REVIEW ARTICLE

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The Role of *Centella asiatica* and Its Main Bioactive Compound, Asiatic Acid in Cardiac Remodeling: A Systematic Review of Animal Studies

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Cardiac remodeling is a phenotype of heart failure characterized by a molecular, cellular, and interstitial change in the heart, which manifests in the change of size and function of the heart after specific insults with multiple mechanisms. *Centella asiatica* (CA) and its main bioactive triterpenoid, asiatic acid (AA), pose antioxidant and anti-inflammatory effects. Still, no adequate clinical trials support the potency of CA and AA as anti-cardiac remodeling. Hence, this systematic review aims to provide an in-depth analysis of CA extract and AA in animal studies' prevention or therapy of cardiac remodeling. The search strategies were conducted based on preferred reporting Items for systematic reviews and meta-analysis (PRISMA) protocol through Pubmed, EMBASE, Scopus, and Web of Science using keywords as follows: "*Centella asiatica*" OR "Asiatic Acid" AND "Cardiac Remodeling" OR "Cardiac Hypertrophy" OR "Cardiac Fibrosis" along with their synonym. The data collected included hemodynamic parameters based on echocardiography, biomolecular tests such as quantitative polymerase chain reaction (qPCR), Western blotting, or biochemistry procedures. The paper quality was assessed using Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias (RoB). The previous selected study has shown that CA and AA might prevent and cure cardiac remodeling by inhibiting various pathways and protein expressions through AMPKα, NOX2/4, PI3K/Akt/mTOR, p70S6K, YAP/TAZ, and IL-1β, IL-6, and IL-18 cytokines. CA and AA, thus, exhibit cardioprotective effects in the animal model, which need to be confirmed in the clinical trials on humans.

Keywords*: cardiac remodeling, cardiac hypertrophy, cardiac fibrosis, Centella asiatica, asiatic acid*

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Introduction

Heart failure has become a major problem globally and causes high morbidity and mortality. It is predicted that around 1-2% of the general population is suffering from heart failure. However, this condition is an "iceberg phenomenon" because more than 2% of people have risk factors for heart failure, such as hypertension, diabetes mellitus, aging, obesity, and other metabolic conditions.[1] This indicates a potential increase in heart failure cases in the future.

Heart failure starts when the heart fails to pump blood adequately to meet the needs of tissue perfusion, resulting in tissue hypoxia and congestion. The imbalance in homeostasis caused by these conditions leads to the initiation of cardiac remodeling as an adaptive mechanism. Cardiac remodeling is a molecular, cellular, and interstitial modification to enhance the heart function capacity and maintain tissue demand. The features of cardiac remodeling are the changes in geometry and size of cardiomyocytes (*i.e.,* cardiac hypertrophy) and the rise of extracellular matrix tissue (*i.e.,* cardiac fibrosis). Despite its main function as an adaptive system, longer periods of cardiac remodeling might evolve into pathological remodeling.[2]

Cardiac remodeling is divided into adaptive and pathological. From a clinical perspective, adaptive remodeling increases contractility to support adequate cardiac output and blood pressure, or the compensated phase, characterized by concentric hypertrophy. Adaptive remodeling is reversible, as observed in athletes. However, disease-related remodeling has pathological features, predominately with concentric or eccentric hypertrophy, and irreversible.[2]

From the molecular perspective, adaptive cardiac remodeling is predominant with activation of many growth factors, such as insulin growth factor (IGF)-1. This further initiates the signal transduction through phosphoinositide 3-kinase (PI3K), Ak strain transforming (Akt), and mammalian target of rapamycin (mTOR), or IGF-1R/PI3K/Akt/mTOR signaling pathway. This results in the expression of hypertrophy protein that leads to cell survival.[3,4] Conversely, G-protein coupled receptor (GPCR) activation commences the pathological remodeling, such as angiotensin receptor 1 (AT1R) or β-adrenergic receptor. Both proteins will activate various conditions, such as calcium handling problems, leading to the electron-excitation coupling (ECC) dysfunction, increasing the production of reactive oxygen species (ROS) through the activation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX),[5] and increasing the production of a proinflammatory cytokine through nuclear factor- κB (NF-κB),[5,6] which induce the process of priming and activation of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), which promote proinflammatory state by releasing the interleukin (IL)-1β, IL-6, and IL-18.[7-10]

Based on the currently available guidelines, heart failure patients are prescribed drugs that primarily target the key molecules or signaling pathways involved in cardiac remodeling to reduce cardiac hypertrophy. For example, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) target the renin-angiotensin-aldosterone system (RAAS). Angiotensin receptor-neprilysin inhibitor (ARNIs) are used to replace ACEIs and ARBs that also inhibit natriuretic peptide degradation facilitated by neprilysin enzyme. β-blockers are prescribed to block beta-adrenergic receptors, downregulating the activation of adrenergic receptor in cardiomyocytes. In addition, other drugs such as vasodilators also alleviate cardiomyocyte stress indirectly by reducing overload pressure resulting from peripheral vasoconstriction.[11,12] Furthermore, some antidiabetic drugs, such as sodium-glucose transporter (SGLT)2 inhibitors, are preferred compared to other drugs to treat heart failure with preserved ejection fraction (HFpEF).[12,13]

