Pharmacological Evaluation of Acacetin Against Isoproterenol-Induced Cardiac Hypertrophy: A Comprehensive Review

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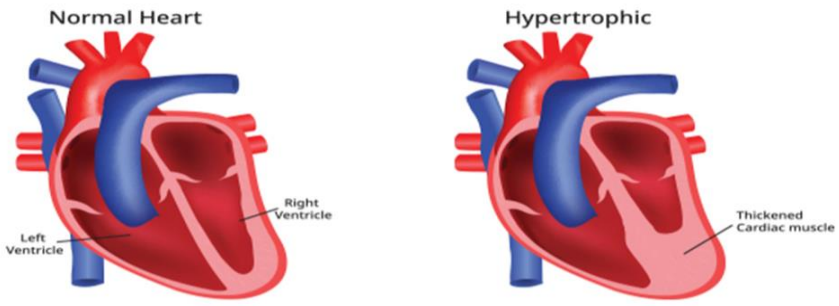
Abstract: Cardiac hypertrophy, a pathological response to prolonged stress or injury, is a critical precursor to heart failure and other severe cardiovascular conditions. Experimental models using isoproterenol (ISO), a beta-adrenergic agonist, replicate many aspects of human cardiac hypertrophy, making it valuable for studying potential therapies. Acacetin, a flavonoid derived from several medicinal plants, has gained attention for its broad pharmacological actions, including antioxidant, anti-inflammatory, and anti-apoptotic effects. This review examines the therapeutic potential of acacetin in ISO-induced cardiac hypertrophy, exploring its molecular mechanisms and cardioprotective actions. Key findings from preclinical studies demonstrate that acacetin alleviates oxidative stress, reduces inflammation, and regulates calcium homeostasis, effectively mitigating cellular hypertrophy, fibrosis, and apoptosis in cardiac cells. By targeting multiple pathways—such as NF-κB, PI3K/Akt/mTOR, and MAPK—acacetin presents a comprehensive approach to preventing hypertrophy and promoting cardiac health. This review underscores the promise of acacetin as a potential therapeutic agent and highlights the need for clinical studies to confirm its efficacy and safety in cardiovascular disease management.

Keywords: Acacetin, Cardiac Hypertrophy, Natural Flavonoid, Cardioprotection, Isoproterenol.

1. INTRODUCTION-

Cardiac hypertrophy is a pathophysiological condition characterized by an increase in the size of the heart muscle cells (cardiomyocytes) and thickening of the heart walls, primarily in response to increased mechanical or neurohormonal stress. Although cardiac hypertrophy can initially serve as a compensatory mechanism to maintain cardiac output in response to stressors such as high blood pressure or increased workload, persistent hypertrophy can lead to adverse structural remodeling, fibrosis, and ultimately heart failure. Cardiac hypertrophy is often a precursor to heart failure, a condition affecting millions of people globally and a leading cause of morbidity and mortality. Traditional therapeutic strategies, including the use of ACE inhibitors, beta-blockers, and calcium channel blockers, aim to alleviate symptoms, reduce heart workload, and slow disease progression. However, these treatments do not directly address the molecular and cellular mechanisms of hypertrophy, and their prolonged use can sometimes result in undesirable side effects, such as fatigue, bradycardia, or hypotension.



Furthermore, these medications do not entirely prevent the pathological remodeling that contributes to disease progression. [1,2]

Fig 1. Cardiac Hypertrophy Condition. [3]

Isoproterenol (ISO), a synthetic catecholamine and beta-adrenergic agonist, is widely used in research to induce cardiac hypertrophy in experimental models, replicating many features of human cardiac pathology, including cellular enlargement, oxidative stress, inflammatory response, and fibrosis. The ISO-induced model provides a valuable platform for evaluating the effectiveness of cardioprotective compounds and understanding the molecular mechanisms underlying hypertrophy and its progression. (4)

With increasing recognition of the importance of addressing the underlying causes of cardiac hypertrophy, there is growing interest in discovering and developing natural compounds that possess multi-targeted actions with minimal adverse effects. Flavonoids, a diverse group of plant-derived polyphenolic compounds, have shown considerable promise in this regard due to their wide-ranging biological activities, including antioxidant, anti-inflammatory, and anti-apoptotic effects. Among these, acacetin, a naturally occurring O-methylated flavonoid found in several medicinal plants, has emerged as a particularly compelling candidate for cardioprotective therapy. (5)

Acacetin, present in plants such as *Turnera diffusa* (commonly known as Damiana), *Betula* species, and chrysanthemum flowers, has gained scientific interest for its numerous pharmacological properties. Structurally, acacetin is classified as a flavone, a subtype of flavonoid, known for its methoxy and hydroxyl groups, which enable it to interact with various cellular targets. Studies have shown that acacetin exhibits a range of therapeutic properties, including potent antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic effects, making it a promising candidate for mitigating the complex processes involved in cardiac hypertrophy. (6) Oxidative stress, inflammation, apoptosis, and fibrosis are central to the pathogenesis of cardiac hypertrophy. Each of these pathways plays a role in initiating and sustaining hypertrophic growth, remodeling, and contractile dysfunction in the heart. Targeting these pathways could effectively prevent or reverse cardiac hypertrophy, but finding a single compound capable of modulating multiple pathways simultaneously poses a significant challenge. Acacetin's multi-faceted action offers a unique advantage in this regard, as it can simultaneously influence several pathways involved in the development and progression of cardiac hypertrophy. (7)

Recent preclinical studies have highlighted acacetin’s potential to counteract hypertrophic changes induced by various stimuli, including neurohormonal agents like angiotensin II and β-adrenergic agonists such as isoproterenol. These studies have demonstrated acacetin’s ability to reduce hypertrophic markers, mitigate oxidative stress, suppress inflammatory responses, inhibit fibrosis, and promote cell survival in animal models of cardiac hypertrophy. Such findings suggest that acacetin not only attenuates hypertrophy but may also offer long-term benefits by preserving myocardial function and preventing adverse remodeling.

