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Review

Curcumin as a potential protective compound against cardiac diseases

Shuai Jiang[a,c,1], Jing Han[b,1], Tian Li[d,1], Zhenlong Xin[d], Zhiqiang Ma[e], Wencheng Di[f], Wei Hu[c], Bing Gong[a], Shouyin Di[e], Dongjin Wang[a,*], Yang Yang[a,c,*]

[a] Department of Thoracic and Cardiovascular Surgery, Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing 210008, Jiangsu, China
[b] Department of Ophthalmology, Tangdu Hospital, The Fourth Military Medical University, 1 Xinsi Road, Xi'an, 710038, China
[c] Department of Aerospace Medicine, The Fourth Military Medical University, 169 Changle West Road, Xi'an, 710032, China
[d] Department of Biomedical Engineering, The Fourth Military Medical University, 169 Changle West Road, Xi'an, 710032, China
[e] Department of Thoracic Surgery, Tangdu Hospital, The Fourth Military Medical University, 1 Xinsi Road, Xi'an, 710038, China
[f] Department of Cardiology, Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing, 210008, Jiangsu, China

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ABSTRACT

Curcumin, which was first used 3000 years ago as an anti-inflammatory agent, is a well-known bioactive compound derived from the active ingredient of turmeric (Curcuma longa). Previous research has demonstrated that curcumin has immense therapeutic potential in a variety of diseases via anti-oxidative, anti-apoptotic, and anti-inflammatory pathways. Cardiac diseases are the leading cause of mortality worldwide and cause considerable harm to human beings. Numerous studies have suggested that curcumin exerts a protective role in the human body whereas its actions in cardiac diseases remain elusive and poorly understood. On the basis of the current evidence, we first give a brief introduction of cardiac diseases and curcumin, especially regarding the effects of curcumin in embryonic heart development. Secondly, we analyze the basic roles of curcumin in pathways that are dysregulated in cardiac diseases, including oxidative stress, apoptosis, and inflammation. Thirdly, actions of curcumin in different cardiac diseases will be discussed, as will relevant clinical trials. Eventually, we would like to discuss the existing controversial opinions and provide a detailed analysis followed by the remaining obstacles, advancement, and further prospects of the clinical application of curcumin. The information compiled here may serve as a comprehensive reference of the protective effects of curcumin in the heart, which is significant to the further research and design of curcumin analogs as therapeutic options for cardiac diseases.

Contents

Abbreviations: H3K9, H3 at lysine 9; ROS, reactive oxygen species; RNS, reactive nitrogen species; GSH, glutathione; HO-1, heme-oxygenase-1; SOD, superoxide dismutase; MDA, malondialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; IR, ischemia reperfusion; RCR, respiratory control ratio; ADP:O, ADP:oxygen; TBHP, tert-butyl hydroperoxide; PI3K, phosphoinositide 3-kinase; ERK1/2, extracellular signal-regulated kinase 1/2; Bcl-2, B-cell lymphoma 2; JAK2/STAT3, janus kinase 2 and signal transducer and activator 3 of transcription; ERS, endoplasmic reticulum stress; CVB3, coxsackievirus B3; IL, interleukin; Egr-1, early growth response-1; CPB, cardiopulmonary bypass; IRI, ischemia/reperfusion injury; LDH, lactate dehydrogenase; CK, creatine kinase; ECM, extracellular matrix; LDH, lactate dehydrogenase; PARP, poly-ADP-ribose polymerase; TLR2, toll-like receptor 2; HSP, heat shock protein; iNOS, inducible NO synthase; GSK-3β, glycogen synthase kinase 3β; MMPs, metalloproteinases; VPB, ventricular premature beats; VT, ventricular tachycardia; VF, ventricular fibrillation; CABG, coronary artery bypass grafting; LV, left ventricular; TBARS, thiobarbituric acid reactive substances; PAC, 5-Bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidone; ANP, atrial natriuretic peptide; MEF, myocyte enhancer factor; OGD/R, oxygen-glucose deprivation and reoxygenation; ECG, electrocardiogram; CI, combination index; VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homolog; AT1R, angiotensin 1 receptor; NC, nicotinate-curcumin; IFN-γ, interferon-γ.

* Corresponding authors at: Department of Biomedical Engineering, The Fourth Military Medical University, 169 Changle West Road, Xi'an 710032, China.
E-mail addresses: dongjinwang210@163.com (D. Wang), yang200214yy@163.com (Y. Yang).
[1] These authors contributed equally to this work.