Despite the advancement in heart failure drug research, not all drugs are readily available to cure patients, especially those with HFpEF.[12] So far, current drugs do not guarantee the suppression of disease progression and mortality. Furthermore, although ACEIs and ARBs are proven safe and routinely prescribed in primary health care, they pose contraindications for pregnancy, renal stenosis, and heart failure with hypotension.[14] Thus, finding other alternative agents is still needed, especially at the preclinical levels. Natural sources, especially herbs, are becoming promising sources as their secondary metabolites have great potential to become lead compounds as therapeutic agents.[15] Preclinical studies have also shown promising results in natural compounds for treating cardiac remodeling. For instance, andrographolide from *Andrographis paniculata*,[16-18] curcumin[19] from *Curcuma longa*, and alpha-mangostin[20] from *Garcinia mangostana*, are potential candidates for anti-cardiac hypertrophy. As a one of native herbs found in Indonesia, *Centella asiatica* (CA) should be investigated as the next of source of natural compounds.

CA is a herb rich in triterpene, with asiatic acid (AA) being one of the most common triterpenoid found in CA.[21] Compared to other triterpenoids found in CA, AA is

abundant in the leaves, either as an aglycone, asiaticoside, or in its free form. Commonly, 30% of the triterpenoids in CA is AA. Furthermore, in eleven accession CA from Nilgiri hill region in India, the AA content ranged from 0.04% to 0.58%.[22] A study characterizing CA leaves from New Zealand using ultrasound high-performance liquid chromatography coupled with mass spectrometry (UHPLC-MS/MS) found the AA content to be 1.11±0.39 mg/g. Another study from New-Zealand reported a similar AA content of 2.49±0.07 mg/g.[23] Therefore, as a part of drug discovery, AA can be abundantly extracted from CA leaves.

Furthermore, CA has various benefits in treating noninfectious diseases, such as dermatological[21], neurological disease[24] metabolic syndrome[15], and infectious disease, especially targeted anaerobic bacteria for treating urinary tract and enteric infections.[25] CA is well-known for its antioxidant, anti-inflammatory, and ability to improve mitochondrial function.[26] Despite CA and AA having a widespread advantage in managing diseases, no previous clinical trials have investigated the relationship between CA or AA and cardiac remodeling progression in human models. Despite these facts, a lot of *in vivo* studies have discovered the benefits of CA or AA against cardiac remodeling progression. Here, this systematic review of animal studies on CA or AA modulates cardiac remodeling progression, providing insight into how CA or AA interacts with the biomolecular changes in the disease.

Material and methods

Eligibility Criteria and Data Extraction

Experimental studies using animal models were included as part of search strategies to evaluate the efficacy of CA or AA in the progression of cardiac remodeling. Populations, intervention, comparison, and outcome (PICO) are important aspects for defining the focus of the systematic review. The population in this paper was animal study, involving any animal subjects with a cardiac remodeling disease model treated with CA or AA. Comparison is not mandatory in the animal study since there were various of golden standard treatments available for cardiac remodeling. Regarding outcomes, this study focuses on identifying the effect of CA and AA on modulating heart functional and biomolecular changes in heart tissue or blood markers, aiming to understand how the CA and AA modulate the disease. The primary data extracted was a significant effect of CA or AA on modulating cardiac hypertrophy or remodeling in functional aspects as defined in the echocardiography results, such as ejection fraction (EF), intraventricular septal (IVS), fractional shortening (FS), left ventricular internal diameter (LVID), and left ventricular posterior wall thickness. This study also notes the effects of CA and AA on specific protein or gene expression alteration in the disease process, which also contribute as downstream effectors, such as PI3K, Akt, mitogen activates protein kinase (MAPK), and extracellular signal-regulated kinase 1/2 (ERK1/2), oxidative stress markers like superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities, and malonaldehyde (MDA) concentration. As well as pro-inflammatory gene or protein expressions (*e.g.*, IL-1β, NLRP3, and NF-κB) and other related genes or proteins associated with specified mechanisms such as mitochondria dysfunction, autophagy, or apoptosis.

Other data to be extracted were as follows: Author and publication year (preferentially ten years previously published paper, but if not present, without year limitation), species, gender, and body weight of the animal model, if present, type of intervention (including CA extract or AA with specific dosage and route of administration), disease type (cardiac hypertrophy or cardiac fibrosis), study model, and subject in each group. Any model of cardiac remodeling, including post-myocardial infarction, hypertensive rats, and others, were included.

Papers that did not present *in vivo* studies, focused on diseases other than cardiac remodeling, were review papers, were abstract-only papers, were written in other language than English, or discussed combination therapy were excluded. If present, clinical trial reported the effect of AA and CA for cardiac remodeling will be supplemented.

Search Strategy and Selection of Studies

Four databases were searched: PubMed, EMBASE, Scopus, and Web of Science (Table 1). The combination words of (*Centella asiatica* OR Asiatic Acid) AND (Cardiac Remodeling OR Cardiac Fibrosis OR Cardiac Hypertrophy) were used. The entire search was checked for animal studies and nonhuman studies.