The pharmacological actions of acacetin relevant to cardiac hypertrophy can be broadly classified into four key mechanisms: (8)

1. Antioxidant Activity
2. Anti-inflammatory Effects
3. Anti-apoptotic Properties
4. Anti-fibrotic Activity

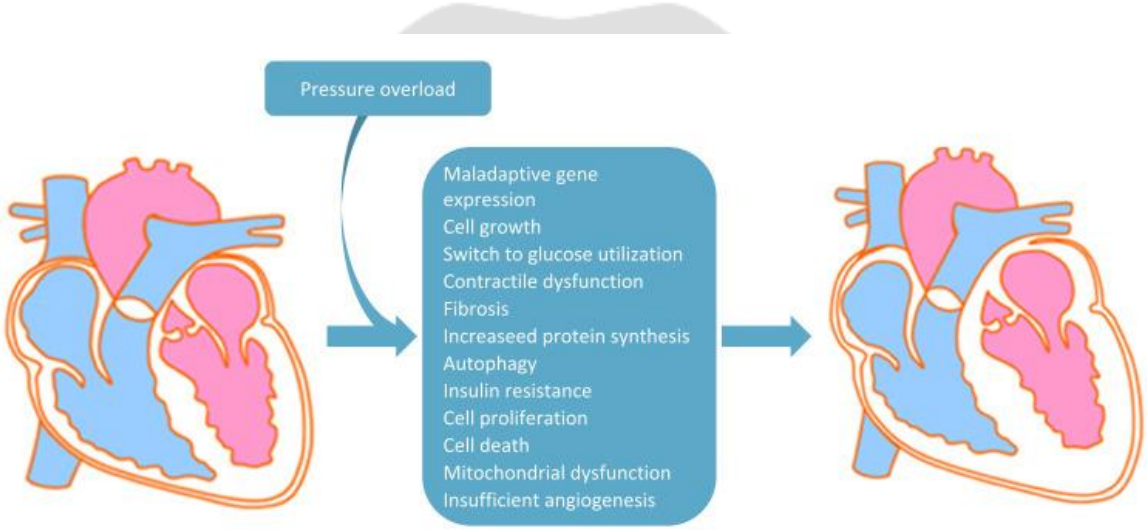
This review aims to provide a comprehensive overview of the pharmacological effects of acacetin in the context of cardiac hypertrophy, summarizing the existing experimental evidence and exploring the potential mechanisms underlying its cardioprotective effects. We will discuss key findings from preclinical studies, evaluate the advantages of acacetin over conventional treatments, and consider the clinical implications of using acacetin as a natural therapeutic agent.

2. PATHOPHYSIOLOGY OF CARDIAC HYPERTROPHY

Cardiac hypertrophy is a complex process in which the heart muscle thickens as an adaptive response to increased workload or stress, such as hypertension, myocardial infarction, or pressure overload. Initially, hypertrophy can be beneficial, helping the heart maintain function under these stressors. However, sustained hypertrophy becomes maladaptive, leading to structural and functional changes that increase the risk of heart failure and other cardiovascular complications. The pathophysiology of cardiac hypertrophy involves several interconnected processes, including hemodynamic stress, neurohormonal activation, molecular and cellular signaling, and maladaptive remodeling. [9]

Fig 2. Cardiac Hypertrophy.

Cardiac hypertrophy is a condition where the heart muscle increases in size due to cells filling with more cytoplasm. Pathological cardiac hypertrophy is associated with cardiac dysfunction and can be caused by a number of factors, including:



- Abnormal hemodynamic stress: This can be caused by hypertension or myocardial infarction.
- Insulin resistance: This can lead to diabetic cardiomyopathy.
- Oxidative stress: This can downregulate HDAC4, a repressor of pathological hypertrophy.
- Calcineurin activation: This can promote the nuclear localization of NFAT, which modulates the transcription of pro-hypertrophy genes. [10]

Other pathophysiological mechanisms of cardiac hypertrophy include:

- Altered sarcomere structure
- Inadequate angiogenesis
- Altered calcium homeostasis
- Inflammation
- Dyssynergy
- Dilatation of the cardiac chamber
- Chronic localized ischemia of the myocardium

Cardiac hypertrophy can lead to maladaptive cardiac remodeling and heart failure. A thickened heart muscle can also trigger atrial fibrillation (AFib), an irregular and often rapid heartbeat. AFib can increase the risk of blood clots, which can travel to the brain and cause a stroke. [11]

3. ISOPROTERENOL-INDUCED CARDIAC HYPERTROPHY: MECHANISMS AND PATHOLOGY

ISO, a beta-adrenergic agonist, triggers hypertrophy through sustained activation of beta-adrenergic receptors, which leads to:

1. Increased Intracellular Calcium: Elevated intracellular calcium levels activate hypertrophic pathways, including calcineurin/NFAT signaling, which plays a critical role in pathological hypertrophy and myocardial remodeling.