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1. Introduction

According to the 2016 Heart Disease and Stroke Statistics report, cardiac diseases are currently the leading causes of mortality in both developed and developing countries and, to a large extent, surpass cancer and cerebrovascular-related deaths worldwide [1]. Cardiac diseases consist of a broad spectrum of diseases, such as myocardial ischemia, cardiomyopathy, hypertension, and arrhythmia, all of which resulted in 17.3 million deaths (31.5%) in 2013 compared to 12.3 million (25.8%) in 1990 [2]. According to a WHO/FAO report (1974), Indian populations who ingest between 2 and 2.5 g turmeric daily are healthier and have lower risk of cardiac diseases [3]. This suggests that cardiac diseases are preventive and depend largely on eating habits, further supporting curcumin as a therapeutic candidate for cardiac diseases.

The last decade has witnessed a surge in the use of plant-derived products (also known as phytochemicals or phytoceuticals) that serve as preventive and therapeutic drugs against various diseases. Turmeric (Curcuma longa), a type of spice in curry dishes, is a major ingredient of mustard preparations used as a garnish in the United States. Turmeric was first used almost 3000 years ago as an anti-inflammatory agent and was introduced to the Europe and North America in the 14th century. In Ayurvedic medicine, turmeric has been used to treat common colds, coughs, jaundice and other common diseases [4]. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], also known as diferuloylmethane, is a well-known dietary polyphenol found in turmeric. It was first discovered approximately two centuries ago when Vogel and Pelletier reported the isolation of a “yellow coloring-matter” from the rhizomes of turmeric and named it curcumin. Thereafter, it was identified by Rougghley and Whitting in 1973 [5] and came into view of researchers progressively. The major curcuminoids present in turmeric are curcumin (curcumin I) demethoxycurcumin (curcumin II), bis-demethoxycurcumin (curcumin III), and cyclocurcumin (curcumin IV) [6,7]. Initially, it was proven that the anti-inflammatory effects of curcumin are comparable to the classical drugs hydrocortisone, phenylbutazone, and ibuprofen. Notably, curcumin almost produces no toxicity in humans compared to common anti-inflammatory drugs but may decrease white blood cell count, promote ulcer formation and intestinal bleeding. Moreover, curcumin has an immense bactericidal effect that can meet the standards and effects of antibiotics. Curcumin exerts protective effects on a variety of diseases such as cardiac diseases [8], cancer [9], diabetes [10], Alzheimer’s disease [11], rheumatoid arthritis [12], and psoriasis [13]. Our laboratory has discovered that curcumin is a protective compound against myocardial ischemia [14] and endothelial injury [15], whereas its relationship with cardiac diseases has not been well reviewed. Therefore, further understanding of the mechanisms by which curcumin produces these effects may aid in experimental studies and provide therapeutic avenues for cardiac diseases.

In this review, we first provide a basic background of cardiac diseases and curcumin and continue with the description of pivotal actions of curcumin in embryonic heart development. Secondly, we introduce the biological actions of curcumin in cardiac diseases, including its anti-oxidative, anti-apoptotic, and anti-inflammatory actions. Thirdly, curcumin can exert its beneficial effects in myocardial ischemia, diabetic cardiomyopathy, hypertrophic cardiomyopathy, arrhythmia, and doxorubicin-related cardiotoxicity. Ultimately, we will discuss the clinical evidence, negative effects, remaining obstacles and advancement, further directions and prospective applications of curcumin. This review highlights recent advances and provides a comprehensive picture of curcumin, which may be helpful in drug design and clinical therapy of cardiac diseases.

2. Curcumin and embryonic heart development

Embryonic heart development is a crucial process throughout the whole growth stage, the dysfunction of which may contribute to postnatal cardiomyopathy or congenital heart disease. Previous studies have revealed that curcumin mediates histone acetylation and the expression of cardiac transcription factors, ultimately controlling the progress of normal heart development [16–18]. Relevant mechanisms involve: 1) curcumin activating the NO signaling and inhibiting the acetylation of histone H3 [19], and 2) curcumin selectively suppressing AdBMP2-induced expression of HAT p300 and histone H3 acetylation [16].

Inhibition of histone acetylation by curcumin plays a pivotal role in cardiogenesis. Alcohol increases the acetylation of histone H3 at lysine 9 (H3K9) by 2.76-fold and significantly enhances the expression of GATA4 and Mef2c in cardiac progenitor cells. Prenatal alcohol exposure may contribute to the acetylation of histone H3 and abnormal heart development, even causing congenital heart disease. When cells were treated with curcumin, the hyperacetylation of H3K9 and overexpression of GATA4 and Mef2c was reversed, indicating that curcumin can inhibit the overexpression of genes that cause cardiac malformations by reversing alcohol-induced hyperacetylation of H3K9 [17]. Curcumin can activate the NO-cGMP axis and downregulate the overexpression of cardiac-specific genes (GATA4, Nkx2.5, Mef2c, and cardiac troponin I),