The results generated by each database were recorded, downloaded as the Bibtex or RIS format, and removed from the citation manager, Mendeley reference manager for Windows (Elsevier, Amsterdam, Netherland). The preferred reporting items for systematic reviews and meta-analysis (PRISMA) guideline protocol was applied to select the studies.[27] The duplicates were eliminated before screening. The retrieved papers were included based on the inclusion and exclusion criteria.

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Table 1. Keywords used in each database.

Database	Keywords
PubMed	(*Centella asiatica* OR Asiatic Acid) AND (Cardiac Remodeling OR Cardiac Hypertrophy OR Cardiac Fibrosis OR Myocardial Remodeling OR Myocardial Hypertrophy OR Myocardial Fibrosis)
EMBASE	(*Centella asiatica* OR Asiatic Acid) AND (Cardiac Remodeling OR Cardiac Hypertrophy OR Cardiac Fibrosis OR Myocardial Remodeling OR Myocardial Hypertrophy OR Myocardial Fibrosis)
Scopus	(*Centella asiatica* OR Asiatic Acid) AND (Cardiac Remodeling OR Cardiac Hypertrophy OR Cardiac Fibrosis)
Web of Science	(*Centella asiatica* OR Asiatic Acid) AND (Cardiac Remodeling OR Cardiac Hypertrophy OR Cardiac Fibrosis OR Myocardial Remodeling OR Myocardial Hypertrophy OR Myocardial Fibrosis)

Risk of Bias (RoB) Assessment

Animal studies are known to exhibit significant differences from clinical studies, especially in terms of animal species or strains, and sometimes the qualities of reporting are poorly and inadequate. Thus, to ensure the integrity of the results of the included studies in this systematic review, we performed a RoB assessment. Selected studies were further assessed by each investigator using Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) RoB tools[28] adapted from Cochrane RoB. Six risk scopes will be measured to judge paper quality, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases implemented in ten questions (Table 2). Different conclusions gathered from each author regarding the data collection and interpretation were resolved through the open discussion of each author that was directed and led by the expert panelists in the authorship (WA, HW, and AB).

Table 2. SYRCLE RoB ten questions.

Item	Scope of Bias (Type, Domain)	Questions Related to the Bias
1	Selection Bias, Sequence Generation	Was the allocation sequence adequately generated and applied?
2	Selection Bias, Baseline Characteristics	Were the groups similar at baseline or were they adjusted for confounders in the analysis?
3	Selection Bias, Allocation Concealment	Was the allocation adequately concealed?
4	Performance Bias, Random Housing	Were the animals randomly housed during the experiment?
5	Performance Bias, Blinding	Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?
6	Detection Bias, Random Outcome Assessment	Were animals selected randomly for outcome assessment?
7	Detection Bias, Blinding	Was the outcome assessor blinded?
8	Attrition Bias, Incomplete Outcome Data	Were incomplete outcome data adequately addressed?
9	Reporting Bias, Selective Outcome Reporting	Are reports of the study free of selective outcome reporting?
10	Other, Other Sources of Bias	Was the study apparently free of other problems that could result in a high risk of bias?

Results and Discussion

Search Results and Selected Studies

Paper searching, screening, and eligibility through four databases are presented in Figure 1. The total collected papers were 33 papers, with 14 duplicate papers. Therefore, 19 papers were included in the screening. After excluding seven papers based on their abstract and title, three additional papers were omitted due to combination therapy (n=1), not using CA or AA (n=1), and not a cardiac remodeling study model. Nine papers were further analyzed for RoB, using SYRCLE RoB.