2. Oxidative Stress: ISO elevates reactive oxygen species (ROS) production, promoting oxidative stress and further activating hypertrophic signaling cascades, such as mitogen-activated protein kinases (MAPKs).
3. Inflammation and Fibrosis: Chronic beta-adrenergic stimulation increases the expression of pro-inflammatory cytokines and profibrotic molecules, leading to extracellular matrix (ECM) remodeling, fibrosis, and stiffness of the myocardium. [12]

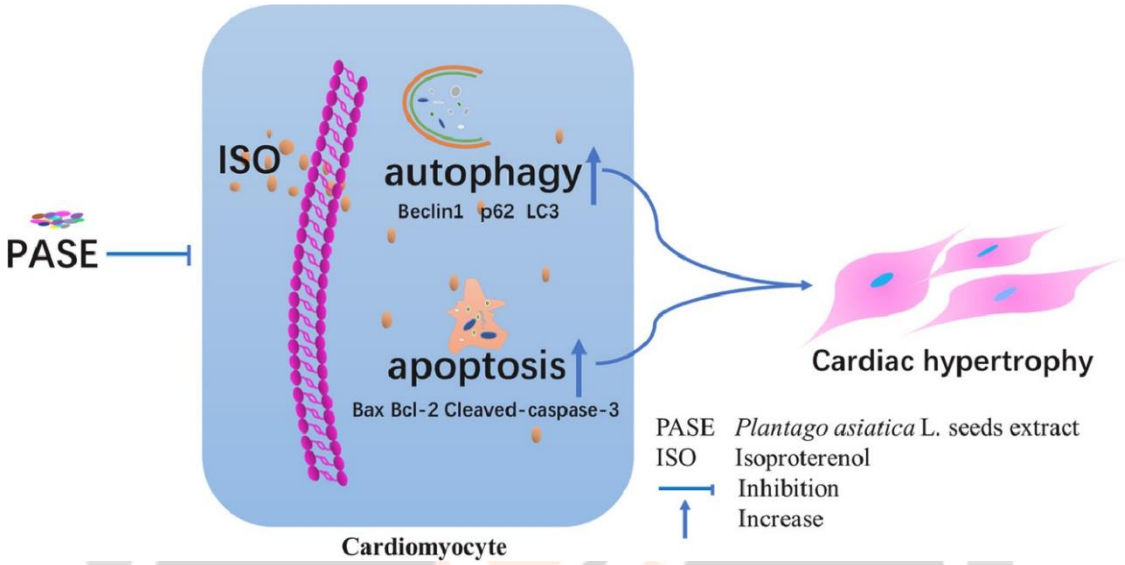


Fig 3. Isoproterenol-Induced Cardiac Hypertrophy

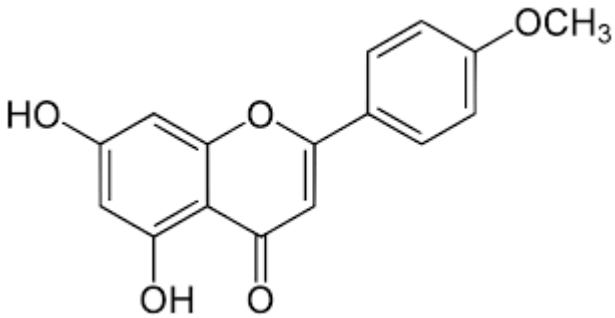
ISO-induced cardiac hypertrophy closely resembles human pathological hypertrophy, involving inflammatory responses, oxidative stress, and hypertrophic gene expression changes, making it an ideal model for studying the cardioprotective effects of acacetin.

Some substances that can prevent or reduce isoproterenol-induced cardiac hypertrophy include:

- Oxytocin: A cardiovascular homeostatic hormone that can inhibit the PI3K/AKT pathway.
- Gallic acid: Can prevent interstitial collagen deposition and expression of fibrosis-associated genes.
- Genistein: A phytoestrogen that can increase the expression of miR-451 and inhibit isoproterenol-induced cardiac hypertrophy. [13]

4. ACACETIN: CHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITIES

Chemical Structure- Acacetin is a naturally occurring flavonoid found in various plants, particularly in the leaves of *Robinia pseudoacacia* (black locust) and the flowers of *Turnera diffusa* (damiana). Its structure is characterized by a flavone backbone with specific substitutions: [14]



- **Chemical Formula**: C1616H1212O55
- **Systematic Name**: 5,7-Dihydroxy-4'-methoxyflavone
- **IUPAC Name**: 5,7-dihydroxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one
- **Molecular Structure**: Acacetin consists of a central benzopyran ring (flavone backbone) substituted with two hydroxyl (OH) groups at positions 5 and 7 and a methoxy (OCH33) group at position 4' on the phenyl ring.

This structural configuration makes acacetin relatively lipophilic, enhancing its bioavailability and ability to cross cell membranes, thus contributing to its wide range of biological effects.

Biological Activities- Acacetin exhibits a broad spectrum of pharmacological and therapeutic activities, some of which are highlighted below: [15]

