REVIEW ON THE CARDIOPROTECTIVE ROLE OF PINOCEMBRIN IN ATHEROSCLEROSIS, MYOCARDIAL INFARCTION, AND ASSOCIATED VASCULAR-MYOCARDIAL REMODELING

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ABSTRACT

Cardiovascular diseases represent a formidable global health challenge, standing as the foremost cause of both mortality and morbidity. Atherosclerosis and myocardial infarction, as primary contributors to this epidemiological burden, underscore the urgent need for effective therapeutic interventions with minimal side effects. Natural compounds derived from plants have emerged as promising candidates, given their enhanced efficacy and reduced adverse effects. Phytochemicals, in particular, have garnered attention for their potential as alternative therapeutic agents. This review delves into the cardioprotective potential of pinocembrin (5,7-Dihydroxy flavanone), a compound extracted from various plants and honey. Renowned for its antioxidant and anti-inflammatory properties, pinocembrin demonstrates significant cardioprotective effects through the modulation of diverse signaling pathways. Atherosclerosis and myocardial infarction entail intricate cellular mechanisms involving oxidative stress, inflammatory responses, cellular remodeling, and programmed cell death. Pinocembrin, by targeting key factors within these pathways, exhibits cardioprotective actions. While existing research underscores its effectiveness, further investigations are warranted to elucidate the impact of pinocembrin on additional cardiovascular conditions and explore novel molecular targets, thus paving the way for future advancements in therapeutic interventions.

Key words: Pinocembrin, atherosclerosis, MI, cardioprotective role

INTRODUCTION

According to data provided by the World Health Organization (WHO), cardiovascular diseases are the leading global cause of death, estimated at around 17.9 million deaths per year. Encompassing various clinical conditions affecting the heart and blood vessels, cardiovascular diseases result from a combination of modifiable and non-modifiable risk factors (Anna Johansson, 2021; Elizabeth Wilkins, 2017). Common risk factors include smoking, alcoholism, metabolic disorders, and hypertension. While lifestyle modifications significantly reduce the incidence of these conditions, pharmaceutical therapies, particularly with advancing age, are often necessary (Dariush Mozaffarian, 2008).

However, prolonged use of synthetic drugs, such as widely used statins, may lead to undesirable side effects, particularly in patients with multiple medical co-morbidities (Satish Ramkumar, 2016). This has spurred interest in researching the cardioprotective effects of plants and plant-derived compounds. Traditional folk medicines, with a history of treating various ailments, present a promising avenue for exploration, though a thorough evaluation of constituent phytochemical compositions and individual activities is essential.

Secondary plant metabolites, including phenolics, terpenes, flavonoids, alkaloids, and stilbenes, are produced in response to plant-environment interactions and serve as both regulatory and primary metabolites (Kliebenstein, 2020). Due to their structural and chemical diversity, these phytochemicals offer potential health benefits and warrant investigation for their various therapeutic effects (Sadaf Mushtaq, 2018).

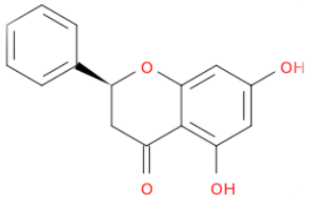
Among the well-studied plant secondary metabolites are flavonoids, abundant in plants and plant products. Possessing antioxidant, anti-inflammatory, antimicrobial, anticancer, and antidiabetic properties, flavonoids, including the natural compound pinocembrin, exhibit cardioprotective potential. This article focuses on

exploring the cardioprotective effects demonstrated by pinocembrin in atherosclerosis, myocardial infarction, and associated vascular and myocardial remodeling.

PINOCEMBRIN (5,7-Dihydroxy flavanone)

Pinocembrin is a primary flavonoid isolated from a variety of plants, including Pinus pinaster, Turnera diffusa, Alpinia mutica, Piper sarmentosum, Combretum collinum, Euphorbia hirta Linn, Dalia elegance, Alpinia galangal, Oxytropis falcate, Litchi sinensis, Lippia graveolens, Boesenbergia pandurata, Cryptocarya chinensis, Syzygium samarangense, Sparattosperma leucanthum, Alpinia pricei, Cleome droserifolia, Centaurea eryngioides, Cistus incanus, and Alpinia katsumadai (Azhar Rasul, 2013). Additionally, it can be obtained from propolis (Cinthia C S Menezesda Silveira, 2021) and isolated from honey (Mandal, 2009).

