAT inhibitory activity	In vitro HAT assay	Curcumin, DMC, BDMC	20–60 μM	[Dose-dependent] ⬇ p300-induced acetylation of histone H3K9; Inhibitory activity at 20 μM: CUR > BDMC > DMC; at 60 μM: CUR ≈ DMC ≈ BDMC	[135]
Cardiac fibrosis	Cardiac fibroblasts (CFs)	Curcumin	5–15 μM	[Dose-dependent] ⬇ Ang II-induced expression of: collagen I, collagen III, and TGF-β1; ⬇ MMP-2 activity; ⬇ Ang II-induced CF cell proliferation and migration (All above effects of curcumin diminished by SIRT1 siRNA.)	[133]
Phenylephrine-induced cardiomyocyte hypertrophy	Primary neonatal rat cardiomyocytes	Curcumin, DMC, BDMC	10 μM	⬇ Phenylephrine-induced: acetylation of histone H3K9, myocardial cell-surface area increase, ANF and BNP expression (CUR ≈ DMC ≈ BDMC) None of the compounds changed morphology of cardiomyocytes	[135]
Noradrenaline-induced cardiomyocyte hypertrophy	Heart-derived H9C2 cardiomyoblast cells, primary neonatal rat cardiomyocytes	Curcumin	8 μM	⬇ Noradrenaline-stimulated increases in: cell size, protein concentration, ANF expression, nuclear localization of GATA4, DNA-binding activity of GATA4	[137]

Table 5 (continued)

Disease/bioactivity	Model	Treatment	Dose	Main outcomes	Reference
Phenylephrine-induced cardiomyocyte hypertrophy	Primary neonatal rat cardiomyocytes	Curcumin	5–10 µM	⬇ Phenylephrine (PE)- or p300-induced increases in: cell surface area, ANF and β-MHC promoter activities, p300-GATA4 association, GATA4 acetylation, GATA4-DNA binding; ⬇ p300-induced increases in: cell surface area, ANF and β-MHC promoter activities	[136]

Bioactivities of turmeric and its constituents against diabetes and CVD

Cellular and molecular mechanisms of the bioactivities of turmeric and several constituents reported from both in vitro (Table 5) and in vivo studies (Table 6) point to chemoprotection against onset of chronic diseases, such as diabetes and CVD. Human clinical trials (Table 7) have also provided positive evidence to recognize clinical efficacy of turmeric and turmeric-derived compounds. Table 8 summarizes the few current meta-analyses that reported on clinical effects of these compounds against CVD and related conditions.

Hypoglycemic and antidiabetic activities

Curcumin and other related bioactive compounds present in turmeric have been proposed to protect against type 2 diabetes (T2D) through different mechanisms that involve a hypoglycemic effect attributed to upregulation of insulin, enhanced insulin sensitivity, and lower cellular uptake of glucose.

The mechanism of which curcumin evokes hypoglycemic and antidiabetic effects involves the pancreatic β-cells (Fig. 4). Curcumin attenuates high glucose-induced insulin resistance in cultured rat insulinoma cells, INS-1, a model by which insulin secretion by pancreatic β-cells has been studied [32]. The underlying mechanism therein is the increased expression and secretion of insulin by activating the phosphatidylinositol-3-kinase/protein kinase B/glucose transporter 2 (PI3K/Akt/GLUT2) signaling pathway. In this pathway, curcumin acts to upregulate phosphorylation of the insulin receptor (IR), insulin receptor substrate (IRS)-1, PI3K, and Akt, all of which in turn increase the expression of pancreatic and duodenal homeobox-1 (PDX-1) and subsequent insulin mRNA. This effect is linked to increased levels of GLUT2 and glucokinase (GCK) activity, which are both required to regulate cellular glucose uptake and metabolism [32]. These processes are otherwise suppressed in the presence of a high glucose concentration. Curcumin is effective at attenuating oxidative stress that is induced by high glucose levels and which triggers apoptosis in a dose-dependent manner, and observation made using in mouse pancreatic β-cells [30]. This occurs by both a downregulated expression of C/EBP homologous protein (CHOP) and an upregulated expression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), along with a suppressing effect on phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) [30].

In adipocytes and hepatocytes, curcumin reduces glucose uptake by inhibiting the translocation of GLUT4 from the cytosol to plasma membrane, and by interfering with the

Table 6 In vivo animal studies on antidiabetic and cardioprotective effects of turmeric and turmeric-derived bioactive compounds