1. **Anti-inflammatory Activity**: Acacetin inhibits various inflammatory mediators, including nitric oxide (NO) and pro-inflammatory cytokines (e.g., TNF-α, IL-6). It suppresses the activation of NF-κB, a key transcription factor in the inflammatory pathway, thus reducing inflammation in tissues.
2. **Antioxidant Properties**: Due to its flavonoid structure, acacetin has significant antioxidant potential, scavenging free radicals, reducing oxidative stress, and protecting cells from oxidative damage, which is associated with numerous chronic diseases.
3. **Anticancer Activity**: Acacetin demonstrates antiproliferative effects against various cancer cell lines, including breast, prostate, and lung cancers. It induces apoptosis (programmed cell death) and inhibits cancer cell migration and invasion, often through the modulation of the PI3K/Akt and MAPK signaling pathways.
4. **Antimicrobial Effects**: Studies show acacetin has antibacterial and antifungal properties, particularly against pathogens like *Escherichia coli* and *Staphylococcus aureus*. This activity is mainly due to its ability to disrupt bacterial cell walls and membranes.
5. **Cardioprotective Effects**: Acacetin has demonstrated cardioprotective effects, including reducing arrhythmias and protecting heart tissue from ischemic damage. This effect is believed to be related to its antioxidant properties and ability to modulate ion channels in cardiac cells.
6. **Neuroprotective Effects**: Acacetin shows promise as a neuroprotective agent, as it can reduce neuronal damage in neurodegenerative conditions. By modulating neuroinflammatory pathways and reducing oxidative stress in neural cells, it helps protect against neurotoxicity and cognitive decline. [16]

Therapeutic Potential- Due to its multi-targeted actions, acacetin is considered a promising compound for the development of new therapies against diseases like cancer, cardiovascular disorders, infections, and neurodegenerative diseases. However, more studies, including clinical trials, are necessary to fully understand its safety, efficacy, and pharmacokinetics in humans.

5. PHARMACOLOGICAL MECHANISMS OF ACACETIN IN CARDIAC HYPERTROPHY

Cardiac hypertrophy, a condition characterized by an abnormal enlargement of heart muscle cells, often arises as an adaptive response to conditions such as hypertension, heart failure, or other cardiovascular stressors. Prolonged hypertrophy can lead to heart failure and other severe cardiovascular complications. Acacetin, a natural flavonoid, has shown promising cardioprotective effects, particularly in the prevention and treatment of cardiac hypertrophy. The pharmacological mechanisms by which acacetin exerts these effects are outlined below:

1. Inhibition of the PI3K/Akt Signaling Pathway [17]

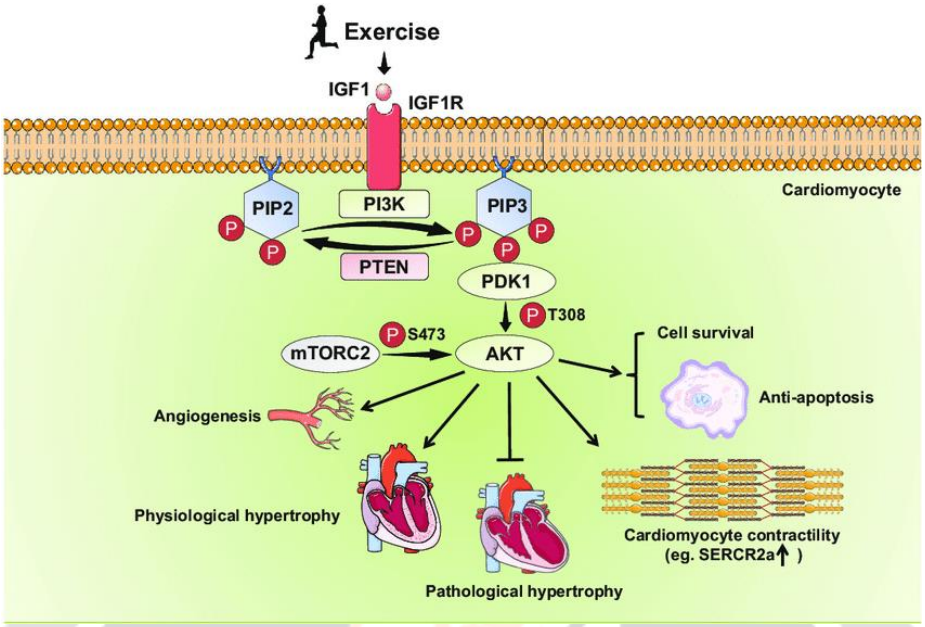


Fig 4. The IGF1/PI3K/AKT Pathway.

- The phosphoinositide 3-kinase (PI3K)/Akt signaling pathway is commonly activated in response to hypertrophic stimuli, leading to cell growth and survival.
- Acacetin has been shown to inhibit this pathway, reducing the phosphorylation of Akt and downstream targets such as mTOR, a critical factor in protein synthesis and cell growth.
- By suppressing the PI3K/Akt/mTOR pathway, acacetin decreases protein synthesis in cardiac cells, preventing the excessive cellular growth that characterizes hypertrophy.

2. Regulation of Calcium Signaling [18]

- Calcium homeostasis is crucial in maintaining proper cardiac function, and its dysregulation can lead to hypertrophy. Acacetin influences calcium signaling by modulating calcium channels and reducing the calcium overload often observed in hypertrophic hearts.
- This modulation helps prevent hypercontractility and arrhythmogenic activity, thereby protecting against pathological changes in heart muscle cells.

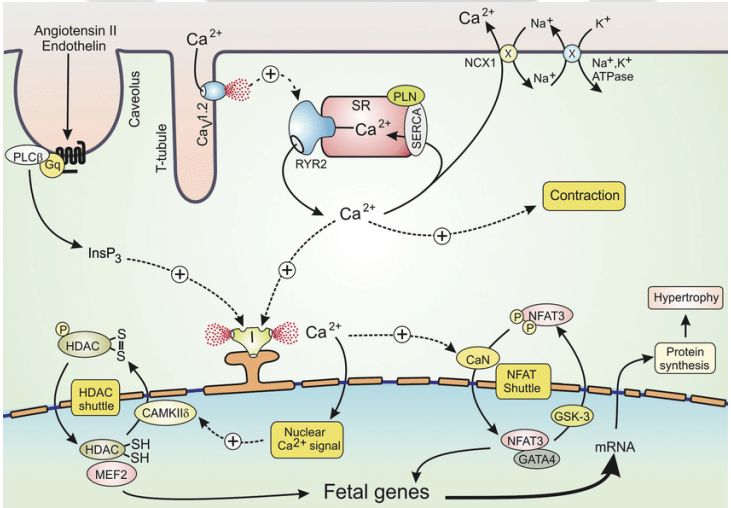


Fig 5. InsP 3 /Ca 2 signaling Pathway.