To enhance cost-effectiveness and yield, microbial biosynthesis from glucose molecules is a preferred method, involving genetic engineered bacteria (Bong Gyu Kim, 2014) (Junjun Wu, 2013). Pinocembrin biosynthesis in E. coli can be achieved by inducing malonyl CoA production (Weijia Cao, 2016) and reducing the accumulation of cinnamic acid (Weijia Cao W. M., 2016).



Structure of Pinocembrin Fig (1)

Pinocembrin can be used in the treatment of many diseases conditions as it shows antibacterial, anti-inflammatory, antimicrobial, anticancer, antifungal, neuroprotective activities (Azhar Rasul, 2013). It has anti-allergic (Hamza Hanieh, 2017) and anti-oxidant activities (Cinthia C S Menezesda Silviera, 2021). Safety and tolerability of pinocembrin administration in healthy subjects were studied and it was proven that 120mg single doses administered were tolerated with no clinically relevant changes (Guoying Cao, 2015).

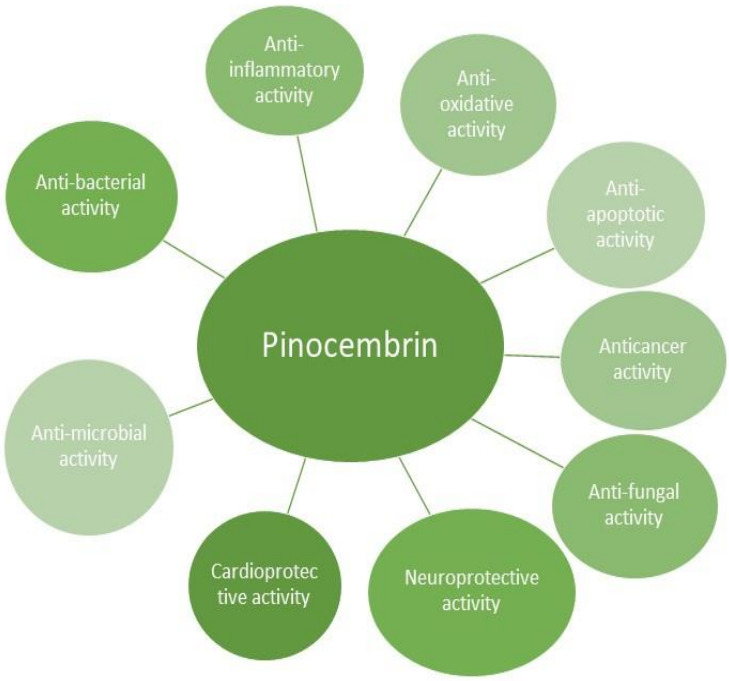


Figure 2 Biological activities of pinocembrin

CARDIOPROTECTIVE ROLE OF PINOCEMBRIN

Cardiovascular diseases, particularly atherosclerosis and myocardial infarction, arise from a variety of cellular at the cellular level including imbalance in cellular redox homeostasis, inflammatory responses and cell death due to apoptosis and necrosis. Pinocembrin, with antioxidant, anti-inflammatory, and anti-apoptotic activities, can thus be evaluated for its cardioprotective roles

, using in vitro and in vivo studies.

ACTION AGAINST ATHEROSCLEROSIS

Atherosclerosis is one of the leading cause of deaths among cardiovascular diseases and it is due to the increased lipid content developing into fat deposition in the intimal parts of aorta and coronary arteries limiting the blood flow to the heart muscles. This is a complex process initiated by the increased oxidation of low-density lipoprotein molecules, leading to the formation of oxidized LDL (oxLDL). Subsequently, these molecules are taken up by macrophages and converted into foam cells. Oxidative stress marks the risk factor of initiating these events. Subsequent changes are coordinated by the inflammatory and immune systems, leading to conditions of fibrosis The atheromatous plaque grows as a result of fibrous cell proliferation, reducing arterial blood flow. Calcium ion deposition in this process makes the plaque hardened and results in thrombosis (Mahmoud Rafieian-Kopaei, 2014). Increased production of reactive oxygen species (ROS) resulting in oxidative stress is initiating this atherosclerotic process as well as mediating its progression leading to adverse events (MitsuhiroYokoyama, 2004). One of the cellular protective mechanisms against oxidative stress is to activate Nrf2/HO-1 signalling pathway (Susanna Fiorelli, 2019).