Disease/condition	Model	Treatment	Dose, administration manner; duration	Main outcomes	Reference
Diabetes					
Glycemic response	KK-A^y mice/Ta mice	Turmeric extract (ethanol)	0.2–1.0 g/100 g diet, ad libitum; 4 weeks	[Dose-dependent] ⬇ Blood glucose	[101]
Glycemic response	KK-A^y mice/Ta mice	Turmeric extracts (ethanol: E-ext; hexane: H-ext; ethanol extraction from hexane extraction residue: HE-ext)	H-ext or HE-ext: 0.1–0.5 g/100 g diet E-ext: 0.2–1.0 g/100 g diet; 4 weeks	⬇ Blood glucose (H-ext and HE-ext at 0.5 g/100 g diet; E-ext at 0.2 and 1.0 g/100 g diet)	[102]
Glycemic response	Alloxan-induced diabetic mice	*C. longa* extract (ethanol:water = 70:30 v/v)	5–15 mg kg^{-1}, i.p.; before alloxan i.p	[Dose-dependent] ⬇ Blood glucose	[103]
T2D-assocaited liver complications	Wild-type and db/db mice	Curcumin	0.75% w/w in diet, ad libitum; 8 weeks	⬇ NF-κB p65 expression; ⬆ AMPK and PPAR-γ expressions	[104]
Glucose tolerance and GLP-1 secretion	Sprague–Dawley rats	Theracurcumin	5 mg kg^{-1} (= 1.5 mg kg^{-1} curcumin equivalent), p.o.; before glucose i.p	⬇ Serum glucose concentration (effect diminished by GW1100); ⬆ Serum levels of: insulin, total & active GLP-1	[31]
High-fat diet-induced obesity and SREBP pathway	C57BL/6 mice	Curcumin	40–80 mg kg^{-1} day^{-1} in high-fat diet (HFD), p.o.; 12 weeks	⬆ Energy expenditure; ⬇ Body weight gain; ⬇ Serum TC, TG and LDL-c; ⬇ Hepatic TC and TG; ⬇ Lipid droplets accumulation in liver [High dose (80 mg kg^{-1})] ⬇ Epididymal fat weigh and adipocyte diameter in white adipose tissue; ⬇ Blood glucose; ⬇ Serum insulin; ⬇ Hepatic expression of: SREBP-1, SREBP-2; ⬆ Tyrosine phosphorylation of: IRS-1, IRS-2; ⬆ Serine 473 phosphorylation of Akt	[107]

Table 6 (continued)

Disease/condition	Model	Treatment	Dose, administration manner; duration	Main outcomes	Reference
CVD					
Atherosclerosis	ApoE$^{-/-}$ mice	Curcumin	0.1% w/w in HFD, p.o.; 16 weeks	⬇ Macrophage infiltration and TLR4 expression in atherosclerosis plaque; ⬇ Aortic NF-κB activation; ⬇ VCAM-1 and ICAM-1 expressions; ⬇ Serum IL-1β and TNF-α levels; ⬇ Aortic sinus plaque area	[27]
Atherosclerosis	ApoE$^{-/-}$ mice	Curcumin	20 mg kg^{-1} day^{-1}, p.o.; 4 weeks	⬇ Atherosclerotic lesion area in aortic roots; ⬇ Serum levels of: IL-6, TNF-α, MCP-1, TC, TG, non-HDL-c; ⬆ Serum HDL-c; ⬆ Aortic ABCA1 level; ⬇ Aortic SR-A level	[28]
Atherosclerosis	ApoE$^{-/-}$ mice	Curcumin	0.2% w/w in diet, p.o.; 4 months	⬇ Atherosclerotic lesion size; ⬇ Macrophage number in atherosclerotic lesions; ⬆ Aortic IκB expression; Modulated 1,670 genes expression in aorta (1,022 ⬆, 648 ⬇)	[123]
Lipid accumulation in macrophage	LDL receptor knockout (LDL-R$^{-/-}$) mice	Curcumin	500–1500 mg kg^{-1} HFD, p.o.; 4 months	⬇ Lipid accumulation in peritoneal macrophages; ⬇ mRNA expressions of: aP2, ABCA1 (all otherwise ⬆ by HFD.)	[125]
Altered gene expression in MI	Sprague–Dawley rats	Curcumin	75 mg kg^{-1} day^{-1}, p.o.; 3 days	⬆ Cardiac function; ⬇ Cardiac infarct size; ⬇ LDH and CK-MB activities Altered expression of genes in particular the one involved in cytokine–cytokine receptor interaction, JAK/STAT pathway, ECM-receptor interaction	[127]

Table 6 (continued)