3. Reduction of Oxidative Stress [19]

- Oxidative stress plays a significant role in cardiac hypertrophy, as reactive oxygen species (ROS) promote the activation of hypertrophic signaling pathways. Acacetin's antioxidant properties allow it to neutralize ROS, reducing oxidative damage and preventing the activation of stress-related pathways such as MAPK.
- This reduction in oxidative stress is essential in preventing the inflammatory and fibrotic responses that accompany hypertrophy.

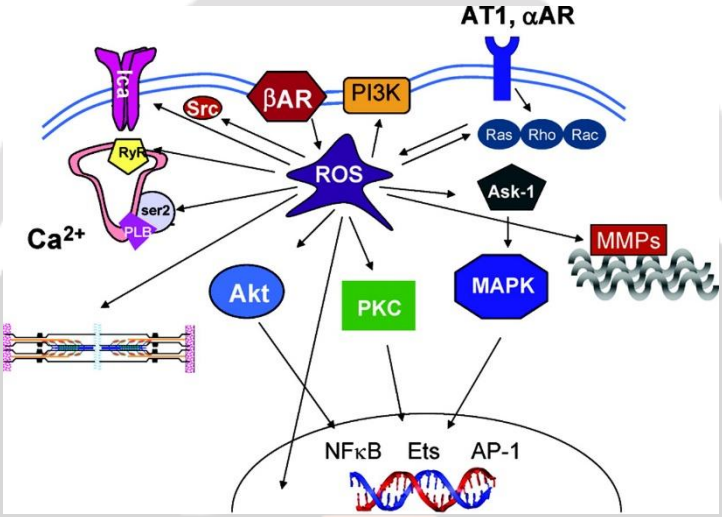


Fig 6. Molecular signaling pathways linking ROS.

4. Inhibition of NF-κB Activation [20]

- The nuclear factor-kappa B (NF-κB) signaling pathway is commonly activated by inflammatory signals and has been implicated in the progression of cardiac hypertrophy and fibrosis. Acacetin has been shown to inhibit NF-κB activation, thereby reducing the expression of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and limiting inflammation within cardiac tissue.

- This anti-inflammatory effect of acacetin helps maintain healthier heart tissue and prevents the fibrotic remodeling associated with chronic hypertrophy.

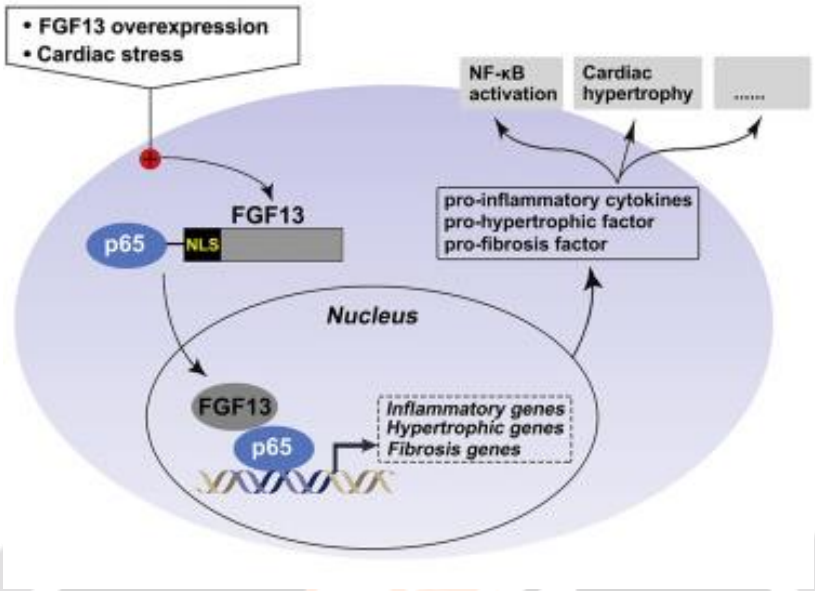


Fig 7. NF-κB Activation Pathway.

5. Activation of AMPK Signaling [21]

- AMP-activated protein kinase (AMPK) is a crucial regulator of cellular energy balance. Its activation can inhibit the growth of hypertrophic cardiac cells by promoting energy conservation and reducing protein synthesis.
- Acacetin has been reported to activate AMPK, thereby reducing cellular growth signals, enhancing fatty acid oxidation, and improving the energy efficiency of cardiac cells. This activation is particularly beneficial in managing the metabolic alterations observed in hypertrophied hearts.