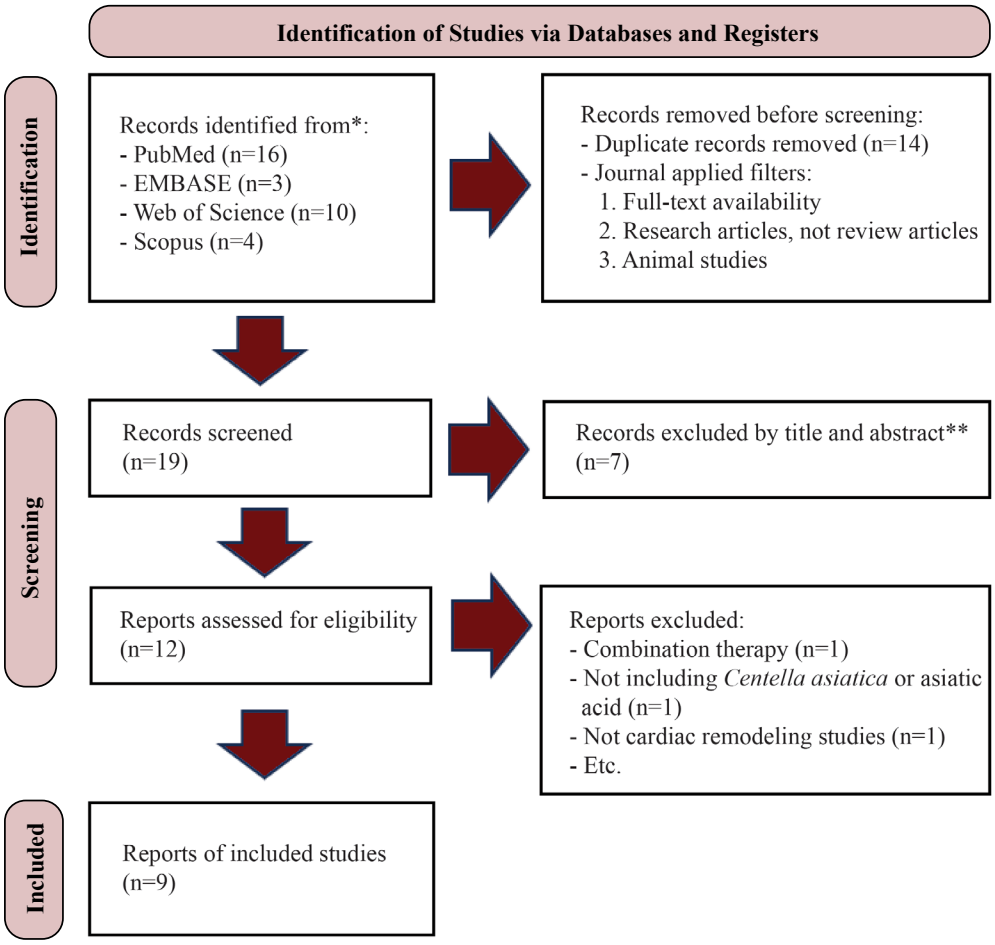

Figure 1. PRISMA Diagram

Results of SYRCLE RoB Assessment

Table 3 summarizes the RoB assessment from the included studies. The entire studies suggested no risk in attrition, reporting, or other bias. However, the main profound unclear bias was the randomization and blinding that was found in most studies, namely concealment in selection bias (8/9 studies), random housing in performance bias (9/9 studies), blinding in performance bias (8/9 studies), random outcome assessment in detection bias (7/9 studies), and blinding in detection bias (8/9 studies). The main reason for unclear reasons was that no adequate explanations were imbued in the articles. On the other hand, one paper only explicitly stated that allocation, procedure, and data analysis were performed randomly and blindly. Thus, most studies were at unclear RoB, especially in performance and detection bias.

The Baseline Characteristics of the Included studies

The selected studies used male rats (Sprague-Dawley or Wistar Rats) or mice (C57BL/6). The total number of rats or mice used in the studies varied from 6 to 10. Age and body weight of the rats were 8-10 weeks and 150-240 g, whereas age and body weight of mice were 6-10 weeks and 20-30 g, respectively. Only one study used CA extract[35], and the rest used AA for the intervention. In terms of administration, the AA dosage in most studies was 20 mg/kg/day and 100 mg/kg/day and given peroral. Two studies provided different dosage ranges in 10 or 30 mg/kg/day[36] and 5, 25, or 50 mg/kg/day peroral.[37] AA was given after the disease was induced.[36,37] Various models were used: spontaneous hypertension rats, transaortic banding (TAB), high-fat diet, isoproterenol injection, angiotensin (Ang) II infusions, Nω-nitro-L-arginine-methyl-ester (L-NAME) injection, and postmyocardial infarction. Transaortic banding was the predominant model to be used.

The Mechanism of Cardiac Remodeling Progression

Cardiac remodeling is a complex process at the cellular and extracellular levels. Cardiac remodeling progresses through cardiac hypertrophy and cardiac fibrosis. Pathological cardiac remodeling shows declining function of the heart contractility. Pathological cardiac remodeling might be initiated by various stimulations, such as Ang II,

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Table 3. Risk of bias assessment.

First Author, Year	Selection Bias			Performance Bias		Detection Bias		Attrition Bias	Reporting Bias	Other
	Sequence Generation	Baseline Characteristics	Allocation Concealment	Random Housing	Blinding	Random Outcome Assessment	Blinding	Incomplete Outcome Data	Free of Selective Outcome Reporting	Other Sources of Bias
Li *et al*., 2021 [29]	Yes	?	?	?	?	Yes	?	Yes	Yes	Yes
Bunbupha *et al*., 2015 [30]	?	Yes	?	?	?	?	?	Yes	Yes	Yes
Si *et al*., 2014 [31]	?	?	?	?	?	?	?	Yes	Yes	Yes
Si *et al*., 2015 [32]	Yes	Yes	?	?	?	?	?	Yes	Yes	Yes
Meng *et al*., 2019 [33]	?	Yes	?	?	?	?	?	Yes	Yes	Yes
Xu *et al*., 2015 [34]	?	?	?	?	?	?	?	Yes	Yes	Yes
Ding *et al*., 2022 [35]	Yes	Yes	?	?	?	?	?	Yes	Yes	Yes
Ma *et al*., 2016 [36]	Yes	?	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes
Huo *et al*., 2016 [37]	?	?	?	?	?	?	?	Yes	Yes	Yes

Yes: Low risk of bias; No: High risk of bias; ?: Unclear risk of bias.

catecholamines, mechanical stimuli, and insulin hormones in their specific receptors. The stimuli lead to the activation of downstream effectors in the transduction signaling process, for example, diacylglycerol (DAG), protein kinase B (PKB), NF-κB, NOX isoforms 2 or 4 (NOX2/4), ERK1/2, and other proteins.[2]

Two studies[29,35] concluded that cardiac remodeling is activated through the PI3K/Akt pathway, along with mTOR.[36] Furthermore, ERK1/2 is also suppressed, with the downregulation of p38 in MAPK. Oxidative stress also becomes one of the hallmark mechanisms in cardiac remodeling which is targeted by AA.[36] Even so, inflammation markers were dominantly increased in most studies and were suppressed by AA. Nitrite oxide synthetase (NOS), adenosine monophosphate-activated protein kinase α (AMPKα), acetyl CoA carboxylase (ACC), ribosomal protein S6 kinase beta-1 (p70S6K), S6, and yes-associated protein (YAP) are other proteins contributing to the disease progression.