Nrf2 is a transcriptional factor mainly involved in evoking the cellular antioxidant defence mechanism once get activated by the oxidative stress signals. In atherosclerosis Nrf2 plays a dual role of defending oxidative stress and in adverse conditions of atherosclerosis Nrf2 signals helps in disease progression. But the main function of Nrf2 is to act as a key agent against oxidative stress induced cellular damage. Oxidative stress is the major factor underlying in cardiovascular diseases (Jialal, 2006).

Nrf2 is seen in the cytoplasm associated with the regulatory protein KEAP-1 under normal redox conditions. But when the oxidant concentration starts elevated KEAP-1 protein changes its conformation and it dissociates from Nrf2. Nrf2 can then translocate into the nucleus where it binds with sMaf proteins to form heterodimer. This dimeric form can bind on specific regions on DNA through ARE (antioxidant response elements) and can transcribe a number of genes encoding antioxidant proteins like heme oxygenases-1 (Jose Angel Alonso-Piñeiro, 2021) (Antonio Cuadrado, 2019). Heme oxygenases (HO) are intracellular microsomal enzymes oxidizing heme into biliverdin, carbon monoxide and ferrous ion. Biliverdin then rapidly forms Bilirubin by biliverdin reductase. All the products formed as a result of HO-1 action play antioxidant, anti-inflammatory, anti-apoptotic and anti-thrombotic properties (Yoshimi Kishimoto, 2019) (Jesus A. Araujo, 2012). Bilirubin is a potent antioxidant in scavenging peroxide radicals in vitro (Roland Stocker, 1987). CO is a vasoconstrictor (Morita, 2005) and the ferrous ion liberated by heme oxidation is immediately trapped by the protein ferritin, thereby reducing the free radical production induced by iron. HO-1 and ferritin are therefore co-expressed intracellularly (Sandra Fogg, 1999). Nrf2/HO-1 pathway is considered as the main pathway to defence oxidative stress in pathological conditions (Qing Zhang, 2021). Effect of Pinocembrin on Nrf2/ARE/HO-1 pathway was shown by its neuroprotective action in neuroblastoma SH-SY5Y cells by reducing the injuries due to oxidative stress (Xiaohua Jin, 2015). The antioxidant activity of pinocembrin can be attributed to its action on Nrf2/ARE/HO-1 pathway (Zhi-Cong Zou, 2021) (Marcos Roberto de Oliveira, 2018).

Doxorubicin, a drug widely used in the treatment of several human malignant conditions exert cardiac toxicity, mostly by triggering inflammatory responses and by inducing oxidative stress. NF- kappa B/p38 MAPK signaling pathway plays the major role in inducing inflammatory responses due to doxorubicin-induced cytotoxicity (Run-Min Guo Wen-Ming Xu Jian-Cong Lin et al, 2013). In vitro studies on the effect of pinocembrin on doxorubin-induced cardiotoxicity using H9c2 cells showed that, pinocembrin could reduce the cytotoxicity exerted by doxorubicin and could improve the cellular antioxidant system. Pinocembrin could improve the mitochondrial function and reduced doxorubicin mediated apoptosis (Nonhlakanipho F Sangweni, 2020). Pinocembrin through NF kappa B/ p38 MAPK pathway helps in scavenging ROS production and thereby reducing ox-LDL induced endothelial injury and reducing the atherogenic process (Qiang Su, 2018).

Nrf2/HO-1 pathway induction may also ameliorate acute inflammatory responses involving cyclooxygenase action (COX) (Kyuhwa Seo, 2014). Cyclooxygenases are responsible for the biosynthesis of prostaglandins under acute inflammatory conditions. In vitro studies using pinocembrin showed its COX-1 and COX-2 inhibitory action. (Casey L Sayre, 2015).