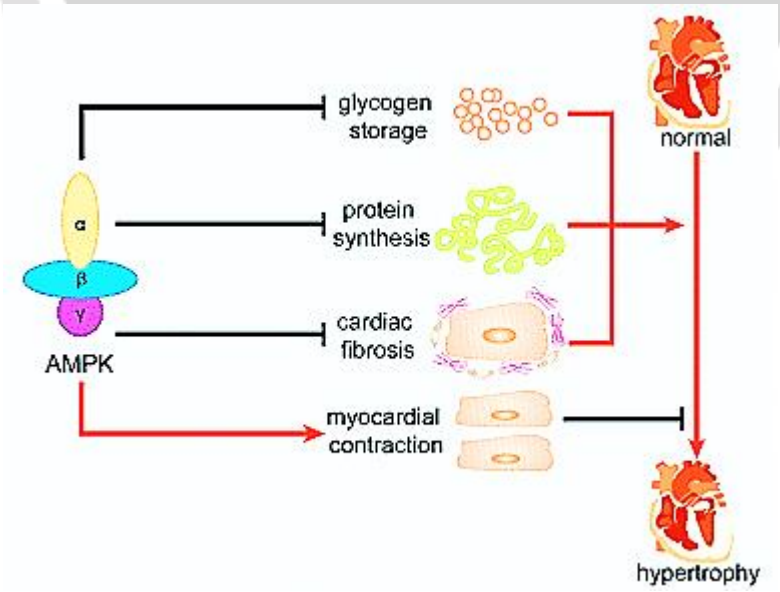


Fig 8. Regulation of AMPK

6. Suppression of Apoptotic Pathways [22]

- In advanced stages of hypertrophy, cardiac cells often undergo apoptosis, contributing to heart failure. Acacetin has shown anti-apoptotic effects by regulating the balance between pro-apoptotic (e.g., Bax) and anti-apoptotic (e.g., Bcl-2) proteins.
- By preventing excessive apoptosis, acacetin preserves the integrity of cardiac muscle cells and helps maintain heart function over time.

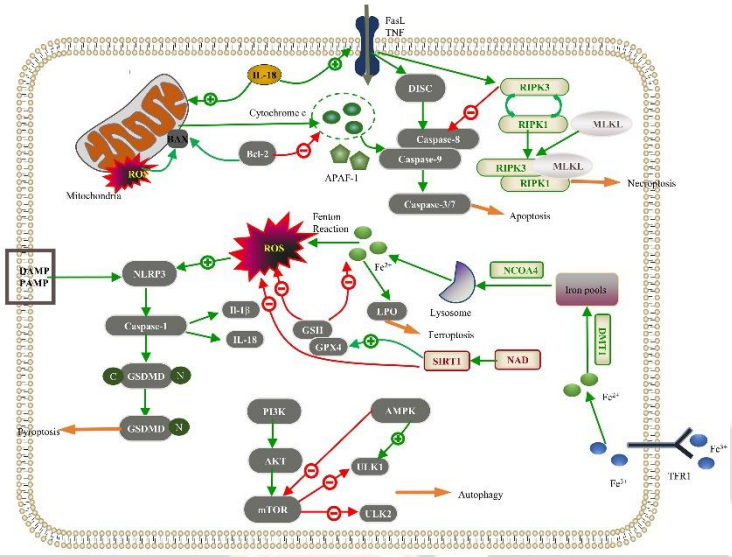


Fig 9. Regulated Cell Death Pathway

Acacetin's ability to inhibit key signaling pathways involved in cellular growth, oxidative stress, inflammation, and apoptosis makes it a promising candidate for mitigating cardiac hypertrophy. By targeting multiple mechanisms, acacetin reduces the pathological remodeling of heart tissue and promotes cardiomyocyte health, potentially preventing the progression from hypertrophy to heart failure.

6. ISOPROTERENOL-INDUCED CARDIAC HYPERTROPHY: MECHANISMS AND PATHOLOGY

Isoproterenol (ISO) is widely used to induce cardiac hypertrophy in animal models, as it mimics the effects of chronic sympathetic activation through β-adrenergic receptor stimulation. The mechanisms by which ISO induces cardiac hypertrophy include:

- **β-Adrenergic Receptor Activation:** ISO binds to β-adrenergic receptors, leading to the activation of downstream signaling pathways, including protein kinase A (PKA), which mediates hypertrophic growth and contractile dysfunction.
- **Oxidative Stress and ROS Production:** ISO administration increases ROS production, particularly in mitochondria, causing oxidative damage to proteins, lipids, and DNA, which exacerbates hypertrophy and cell death.
- **Inflammation and Cytokine Release:** ISO stimulates the release of pro-inflammatory cytokines, such as TNF-α and IL-6, which contribute to fibrosis and ECM remodeling, leading to stiffening of the myocardium.
- **Calcium Overload and Mitochondrial Dysfunction:** ISO disrupts calcium handling in cardiomyocytes, leading to calcium overload in mitochondria, impaired ATP production, and increased apoptosis.

ISO-induced cardiac hypertrophy is thus a multifactorial process, involving oxidative stress, inflammation, and remodeling, making it an ideal model to study the cardioprotective effects of compounds like acacetin.

7. PRECLINICAL EVIDENCE OF ACACETIN IN ISO-INDUCED CARDIAC HYPERTROPHY

Studies have shown that acacetin administration in isoproterenol-induced cardiac hypertrophy models results in a significant reduction in heart weight, myocardial cell size, and left ventricular wall thickness, indicating a reversal of hypertrophy. In animal models, acacetin treatment was associated with improved cardiac function, as evidenced by normalized heart rate, blood pressure, and enhanced left ventricular ejection fraction. These findings indicate that acacetin not only prevents but may also reverse structural and functional changes induced by isoproterenol. (23)