Cardiac remodeling comprises two types: adaptive and pathological remodeling. Adaptive remodeling might be produced by stimulation growth factors such as IGF, which leads to activation of the PI3K/Akt/mTOR pathway, whereas the pathological one presents as a result of activation of neurohumoral factors through GPCR[38] such as AT1R and catecholamine receptor.[39] Nitrite oxide (NO) and vasoactive peptides, such as atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP), are released to oppose the pathological signaling through cyclic guanosine monophosphate (cGMP), and the alteration of these substances might propagate the remodeling process.[40]

Oxidative stress, without a doubt, is one initiator in cardiac remodeling and becomes a potential therapeutic target.[41] An imbalance of redox results in uncontrolled increasing production of ROS or reactive nitrogen species (RNS) and a decline in the capacity of internal antioxidant systems, such as SOD, GPx, catalase (CAT), and glutathione (GSH). Superoxide, peroxynitrite, and hydrogen peroxide is one of an example of ROS/RNS that might initiate cardiac hypertrophy, primarily through GPCR activation.[42] ROS might activate multiple cardiac remodeling pathways, such as ERK1/2, NF-κB, NLRP3, PKB, MAPK, and matrix metalloproteinase (MMP).[7,10,42,43] Uncontrolled ROS leads to mitochondrial damage and dysfunction as well. NOX2/4 have been known to increase cardiac hypertrophy, along with its subunits such as $p22^{phox}$, $gp91^{phox}$, $p67^{phox}$, and $p47^{phox}$.[5,44] Nuclear erythroid factor (Nrf)2 plays a vital role in increasing the expression of cellular antioxidant proteins, thus alleviating cardiac remodeling process. This effect was observed in mice with diabetes mellitus treated with empagliflozin.[45,46]

The pro-inflammatory condition might be initiated by the increasing rate of ROS. The master regulator in this context is NF-κB, as described in the included studies.[6] Phosphorylation of NF-κB leads to the binding of this protein to the κB site, which initiates the activation of angiogenesis, inflammation, and proliferation. NF- κB also has a pivotal role in the priming and activating NLRP3 inflammasome, which increases proinflammatory cytokine production (*e.g.,* IL-1β, IL-6, and IL-18, and extracellular matrices).[7,8] TGF-β/Smad has contributed to the increasing expression of collagen tissue growth factor (CTGF), collagen, and fibronectin[47] Interestingly, the pro-inflammatory state also increases NOX2/4 expression. In other words, this condition will further deteriorate the intracellular concentration, which results in cardiomyocyte death.

There is growing evidence that heart size is controlled by the Hippo pathway, a conservational cell survival pathway through Wnt[48] and IGF signaling.[49] YAP and transcriptional coactivator with PDZ-binding (TAZ) mediate this pathway. Protein kinase, mammalian sterile 20-like kinase 1 and 2 (MST1/2), large tumor suppressor 1 and 2 (LATS1/2), scaffold protein Salvador (SAV), and Mps one binder kinase activator 1A and B (MOB1A/B) initiate the phosphorylation of YAP/TAZ protein. When YAP/TAZ complex is not phosphorylated, it will bind in its activation site in the genes, especially in TEA domain (TEAD) transcription factor. This pathway also mediates the metabolism of the heart and mitochondrial function. In other words, YAP/TAZ activation might alleviate the cardiac remodeling.[35] Oxidative stress, cytokine, and endoplasmic reticulum stress inhibit this protein's phosphorylation, thus inactivating the Hippo pathway.[50]

Intriguingly, p70S6K, AMPKα, and ACC protein intracellular pathway has vital role towards remodeling in cardiomyocytes, which plays importantly in the cellular metabolism.[36] p70S6K poses multiple intracellular roles, such as regulation of translation process in protein synthesis, cell growth and size, cell cycle progression in promoting G1 to S phase, and cell survival. mTOR/p70S6K is activated through insulin signaling.[51] AMPK knock-out mice with α1 and α2 isoforms reduced the basal metabolic rate, including oxygen uptake and energy expenditure.[52] Furthermore, its activation is not related to the activation of p706SK, ERK, and

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nuclear factor of activated T cell (NFAT) but instead through O-linked-N-acetylglucosaminylation modification.[53] AMPK serves important adaptation in cardiac dysfunction, especially in metabolic syndrome, by enhancing fatty acid oxidation, autophagy, and mitochondrial biology, while also reducing apoptosis levels.[54] ACC2 is important in cardiac metabolism and fatty acid oxidation which is also linked directly to the AMPK as a master regulator of cellular metabolism.[55] This condition is proven by a previous study suggested that genetically modified mouse ACC2 flox/flox ($ACC2^{f/f}$) found that increasing fatty acid oxidation increased without overloading the mitochondria, good cardiac function, improved myocardial energy, resistance to metabolic remodeling, and attenuated cardiac hypertrophy and fibrosis.[56]

Molecular Target of Cardiac Remodeling by CA Extract and AA

Cardiac dysfunction is reported through hemodynamic parameters (heart rate or blood pressure) and echocardiography. Blood pressure is a standard parameter that has been reported, and all studies have observed a decrease in blood pressure. This evidence is also profound in the previous studies that CA prevented high blood pressure.[57] All selected studies that conducted echocardiography also reported improvements in ejection fraction (EF) or fractional shortening (FS), along with other parameters.