Disease/condition	Model	Treatment	Dose, administration manner; duration	Main outcomes	Reference
Cardiac ischemia/reperfusion (I/R) injury	Sprague–Dawley rats	Curcumin	10–30 mg kg^{-1} day^{-1}, p.o.; 20 days before I/R injury	[Dose-dependent] ⬆ Cardiac function; ⬇ Cardiac infarction size; ⬇ Myocardial MDA level; ⬆ Myocardial SOD, CAT, GSH-Px, GR activities; ⬇ Myocardial LDH, CK-MB activities; ⬇ Myocardial Bax and Caspase-3; ⬆ Myocardial Bcl-2 level; ⬆ JAK2 and STAT3 phosphorylation	[25]
Cardiac I/R injury	Sprague–Dawley rats	Curcumin	300 mg kg^{-1} day^{-1}, p.o.; 7 days before and 14 days after I/R injury	⬇ TLR2 mRNA and protein expressions; ⬇ Macrophage infiltration (CD68); ⬇ cardiac fibrosis (otherwise ⬆ by I/R); ⬆ Cardiac contractility; ⬆ Cardiac function parameters (otherwise ⬇ by I/R.)	[130]
Cardiomyocyte apoptosis	Sprague–Dawley rats	Curcumin	150 mg kg^{-1} day^{-1}, p.o.; 4 weeks	⬇ Morphological changes and apoptosis index of myocardial cells; ⬇ NF-κB p65 expression; ⬆ PPAR-γ and Bcl-2 expressions	[128]
Cardiomyocyte apoptosis	C57BL/6 mice	Curcumin	50 mg kg^{-1} day^{-1}, p.o.; 4 weeks	⬇ Myocardial infarct size; ⬆ LDH release; ⬆ miR-7a and miR-7b levels; ⬇ SP1 mRNA and protein levels	[129]
MI and cardiac fibrosis	C57BL/6 J mice	Curcumin	100 mg kg^{-1} day^{-1}, p.o.; 4 weeks	⬇ Interstitial fibrosis; ⬇ Myocardial expressions of: collagen I, collagen III, TGF-β1; ⬇ Infarct size; (otherwise ⬆ by MI) ⬆ SIRT1 in heart tissues (otherwise ⬇ by MI)	[133]

Table 6 (continued)

Disease/condition	Model	Treatment	Dose, administration manner; duration	Main outcomes	Reference
Hypertension- and MI-induced heart failure	Salt-sensitive/resistant Dahl (DS/DR) rats, MI rats	Curcumin	50 mg kg^{-1} day^{-1}, p.o.; 7 weeks	In DS rats: ⬇ Hypertension-induced heart failure; ⬇ GATA4 acetylation; ⬇ p300/GATA4 complex In MI rats: Prevented MI-deteriorated left ventricular systolic function	[136]

IRS/PI3K/Akt signaling pathway [94, 95]. Curcumin has also been shown to directly inhibit GLUT1, thus lowering glucose uptake in GLUT1-expressing cells. It is noteworthy that the selective binding of curcumin to GLUT1 overlaps with the binding site of cytochalasin B, a mycotoxin that also has been shown to inhibit glucose transport [96].

The in vitro antidiabetic potentials of the turmeric extract, BDMC [97, 98], TO, and its major component *ar*-turmerone [99] have in common a capacity to inhibit the activities of α-amylase and α-glucosidase, two key enzymes involved in glucose digestion and also linked to T2D. These enzymes are the targets for specific antidiabetic drugs that control postprandial increase of blood glucose. Regardless of the forms of which turmeric is administered, for example, TO recovered from both fresh and dried rhizomes, turmeric extracts using different solvents, and the isolated *ar*-turmerone, there is sufficient evidence that these compounds show inhibitory effects on both glucose digestion enzymes; in fact they are relatively stronger than the standard antidiabetic drug, acarbose, an inhibitor of both α-amylase and α-glucosidase that reduces the breakdown of complex carbohydrates to glucose [97–99]. In addition, the turmeric extract also has notable antiglycation effects [97]. Protein glycation is the formation of advanced glycation end-products (AGEs) resulting in structurally and functionally altered proteins that contribute to various metabolic complications; the process could be accelerated by high levels of reducing sugars, such as glucose [97]. Antiglycation activity refers to delaying production of AGEs by suppressing oxidation of Amadori products and metal-catalyzed glucose oxidation [100].

Ethanol-derived turmeric extracts yield both curcuminoids and sesquiterpenoids, whereas hexane extracts yield mainly sesquiterpenoids. Further extraction of the hexane extraction with ethanol has been successful to improve recovery of DMC, BDMC, and *ar*-turmerone. These components were also effective at significantly increasing peroxisome proliferator-activated receptor gamma (PPAR-γ) ligand-binding activity, whereas the turmeric ethanolic extract stimulated human adipocyte proliferation in vitro [101, 102]. In vivo studies using genetically diabetic KK-A^y mice showed that turmeric extracts suppressed diet-induced increases in blood glucose level [101, 102]. Similarly, in alloxan-induced diabetic mice, a hydroethanolic extract of turmeric was effective to control blood glucose levels [103].

In genetically diabetic db/db mice, upregulation of PPAR-γ expression by dietary curcumin occurs in the liver and is associated with the upregulation of 5′ adenosine monophosphate-activated protein kinase (AMPK) expression and downregulation of p65 Nuclear factor kappa B (NF-κB). These effects are regarded as being beneficial to reduce T2D complications [104]. In other studies conducted in mice, curcumin improved glucose tolerance by

Table 7 Double-blind RCTs on antidiabetic and cardioprotective effects of turmeric and turmeric-derived bioactive compounds