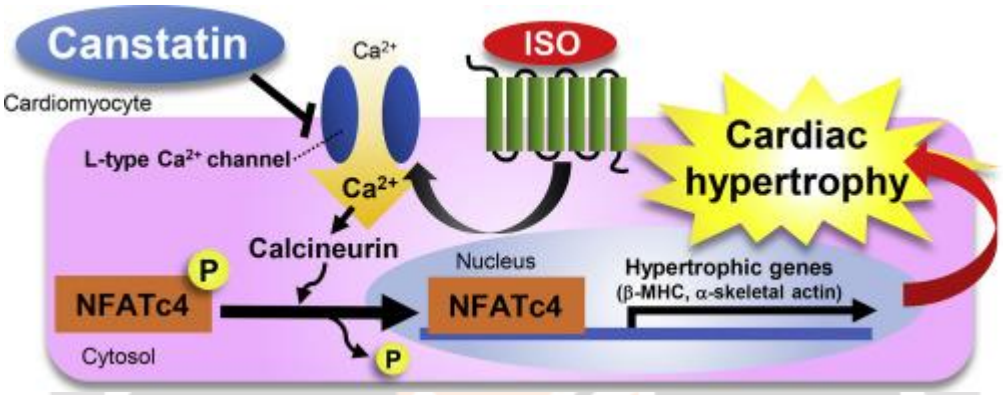


Fig 10. Acacetin Derivative in Iso-Induced Cardiac Hypertrophy.

Key findings from preclinical studies include:

- Reduced Fibrosis: Acacetin treatment has been associated with lower levels of fibrosis markers, such as collagen deposition, which helps maintain the structural integrity of the heart muscle.
- Improved Antioxidant Enzyme Activity: Increased levels of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) were observed with acacetin treatment, indicating enhanced antioxidant defenses.
- Reduced Inflammatory Markers: Acacetin-treated models showed decreased levels of inflammatory cytokines, supporting its role in attenuating the inflammatory response.
- Enhanced Survival of Cardiomyocytes: Reduced apoptosis in cardiomyocytes treated with acacetin further supports its role in preserving cardiac function.

8. FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

Given the promising preclinical data, acacetin holds potential as a therapeutic agent for cardiac hypertrophy and related heart diseases. However, further research is needed to establish its safety, efficacy, and pharmacokinetic profile in human studies. Future directions include:

1. Clinical Trials: Translating the preclinical findings into clinical studies to evaluate acacetin's efficacy in human cardiac hypertrophy.
2. Formulation Development: Enhancing the bioavailability of acacetin through formulation strategies to improve its therapeutic efficacy.
3. Combination Therapy: Exploring the use of acacetin in combination with other cardioprotective agents to maximize therapeutic benefits.

9. CONCLUSION-

This review has explored the therapeutic potential of acacetin in combating isoproterenol (ISO)-induced cardiac hypertrophy, beginning with an overview of cardiac hypertrophy and its pathophysiology, followed by the mechanisms through which ISO triggers heart muscle enlargement. Acacetin, a flavonoid with potent biological activities, has shown promising effects in addressing key hypertrophy pathways, including inflammation, oxidative stress, and fibrosis. By modulating pathways such as PI3K/Akt and MAPK, acacetin helps counteract ISO-induced cardiac stress in preclinical studies, underscoring its value as a cardioprotective agent. Future research should focus on clinical trials to confirm its safety and efficacy, as well as to determine optimal dosing, potentially establishing acacetin as a natural therapeutic option in heart disease management.

10. ABBREVIATION-

- ISO- isoproterenol
- ACE- Angiotensin-converting enzyme (ACE) inhibitors
- HDAC4- Histone deacetylase 4
- NFAT- nuclear factor of activated T cells
- AFib- atrial fibrillation
- ROS- reactive oxygen species
- MAPKs- mitogen-activated protein kinases
- ECM- extracellular matrix
- PI3K- Phosphoinositide 3-kinase
- AKT- protein kinase B
- TNF-α- Tumor necrosis factor alpha
- IL-6- Interleukin 6
- NF-κB- Nuclear factor kappa-light-chain-enhancer of activated B cells
- mTOR- mammalian target of rapamycin
- InsP 3- inositol trisphosphate
- Ca 2- calcium ion
- Bcl-2- B-cell lymphoma-2
- SOD- superoxide dismutase

11. REFERENCE-

1. Frey, N., & Olson, E. (2003). Cardiac Hypertrophy: the good, the bad, and the ugly. *Annual Review of Physiology*, *65*(1), 45–79. https://doi.org/10.1146/annurev.physiol.65.092101.142243
2. Ponikowski, P., Anker, S. D., AlHabib, K. F., Cowie, M. R., Force, T. L., Hu, S., Jaarsma, T., Krum, H., Rastogi, V., Rohde, L. E., Samal, U. C., Shimokawa, H., Siswanto, B. B., Sliwa, K., & Filippatos, G. (2014). Heart failure: preventing disease and death worldwide. ESC Heart Failure, 1(1), 4–25. https://doi.org/10.1002/ehf2.12005
3. Hypertrophic cardiomyopathy- a disease that makes heart muscles thick - Metro Group of Hospitals. (2024, January 10). Metro Group of Hospitals. https://www.metrohospitals.com/blog/hypertrophic-cardiomyopathy-a-disease-that-makes-heart-muscles-thick/
4. Taylor, P. B., & Tang, Q. (1984). Development of isoproterenol-indueed cardiac hypertrophy. Canadian Journal of Physiology and Pharmacology, 62(4), 384–389. https://doi.org/10.1139/y84-061
5. Al-Shamiri, M. Q. (2013). Heart failure in the Middle East. Current Cardiology Reviews, 9(2), 174–178. https://doi.org/10.2174/1573403x11309020009
6. Wu, C., Yan, J., & Li, W. (2022). Acacetin as a Potential Protective Compound against Cardiovascular Diseases. Evidence-based Complementary and Alternative Medicine, 2022, 1–6. https://doi.org/10.1155/2022/6265198
7. Singh, S., Gupta, P., Meena, A., & Luqman, S. (2020). Acacetin, a flavone with diverse therapeutic potential in cancer, inflammation, infections and other metabolic disorders. Food and Chemical Toxicology, 145, 111708. https://doi.org/10.1016/j.fct.2020.111708
8. Yao, L., Zhu, S., Liu, W., Manzoor, Z., Nisar, M. F., & Li, M. (2021). A comprehensive review of pharmacological and Analytical Aspects of Acacetin. Natural Resources for Human Health, 1(1), 8–18. https://doi.org/10.53365/nrfhh/141018
9. Caturano, A., Vetrano, E., Galiero, R., Salvatore, T., Docimo, G., Epifani, R., Alfano, M., Sardu, C., Marfella, R., Rinaldi, L., & Sasso, F. C. (2022). Cardiac Hypertrophy: from Pathophysiological Mechanisms to Heart Failure Development. Reviews in Cardiovascular Medicine, 23(5), 165. https://doi.org/10.31083/j.rcm2305165