The summary of molecular targets and interaction by CA and AA in cardiac remodeling progression are summarized in Table 4. CA has well-known antioxidant and anti-inflammatory effects, especially from its triterpene, such as AA, through both cardiovascular and non-cardiovascular contexts.[58,59] One of the included studies concluded that through the *in silico* model, AA has 58.97% of the protein target compared to other components in CA, and this finding was confirmed in the *in vivo* study.[35] However, based on the retrieved previous study, only one study discusses the role of CA extracts in cardiac remodeling.

On the related cardiac remodeling pathway,[35] the target proteins of AA, included CDP/cut alternatively spliced product (CASP), hypoxia-inducible factor (HIF)-1α, c-jun N-terminal kinase (JNK), cyclin-dependent kinase(CDK)6, Cyclin (CCN) D1, NF-κB, lactic dehydrogenase (LDH)A, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF)[30,60], transforming growth factor (TGF)-β, IL-6, PI3K, Akt, glycogen synthase kinase (GSK)3, signal transducer and activator of transcription (STAT)3, caspase-3, and B-cell lymphoma (Bcl)-2 as mentioned by selected studies. These target proteins contribute to oxidative stress, inflammation, apoptosis, and cell cycle. In the same studies, CA and AA reduced the inflammatory and oxidative stress markers and apoptosis. Phosphorylated YAP was also decreased, which is a sign of activation of the cell survival pathway mediated by PI3K/Akt.[35]

The mechanism inhibited by AA in each study was identical, including modulating PI3K/Akt, NF-κB, inflammatory marker expression, oxidative stress, and apoptosis. AA might have become an important modulator of mTOR, AMPKα, and p70S6K that control the cell size and protein synthesis in cardiomyocytes.[36] In brief, it is acceptable that CA and AA might have potential multiple possibility mechanisms of action in the known pathway.

However, a "missing link" might need to be explored in further research on CA or AA, as summarized in Figure 2. It is strong enough to affirm that CA and AA might inhibit oxidative stress as it has strong evidence as antioxidants in the previous studies. However, NLRP3 inflammasome and receptor for advanced glycation end products (RAGE) signaling pathways are the mechanisms that need further investigation. The suspicion regarding how AA might alleviate this pathway lies in its capability to inhibit cardiac fibrosis mediated through TGF-β/Smads pathway.[33] An *in vitro* study using H9c2 cells found that RAGE and high-mobility group box (HMGB)1 had a link to the activation of AT1R to the activation of NF-κB and NLRP3. RAGE is an analog to the Toll-like receptor activation, which is activated in the inflammatory state.[10] Another mechanism that needs to be discussed is the imbalance of Ca^{2+} due to disturbance in the sarcoplasmic reticulum proteins, such as sarcoendoplasmic reticulum calcium ATPase (SERCA)2a, ryanodine receptor (RyR)2, or transient receptor protein (TRP). In addition, the interactions of calmodulin, calcineurin, and NFAT with CA or AA must be investigated to determine their contribution to Ca^{2+} imbalance.

Conclusion

This systematic review identified many studies suggesting the complex interaction of CA and AA within the cardiac remodeling pathway. This biological plausibility has become a pillar for clinical studies that support the use CA or AA to prevent and alleviate pathological cardiac remodeling progression. Nevertheless, there is a fact that almost all included studies have questionable risk of bias, especially

Table 4. Summary and results of selected paper.