Disease/condition	Sample population (n = sample size)	Duration	Treatment	Dose, administration manner	Outcome	Reference
Diabetes						
Anthropometric parameters and serum lipid profile	Hyperlipidemic T2D patients (n = 72)	8 weeks	Turmeric rhizome powder	2100 mg day^{-1}, p.o	Compared to baseline: ⬇ Body weight; ⬇ Serum TG; ⬇ Serum LDL-c Compared to control: ⬇ BMI; ⬇ Serum TG; ⬇ Serum TC	[112]
Serum lipid profile and inflammation status	T2D patients (n = 44)	10 weeks	Curcumin capsule (69.4% curcumin, 16.8% DMC, 1.8% BDMC, and 7.6% TO)	1500 mg day^{-1}, p.o	Compared to baseline: ⬇ Serum TG Compared to control: ⬇ Serum hs-CRP	[113]
Serum lipid profile	T2D patients (n = 118)	12 weeks	Curcuminoids + piperine	1000 mg day^{-1} curcuminoids + 10 mg day^{-1} piperine, p.o	Compared to control: ⬇ Serum TC; ⬇ Serum non-HDL-c; ⬇ Serum Lp(a); ⬆ Serum HDL-c	[114]
Diabetic sensorimotor polyneuropathy (DSPN)	T2D patients (n = 80)	8 weeks	Nano-curcumin	80 mg day^{-1}, p.o	⬇ Glycemic indices: HbA1c, FBS; ⬇ DSPN severity: total score of neuropathy, total symptom score, total reflex score	[29]
Metabolic syndrome (MetS)	Apparently healthy males screened positive for MetS (n = 250)	8 weeks	Turmeric	2.4 g day^{-1}, p.o	At 4 weeks: ⬇ BMI; ⬇ WC; ⬇ %BF At 8 weeks: ⬇ LDL-c; CRP	[109]
MetS	Individuals with MetS (n = 120)	6 weeks	Curcumin (native or phospholipidated)	1 g day^{-1}, p.o	⬆ Serum PAB (native curcumin, but not phospholipidated curcumin)	[18]
MetS	Individuals with MetS (n = 120)	6 weeks	Curcumin (native or phospholipidated)	1 g day^{-1}, p.o	No significant effects on serum anti-Hsp 27 concentrations	[138]
MetS	Individuals with MetS (n = 120)	6 weeks	Curcumin (native or phospholipidated)	1 g day^{-1}, p.o	⬆ Serum Zn; ⬆ Serum Zn/Cu ratio Phospholipidated curcumin resulted in higher increases than native curcumin	[110]
MetS	Individuals with MetS (n = 117)	8 weeks	Curcuminoids + piperine	1000 mg day^{-1} curcuminoids + 10 mg day^{-1} piperine, p.o	⬆ Serum SOD activity; ⬇ Serum MDA; ⬇ Serum CRP	[111]
CVD						
Atherogenic risk	T2D patients (n = 117)	6 months	Curcuminoid	750 mg day^{-1}, p.o	⬇ Pulse wave velocity; ⬇ Serum leptin; ⬆ Serum adiponectin	[126]

Table 7 (continued)

Disease/condition	Sample population (n = sample size)	Duration	Treatment	Dose, administration manner	Outcome	Reference
Acute myocardial infarction (MI) associated with coronary artery bypass grafting (CABG)	Patients undergoing CABG without valve surgery (n = 121)z	8 days	Curcuminoid	4 g day^{-1}, p.o	⬇ In-hospital MI incidence; ⬇ Postoperative levels of: CRP, MDA, NT–pro-BNP	[26]

stimulating secretion of the glucagon-like peptide-1 (GLP-1), and also incretin from enteroendocrine L (GLUTag L) cells [31]. These activities are connected to the stimulated proliferation of β-cells and glucose-dependent insulin secretion, both of which are important for T2D treatment and prevention. Kato et al. [31] reported a similar finding regarding curcumin stimulation of GLP-1 secretion in GLUTag L cells in vitro. G-protein-coupled receptors (GPRs) are a group of free fatty acid receptors (FFARs) on the surface of β-cells, among which GPR 40 and GRP 120 are important for β-cells in the mediation of insulin secretion upon stimulation by long-chain fatty acids [105]. Both in vivo and in vitro studies have confirmed that activation of the GPR 40/120 pathway is involved in the GLP-1-stimulating effect of curcumin; this conclusion was reached by the observation that this effect was also reduced when cells were treated with GW1100, a GPR 40/120 antagonist [31].

Obesity is a major co-morbidity of T2D, and strategies that have been developed to treat this disorder by inhibiting the sterol regulatory element-binding protein (SREBP) pathway, important for regulating gene expressions that stimulate fatty acid, triacylglyceride, and cholesterol biosynthesis [106]. Ding et al. [107] reported that curcumin was an active inhibitor of triacylglyceride and cholesterol synthesis by downregulating expressions of both SREBP-1 and SREBP-2, respectively. Curcumin also has been shown to improve glucose homeostasis and insulin sensitivity by upregulating the phosphorylation of IRS-1, IRS-2, and Akt in these mice [107].