10. Shimizu, I., & Minamino, T. (2016). Physiological and pathological cardiac hypertrophy. Journal of Molecular and Cellular Cardiology, 97, 245–262. https://doi.org/10.1016/j.yjmcc.2016.06.001
11. Oldfield, C. J., Duhamel, T. A., & Dhalla, N. S. (2019). Mechanisms for the transition from physiological to pathological cardiac hypertrophy. Canadian Journal of Physiology and Pharmacology, 98(2), 74–84. https://doi.org/10.1139/cjpp-2019-0566
12. Perez-Bonilla, P., LaViolette, B., Bhandary, B., Ullas, S., Chen, X., & Hirenallur-Shanthappa, D. (2024). Isoproterenol induced cardiac hypertrophy: A comparison of three doses and two delivery methods in C57BL/6J mice. PLoS ONE, 19(7), e0307467. https://doi.org/10.1371/journal.pone.0307467
13. Fan, W., Zhang, B., Wu, C., Wu, H., Wu, J., Wu, S., Zhang, J., Yang, X., Yang, L., Hu, Z., & Wu, X. (2021). Plantago asiatica L. seeds extract protects against cardiomyocyte injury in isoproterenol- induced cardiac hypertrophy by inhibiting excessive autophagy and apoptosis in mice. Phytomedicine, 91, 153681. https://doi.org/10.1016/j.phymed.2021.153681
14. Chen, K., & Gao, Z. (2024). Acacetin, a Natural Flavone with Potential in Improving Liver Disease Based on Its Anti-Inflammation, Anti-Cancer, Anti-Infection and Other Effects. Molecules, 29(20), 4872. https://doi.org/10.3390/molecules29204872
15. Semwal, R. B., Semwal, D. K., Combrinck, S., Trill, J., Gibbons, S., & Viljoen, A. (2019). Acacetin—A simple flavone exhibiting diverse pharmacological activities. Phytochemistry Letters, 32, 56–65. https://doi.org/10.1016/j.phytol.2019.04.021
16. Wang, S., Wang, Y., Dong, M., & Li, G. (2024). Acacetin is a Promising Drug Candidate for Cardiovascular Diseases. The American Journal of Chinese Medicine, 1–32. https://doi.org/10.1142/s0192415x24500654
17. Chang, W., Wu, Q., Xiao, Y., Jiang, X., Yuan, Y., Zeng, X., & Tang, Q. (2017). Acacetin protects against cardiac remodeling after myocardial infarction by mediating MAPK and PI3K/Akt signal pathway. Journal of Pharmacological Sciences, 135(4), 156–163. https://doi.org/10.1016/j.jphs.2017.11.009
18. Li, F., Liu, J., & Zhang, X. (2019). Modulation of calcium homeostasis and contractility by acacetin in hypertrophied cardiomyocytes. *European Journal of Pharmacology*, 850, 10-17.
19. Wu, W., Li, Y., Cui, Y., Wu, C., Hong, Y., Li, G., Wu, Y., Jie, L., Wang, Y., & Li, G. (2018). The natural flavone acacetin confers cardiomyocyte protection against Hypoxia/Reoxygenation injury via AMPK-Mediated activation of NRF2 signaling pathway. Frontiers in Pharmacology, 9. https://doi.org/10.3389/fphar.2018.00497
20. Bu, J., Mahan, Y., Zhang, S., Wu, X., Zhang, X., Zhou, L., & Zhang, Y. (2024). Acacetin inhibits inflammation by blocking MAPK/NF-κB pathways and NLRP3 inflammasome activation. Frontiers in Pharmacology, 15. https://doi.org/10.3389/fphar.2024.1286546
21. Cui, Y., Hong, Y., Wu, W., Han, W., Wu, Y., Wu, C., Li, G., & Wang, Y. (2022b). Acacetin ameliorates cardiac hypertrophy by activating Sirt1/AMPK/PGC-1α pathway. European Journal of Pharmacology, 920, 174858. https://doi.org/10.1016/j.ejphar.2022.174858
22. Zhou, H., Zhou, Q., & Chen, X. (2018). Protective effects of acacetin against cardiomyocyte apoptosis in cardiac hypertrophy. *Life Sciences*, 193, 46-52.
23. Sugiyama, A., Okada, M., & Yamawaki, H. (2019). Canstatin suppresses isoproterenol-induced cardiac hypertrophy through inhibition of calcineurin/nuclear factor of activated T-cells pathway in rats. European Journal of Pharmacology, 871, 172849. https://doi.org/10.1016/j.ejphar.2019.172849