No	Author, Year	Age, Species	Body Weight	Sex	Intervention	Disease	Study Model	Total Subject	Significant Related Outcome in Experimental Group
1	Li *et al*., 2021 [29]	8 weeks, Sprague Dawley rats	150-170 g	Male	AA 20 mg/kg/day for four weeks by oral gavage	Cardiac remodeling	Ang II infusion 400 ng/kg/min through implanted minipump subcutaneously	Four groups, 10 rats/groups, wild and sham group, Ang II and Ang II with AA	• HW/TL ↓ • LPWs ↓, LPWd ↓ • Relative cell size ↓ • LV collagen area ↓ • Heart expression of ANP↓, β-MHC ↓, miRNA-126/U6 ↓ • Heart expression of PI3KR2 ↓, PI3K ↓, Akt↓
2	Bunbupha *et al*., 2015 [30]	N/A, Sprague Dawley rats	220-240 g	Male	AA 20 mg/kg/day for 2 weeks intragastric	Cardiac remodeling	L-NAME administration 40 mg/kg/day perorally through drinking water	Four groups, 10 rats/groups, two control groups, combined either vehicle or AA, and two group experimental L-NAME, combined either vehicle or AA	• SBP ↓ • LVW/BW↓ • LV and aorta wall thickness↓, LV and aorta CSA↓, and LV luminal area↓ • LV Fibrosis and Aortic Collagen↓ • Plasma NOx concentration↑, Plasma TNF-α concentration ↓ • Heart iNOS and eNOS protein expression↓ • Heart MDA concentration↓
3	Si *et al*., 2014 [31]	8-10 weeks, C57BL/6 mice	20-30 g	Male	AA 100 mg/kg/day through oral gavage for 2 weeks	Pressure overload cardiac hypertrophy	Transverse aortic constriction	Five groups, sham, sham+AA, untreated TAC, TAC+vehicle, and TAC+AA	• HW/BW↓ • IVSD ↓, LVPWD ↓, LVEDD ↓, %FS↓ • Cardiomyocytes CSA↓ • Heart mRNA expression ANP↓ and TGF-β 1 ↓ • Heart protein expression p-p38↓ and p-ERK1/2, NF- κB binding activity ↓
4	Si *et al*., 2015 [32]	8-10 weeks, C57BL/6 mice	N/A	Male	AA 100 mg/kg/day through oral gavage for 4 weeks	Pressure overload cardiac hypertrophy	Transverse aortic constriction	Five groups, sham, sham+AA, untreated TAC, TAC+vehicle, and TAC+AA	• HW/BW↓, LW/BW↓ • IVSD ↓, LVPWD ↓, LVEDD ↓, %FS↓, Stroke Volume↓, Cardiac Output↑, HR ↓ • Cardiomyocyte cross-sectional area↓, Collagen cross-sectional area ↓, Apoptotic index% ↓ • Gene expression of TNF- α and IL-6 ↓ • Mitochondria size↑, Population of Mitochondria↑ • Protein expression of Bax/Bcl2 ↓, Caspase 9↓, Cleavage-caspase 8↓, Cyto-c ↓, TGF-β ↓, α-SMA↓, and Collagen-I↓
5	Meng *et al*., 2019 [33]	8 weeks, Wistar Kyoto rats	N/A	Male	AA 20 mg/kg/day peroral for 12 weeks	Overpressure-induced cardiac fibrosis	Spontaneous hypertension rats	Four groups, 10 rats/group, control group, AA, SHR, and SHR+AA	• SBP↓ • HW/BW↓, LVW/BW↓, Plasma Ang II concentration↓ • Collagen I, Collagen III, CTGF, and PAI-1 mRNA and Protein expression ↓ • MDA Concentration↓, SOD activity↑, GSH activity ↑, ROS level ↓ • HO-1, Nuc-Nrf2, and NQO-1 expression↑ • TGF-β 1 ↓, p-Smad2/3↓, Smd7↓
6	Xu *et al*., 2015 [34]	8-10 weeks, C57BL/6 mice	20-30 g	Male	AA 100 mg/kg/day through oral gavage for 2 weeks	Overload-induced cardiac hypertrophy	Transverse aortic constriction	Five groups, 10 rats/group, sham, sham+AA, saline+TAC, vehicle+TAC, and AA+TAC	• HW/BW↓ • Cardiomyocyte CSA ↓, LV Mass ↓ • IVSD ↓, IVSS ↓, LVEDD ↑, LVPWD ↓, LVPWS ↓, %EF ↑, %FS↑ • mRNA ANP ↓ and IL-1β ↓. Protein expression of IL-1β ↓ • NF-κB binding activity ↓
7	Ding *et al*., 2022 [35]	6-8 weeks, C57BL/6L mice	18-22 g	Male	CA extract adopted intragastric gavage for 14 days after ISO treatment	Cardiac hypertrophy	Daily subcutaneous injections of isoproterenol (ISO) (5 mg/kg) for 7 days	Four groups (n = 6 per group): control group (saline); ISO group (ISO + saline); positive group (Pro) (ISO + pro- pranolol hydrochloride, 40 mg/kg/d); CA group (ISO + CA extract, 250 mg/kg/day)	ANP ↓, collagen type I ↓, TNF-α ↓, IL-6 ↓, IL-2 ↓, SOD ↑, BAX ↓, Casp3↓, C-Casp3↓, NF-κB ↓ p-NF-κB ↓, p-PI3K ↑, p-Akt ↑, YAP ↑
8	Ma *et al*., 2016 [36]	8-10 weeks, C57/B6 mice	25.5±2 g	Male	Orally given AA (10 or 30mg/kg) for 7 weeks after being subjected to aortic banding (AB)	Cardiac hypertrophy	Transverse aortic banding, and injected with CpC to inhibit AMPKα	Three groups: a control group with AB, AB + AA 10/mg/kg, and AB with knockout AMPKα + AA 30mg/kg	ANP ↓, BNP ↓, β-MHC↓, TGF-β ↓, collagen I ↓, collagen III ↓, CTGF ↓, fibronectin ↓, p-AMPKα ↑, p-ACC ↑, p-mTOR ↑, p-P70S6K ↓, p-S6 ↓, ERK ↓
9	Huo *et al*., 2016 [37]	Sprague-Dawley rats	220-240 g	Male	Orally given AA (5/25/50 mg/kg) after being subjected to myocardial infarction (MI)	Ventricular remodeling	Myocardial infarction (MI) induced by permanent left anterior descending (LAD) coronary artery ligation	8 groups (n=15 per group): i) S + V, sham rats treated with vehicle; ii) S + AA5, sham rats treated with 5 mg/kg/day AA; iii) S + AA25, sham rats treated with 25 mg/kg/day AA; iv) S + AA50, sham rats treated with 50 mg/kg/day AA; v) MI + V, MI rats treated with vehicle; vi) MI + AA5, MI rats treated with 5 mg/kg/day AA; vii) MI + AA25, MI rats treated with 25 mg/kg/day AA; and viii) MI + AA50, MI rats treated with 50 mg/kg/day AA	TGF-β1↓, NF-κB ↓, TNF-α ↓, interstitial fibrosis ↓, p38 MAPK ↓, ERK1/2 ↓