ACTION IN MYOCARDIAL INFARCTION (MI)

Antioxidant role of pinocembrin in ISO-induced MI rat model showed significant rise in total antioxidant capacity by estimating reduced MDA, hydrogen peroxide, oxidized glutathione levels and increased superoxide dismutase activity and circulating glutathione. NADH oxidase and NADPH oxidase activities were also lowered after treating with pinocembrin which were mostly contributing to the vascular oxidative stress level. This antiarrhythmic effect of pinocembrin was mediating through Nrf2/HO-1 signalling pathway indicated by both of these parameters at elevated level (Xiaoli Chen, 2022).

Myocardial infarction indicates myocardial necrosis due to prolonged ischemia (Kristian Thygesen, 2007). Acute myocardial infarction denotes an infarction less than 3-5 days old and an irreversible necrosis of myocardium > 1cm, and it usually happens because of the clot formation or atherosclerotic plaque formation within the arteries. But generally acute myocardial infarction depends on the supply of oxygen to the muscle cells and oxygen demand of these cells. When there is too much oxygen demand as in increased heart rate, or less oxygen supply to the cells due to low blood pressure myocardial cell damage can happen without any such blood flow obstructions (Ambrose, 2018) (Allen Patrick Burke, 2021). Prolonged myocardial ischemia brings a lot of biochemical changes within the affected cardiomyocytes. Lack of oxygen leads to metabolic alterations,

switching on anaerobic metabolic pathways. Lactate produced as a result of anerobic glycolysis results a fall in intracellular pH and to balance this Na^+-H^+ exchanger gets activated to eliminate the excess proton produced, further leading to intracellular sodium overload. When oxygen supply gets reduced oxidative phosphorylation reaction stops leading to depolarization of mitochondrial membrane and ATP scarcity limits Na^+-K^+ ATPase functioning resulting in sodium overload. Triggering the action of Na^+-Ca^{2+} exchanger to balance the intracellular sodium level builds up intracellular Ca^{2+} overload (Marber, 2002). These metabolic changes along with oxidative stress, inflammatory and immune reactions within cardiomyocytes bring irreversible changes of these cells and it later on affects the thickness of the entire ventricular wall. So, the repair mechanism triggered by cytokines and inflammatory chemokines build up collagen-based scar in the affected area to prevent cardiac rupture, ultimately leads to ventricular remodeling process (Al-Salam, 2015).

The post-infarct remodeling is mainly initiated by the TGF-β superfamily cytokines, especially TGF-β1 released by cardiomyocytes, macrophages, endothelial cells etc. in response to redox imbalance. The signal cascade starts when TGF-β1binds with its receptor TGF-β1RII which then phosphorylates TGF-β1RI and this dimerized receptor-ligand complex can further phosphorylate and start intracellular signaling pathways, of which SMAD superfamily plays the major role. Smad 2/3 gets phosphorylated at first and then it binds with Smad4 to form a heterodimer and this in turn can translocate into the nucleus. TGF-β1-induced Smad signaling can then induce or repress DNA transcription within the nucleus giving rise to several inflammatory and immune components required for myocardial fibrosis and remodeling (Euler, 2015). Anti-inflammatory and antioxidant properties of pinocembrin play together in producing antifibrotic effect in liver through TGF- β/ Smad signaling pathway inhibition and by reducing proinflammatory cytokine production (Marwa M Said, 2018). Pinocembrin also have shown to alleviate ventricular arrythmia in I/R rat models through Na^+-K^+ ATPase and Ca^{2+}-Mg^{2+} ATPase activity enhancements (Peng Zhang, 2018).It has also shown ameliorating MI-induced atrial arrythmias by suppressing inflammatory responses and by decreasing atrial remodelling, atrial fibrosis, atrial electrical remodelling etc (Tianxin Ye C. Z., 2019). Pinocembrin has shown to upregulate anti-apoptotic protein bcl-2 expression and downregulate the expression of pro-apoptotic proteins like p53, bax and cleave caspases. The p53 protein downregulation by pinocembrin also plays a role in restoring the altered function and distribution of VEGFR2 by attenuating the anti-angiogenesis effect of p53 by inhibiting hypoxia inducible factor- 1α (HIF-1α). The Post-MI ventricular remodelling was attenuated by decreasing the collagen fibres deposition by approximately two folds in the untreated condition and by exerting antioxidant effects through Nrf2/HO-1 pathway activation. Therefore, the anti-apoptotic, anti-fibrotic and angiogenesis effect of pinocembrin helps to prevent tissue remodelling in post MI (Xiuhuan Chen, 2021).