Metabolic syndrome (MetS), a term that refers to the co-occurrence of morbidities that increase the risk of heart attack, stroke, and T2D, engages several dysfunctional metabolic outcomes that include excess fat around the waist, insulin resistance, hyperglycemia, atherogenic dyslipidemia, and hypertension [108]. Randomized clinical trial (RCT) studies conducted with MetS subjects reported that turmeric, curcumin, and curcuminoids are effective at improving pertinent anthropometric and biochemical-metabolic parameters in these patients. Turmeric improves body mass index (BMI), waist circumference (WC), and the percent body fat (%BF) and also lowers serum low-density lipoprotein cholesterol (LDL-c) and C-reactive protein (CRP) levels in MetS patients [109]. Curcumin significantly increases the serum pro-oxidant-antioxidant balance (PAB) and the zinc-to-copper (Zn/Cu) ratio, and in addition will also increase serum Zn/Cu ratios without affecting PAB [18, 110]. Short-term supplementation with a curcuminoid-piperine combination also improves oxidative stress and inflammatory status in MetS patients, as evidenced by increased serum superoxide dismutase (SOD) activity and a decrease in serum malondialdehyde (MDA) and CRP levels [111]. Piperine, a pungent alkaloid recovered from black pepper, enhances bioavailability of curcuminoids [111]. The CRP-lowering effect observed in MetS patients fed various purified or standardized preparations of curcumin or curcuminoids leads to a final conclusion derived from a meta-analysis [111]. By alleviating MetS, turmeric and related curcuminoids actively prevented the development of T2D. Notwithstanding this, similar results that pointed to improved metabolic parameters due to curcumin treatment were also reported in patients with existing T2D. Three double-blind RCTs [112–114], involving 44 to 118 T2D patients supplemented with turmeric rhizome powder, a curcumin capsule consisting of curcuminoids and TO, or a curcuminoid-piperine combination over an 8- to 12-week treatment duration, showed similar improvements in anthropometric parameters. These parameters included lowered body weight and BMI, and positive changes in serum lipid profiles that included reduced triglyceride (TG), total cholesterol (TC), LDL-c, and lipoprotein a [Lp(a)], and increased high-density lipoprotein cholesterol (HDL-c). In addition, the inflammation status was amended by a reduction in serum high-sensitivity CRP levels [112–114]. A systematic review and meta-analysis of RCTs [115] has recently reported that curcumin or curcuminoids preparations are effective at lowering body weight and BMI in subjects with obesity or T2D. Nano-curcumin, a nano-formulation of curcumin with enhanced bioavailability, can also improve glycemic indices in T2D subjects. This finding was based on observed reductions in serum glycated hemoglobin (HbA1c) and fasting blood sugar (FBS), and improved severity of diabetic sensorimotor polyneuropathy (DSPN), known to be a common T2D complication [29]. Taken together, the data are very convincing as to the benefits of turmeric and curcumin to improve both the serum

Table 8 Meta-analyses of RCTs on cardioprotective effects of turmeric and turmeric-derived bioactive compounds

Disease/condition	No. of Articles included	Sample population (n = total sample size)	Duration	Treatment	Dose	Outcome[a]	Reference
Blood lipid profile	7	Subjects with CVD risk factors, e.g., dyslipidemia, T2D, prediabetes, MetS, hypertension, prehypertension, or obesity (n = 649)	4 weeks–6 months	Purified curcumin/curcuminoids, turmeric powder, turmeric extract	70–1890 mg day^{-1} curcuminoid equivalent, or 2–2.4 g day^{-1} turmeric powder, p.o	⬇ Serum LDL-c (SMD = −0.340 [−0.530, −0.150]); ⬇ Serum TG (SMD = −0.214 [−0.369, −0.059])	[118]
MetS	8	Subjects with MetS (n = 562)	2–12 weeks	Purified or standardized preparations with known amounts of curcumin/curcuminoids	80 mg day^{-1}–6 g day^{-1}, p.o	⬇ Serum CRP (WMD = −2.20, [−3.96, −0.44])	[111]
Atherosclerosis and CVD	6	Diverse subjects (n = 312)	6 days–3 months	Purified or standardized preparations with known amounts of curcumin/curcuminoids	80 mg day^{-1}–6 g day^{-1}, p.o	⬇ Serum CRP (WMD = −6.44, [−10.77, −2.11]) Stronger effect in subgroups that used bioavailability-improved preparations, and had intervention duration ≥ 4 weeks	[119]

[a]*SMD* standardized mean difference; *WMD* weighted mean difference; numbers in square brackets represent the 95% confidence interval