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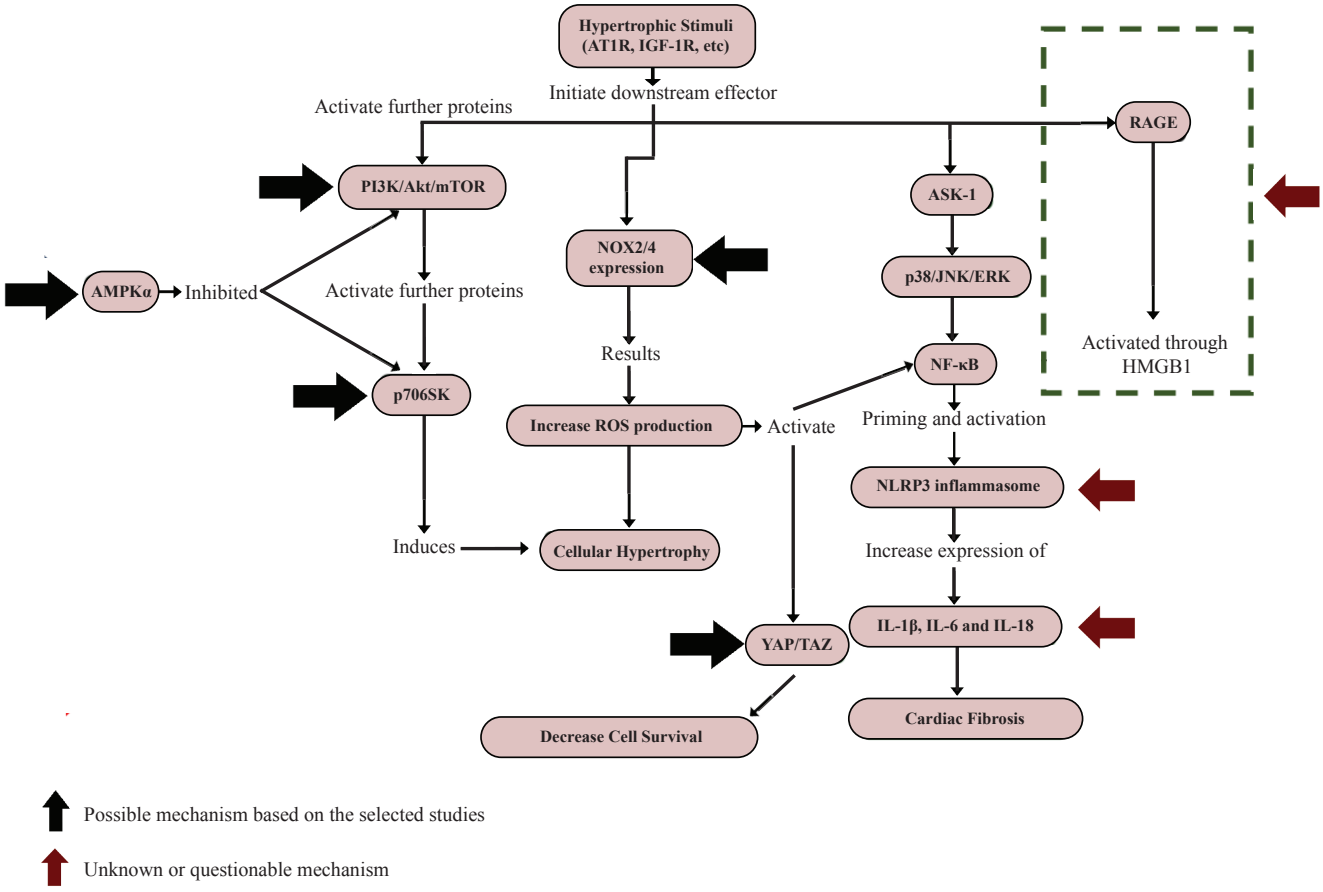

Figure 2. Possible mechanism of action of CA and AA in cardiac remodeling progression.

in the randomizing and blinding aspects. Hence, further studies must avoid these biases by reporting them well and creating high-quality research. In brief, we concluded that CA and AA, could potentially prevent cardiac remodeling. It is suggested that clinical studies in humans, along with high-quality preclinical studies, should be performed.

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Authors' Contributions

MRF and WA were involved in concepting the manuscript topic, MRF, WA, HW, SWP, and AB prepared the manuscript draft, MRF, NGK, RCP, CRA and NA designed the figures and tables. MRF, WA, HW, AB, SWP, NGK, RCP, CRA, and NA took part in a critical revision of the manuscript.

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