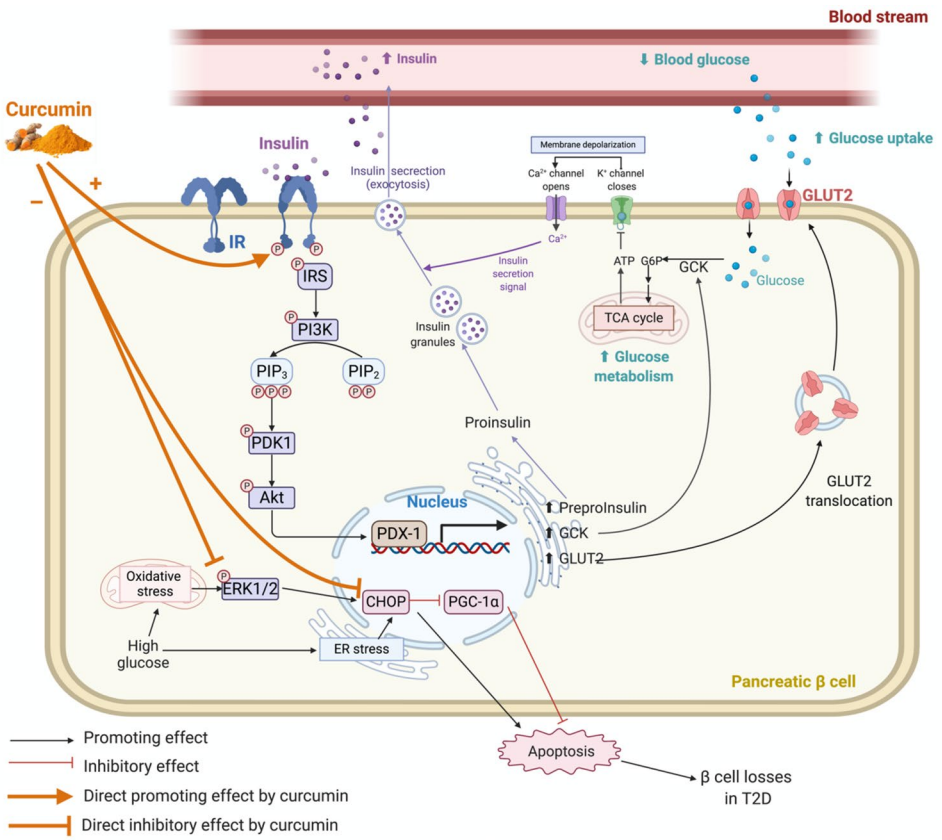


Fig. 4 Pancreatic β-cell signaling mechanisms involved in hypoglycemic and antidiabetic events attributed to curcumin (created with https://BioRender.com). Abbreviations are given below

lipid profile, glycemic indices, hemoglobin glycation, and inflammatory conditions of T2D patients.

Hypolipidemic, atheroprotective, and cardioprotective activities

Studies conducted in vitro, in vivo, and also in human clinical trials have collected considerable evidence to indicate that turmeric and associated bioactive components, especially curcumin, can protect against CVD; albeit underlying mechanisms can differ (Fig. 5). A very strong line of evidence for protection has been attributed to the antioxidant and anti-inflammatory effects of curcumin that involve the regulation cell signaling pathways, such as mitogen-activated protein kinase (MAPK), NF-κB, and nuclear factor erythroid 2-related factor 2–Kelch-like ECH-associated protein 1 (Nrf2-Keap1). These molecular redox signaling pathways combat oxidative stress and inflammation—two highly recognized factors associated with the etiology and pathogenesis of CVDs [116, 117]. In addition, the onset of MetS, as discussed previously in T2D subjects, is another risk factor for the development of CVD which curcumin was effective to mitigate. Of particular interest is that turmeric, curcumin, and curcuminoids are all effective in preventing CVD in both healthy individuals, as well as those individuals that have underlying CVD risk factors. The biomarkers that have been used to indicate these outcomes include reductions in serum LDL cholesterol, TG, and CRP [118, 119].

Atherosclerosis associated with CVD involves the narrowing or hardening of coronary arteries due to the deposition of cholesterol plaques initiated by an increase in serum oxidized low-density lipoproteins (oxLDL) [120]. Curcumin activates increased expression of low-density lipoprotein (LDL) receptors, both in cultured human liver cancer cell line HepG2 [121] and mouse macrophage [122], thus contributing to increased LDL uptake, an important step in protection against atherosclerosis. In the apolipoprotein E knockout ($ApoE^{-/-}$) mouse model, dietary curcumin prevented the incidence and progression of atherosclerosis [27, 28, 123]. Coban et al. [123] reported that curcumin was effective at inducing significant changes in aortic gene expression, in particular those associated with monocyte adhesion to aortic endothelial cells and transmigration through to the aortic endothelium. Curcumin also downregulated the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) in vitro [123] and in vivo [27]. VCAM-1 and ICAM-1 have important roles in the adhesion of monocytes to aortic endothelial cells in the early formation of atherosclerosis, and both are upregulated by NF-κB [124]. Correspondingly, curcumin increases inhibitor of NF-κB (IκB) expression [123], while also decreasing NF-κB activation

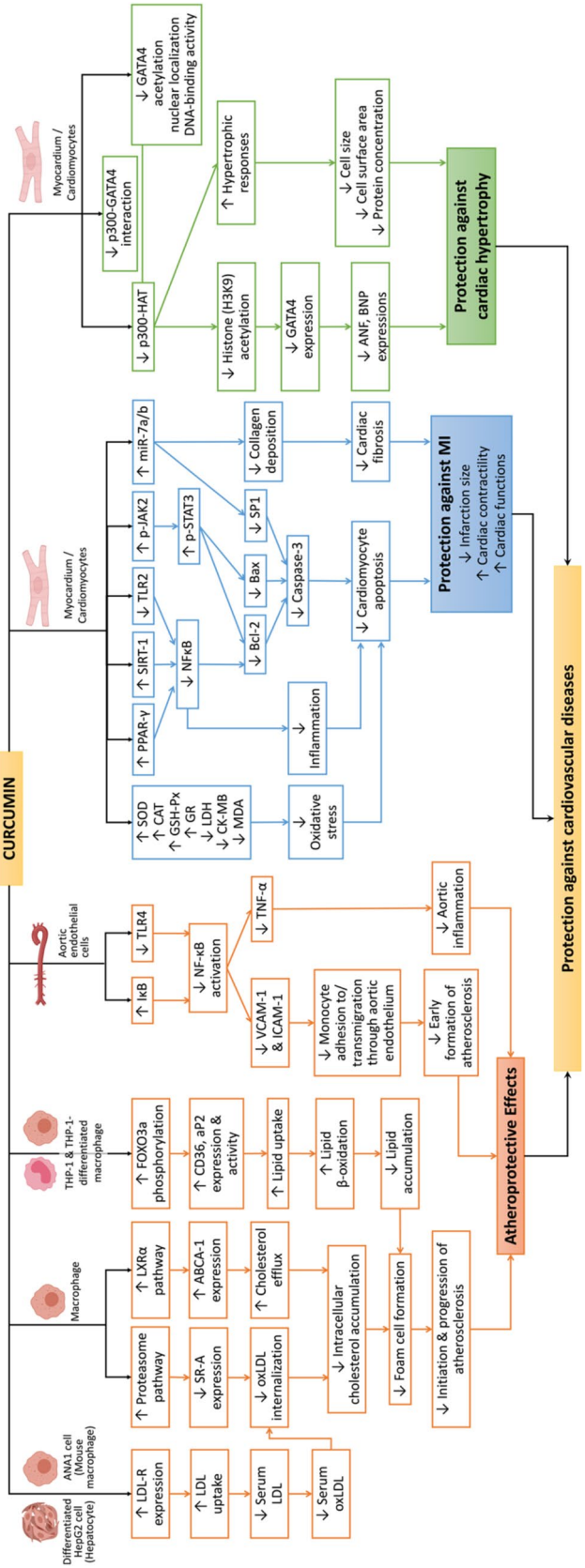


Fig. 5 A schematic of mechanisms that have been attributed to the protective effects of curcumin against etiology of CVD. Abbreviations are given below

and tumor necrosis factor α (TNF-α) [27], in aortic tissue. Expression of toll-like receptor 4 (TLR4), an upstream mediator of NF-κB, was shown to be suppressed by curcumin [27]. Serum levels of NF-κB-associated inflammatory cytokines were also significantly reduced by curcumin treatment in ApoE$^{-/-}$ mice [27, 28]. These researchers found that the atheroprotective capacity of curcumin was due to an affinity to reduce oxLDL-stimulated foam cell development, a crucial step in the initiation and progression of atherosclerosis. Curcumin suppresses intracellular cholesterol accumulation in macrophages by decreasing both oxLDL internalization and increasing cholesterol efflux. Furthermore, molecular studies revealed that these two effects are attributed to downregulation of scavenger receptor class A (SR-A) expression, via proteasome activation, and upregulation of adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) expression, via liver X receptor α (LXRα) pathway, respectively [28].

The affinity of curcumin to upregulate Forkhead box O3a (FOXO3a) activity, a central transcription factor that regulates lipid transport genes in macrophage LDL, and recovered from LDL receptor knockout (LDL-R$^{-/-}$) mice fed a high-fat diet [125], is important for recognizing its potential role to prevent atherosclerosis. Curcumin improves the serum lipid profile of ApoE$^{-/-}$ mice by reducing TC, TG, non-HDL-cholesterol, and increased HDL-cholesterol [28]. These activities correspond to an early retarded progression of atherosclerosis by alleviating oxidation and inflammation and by supporting cholesterol homeostasis through stabilizing the serum lipid profile and preventing endothelial dysfunction. Although human clinical trials designed to show the efficacy of curcumin/curcuminoids to treat atherosclerosis have not yet been established, a daily intake of curcuminoids at 750 mg effectively reduced atherogenic risk in T2D patients in a 6-month double-blind RCT [126].

Myocardial infarction (MI) is frequently associated with underlying atherosclerotic conditions, due to a sudden diminished supply of oxygenated blood caused by narrowing of blood vessels [120]. Hong et al. [127], using an experimental MI rat model, demonstrated numerous benefits of curcumin that included significant protection of cardiac function and reduced cardiac infarction size. Connected with these observations were anti-inflammatory responses related to regulation of genes involved in cytokine–cytokine receptor interaction, extracellular matrix (ECM) receptor interaction, and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway [127]. In particular, the activation of JAK2/STAT3 signaling pathway by curcumin is associated with reduced infarction size in rats injured with cardiac ischemia/reperfusion (I/R) and curcumin induced reduction in oxidative stress, inflammation, and cardiomyocyte apoptosis [25]. The anti-apoptotic effect of curcumin on cardiomyocytes was also reported to be mediated through the downregulation of NF-κB expression and upregulation of expression PPAR-γ and B-cell lymphoma-2 (Bcl-2), an apoptotic factor [128]. Others have reported that curcumin induced upregulation of microRNA-7a/b (miR-7a/b), while also downregulating specific protein 1 (SP1) [129]. Kim et al. [130] reported that curcumin was able to protect cardiac contractibility and cardiac function in I/R-injured rats, and this effect could be mediated by decreasing toll-like receptor 2 (TLR2) expression and macrophage infiltration. TLR2, a key mediator of the innate immune system, is involved in MI by activating the NF-κB pathway that results in cardiomyocyte inflammation and contractile dysfunction [131, 132]. An in vitro model of neonatal rat cardiomyocytes treated with curcumin confirmed the downregulation of TLR2 expression, when MI cells were challenged with hypoxia/reoxygenation (H/R) to mimic the in vivo I/R process [130]. Post-MI cardiac fibrosis was prevented by curcumin, restoring MI-induced downregulation of nicotinamide adenine dinucleotide (NAD)-dependent deacetylase sirtuin-1 (SIRT-1) expression, and collagen deposition in heart tissues [133]. Taken together, these findings show that the capacity of curcumin to ameliorate MI and MI-induced injury is by attenuating oxidative stress, inflammatory status, cardiomyocyte apoptosis, and collagen deposition in the infarcted area, all of which contribute to a reduced infarction size and improved cardiac function. An RCT study reported that curcuminoid administration at 4 g day^{-1} for 3 days before coronary artery bypass grafting (CABG) surgery and 5 days after the surgery, significantly reduced the incidence of in-hospital MI events associated with CABG [26]. In this study, postoperative levels of CRP, MDA, and N-terminal pro-B-type natriuretic peptide were also improved. These biomarkers indicate a direct involvement of antioxidant and anti-inflammatory effects of curcuminoids in the protection against CABG-associated MI. The efficacy of curcuminoids, or other turmeric bioactives, on prevention and treatment of MI in a more general population has not yet been established.

Cardiac hypertrophy is characterized by abnormal enlargement or thickening of heart muscle caused by increased cardiomyocyte size. The more intensive sarcomere is an adaptive response to hemodynamic stresses that results from various pro-hypertrophic stimuli [134]. Although it is compensatory to improve cardiac performance under a stress-induced condition, persisted hypertrophy can cause cardiac decompensation and contractile dysfunction, which will eventually lead to heart failure [134]. Curcumin, DMC, and BDMC have protective effects against cardiac hypertrophy, and one of the most critical mechanisms involves the inhibition of p300-specific histone acetyltransferase (HAT) activity [135]. p300-HAT is a transcriptional coactivator of several transcription factors, e.g., GATA-binding factor 4 (GATA4), critically important for both the development and

differentiation of cardiomyocytes, which precede the progression of cardiac hypertrophy and heart failure. Indeed, histone acetylation is a notable transcriptional modification that mediate the activation of these transcription factors. Inhibition of p300-HAT activity was associated with reduced histone acetylation and hypertrophic responses in rat cardiomyocytes [135]. Curcumin, DMC, and BDMC had positive effects on p300-HAT inhibitory activity and anti-hypertrophic effects to a similar extent. In cardiomyocyte models, curcumin inhibited not only p300-HAT but also the nuclear localization and DNA-binding activity of GATA4 [136, 137], and p300-GATA4 interaction [136]. These effects were associated with repressed hypertrophic responses of the cardiomyocytes, and prevention of heart failure in both hypertension-induced and MI-induced heart failure rat models [136].

Associated with these protective effects of curcumin on molecular signaling of myocardial health is the observation that curcuminoid supplementation reduced circulating CRP levels, a chronic inflammatory biomarker that predicts risk to atherothrombosis and CVD in both normal healthy individuals and individuals with chronic health conditions [119]. However, more human clinical evidence for turmeric having protective and therapeutic efficacies against CVD, in particular, is needed. Furthermore, well-designed and longer-term RCTs with specific CVD outcome measures are required to confirm the potential health benefits of curcumin in lowering incidence of CVD.

Conclusion

This review summarized the complex chemical composition and specific bioactivities of turmeric and turmeric-derived constituents, such as curcumin, DMC, BMC, and TO. A focus was placed on describing cellular and molecular mechanisms that underlie the etiology and pathogenesis of diabetes, and CVD disorders, and how the protective properties of turmeric and its constituents can lessen these chronic disease conditions. Favorable results generated from human RCTs on the efficacies of these bioactives that mitigate risk factors for the aforementioned health conditions further support the use of turmeric constituents as ingredients in functional food and nutraceutical preparations. To fully evaluate the long-term preventative and therapeutic efficacies of these compounds, RCTs with subjects from a more general population, having longer intervention durations and a specific endpoint for reduction in disease outcomes are warranted.

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