In vivo studies on ischemia-reperfusion (I/R) injury in rats showed that pinocembrin could protect heart from acute myocardial infarction I/R injury and improved post-ischemic cardiac function. This protective effect of pinocembrin is through enhancing glycolysis in cardiomyocytes and through the activation of PFKFB3. The reduced glycolysis in myocardial infarction I/R injury can be compensated through pinocembrin administration, as the result of this glucose oxidation increases and PFKFB3 gets upregulated and cellular glucose from PPP redirects to glycolytic pathways, by upregulating the expression of the key transcription factor H1F1α (Yanjun Zheng, 2020). When studied I/R in Wistar rat models pinocembrin treated animals were showing improved MDA levels and decreased Bax/Bcl2 ratio. Infarcted issues showed increase in the ratio of phosphorylated connexin43 to total connexin43 showing improved cardiac function in pinocembrin treated animals. Pinocembrin can elevate the phosphorylation of connexin43 in ischemic myocardium and can also reduce arrythmias (Anusorn Lungkaphin, 2015). Pinocembrin also exerts protective effect in cerebral ischemic injury in rat models (Li-li Shi, 2011).

Anxiety and depression in patients during postoperative period were found closely associated with atrial fibrillation (AF) (Phillip J.Tully, 2011). Effect of pinocembrin on atrial fibrillation induced by depression was studied in rodent and rat models and it clearly showed multiple therapeutic effects on using this compound in ameliorating the AF susceptibility in depressed rats by reducing oxidative stress, atrial βchannels and gap junctions (Qian Ran, 2022) (Tianxin Ye, 2020).

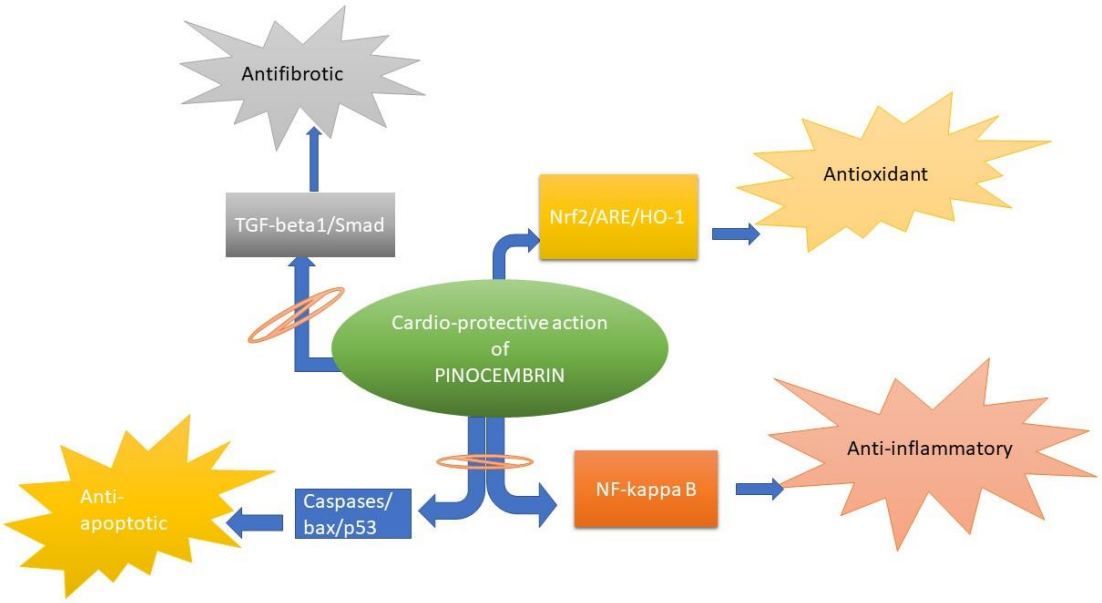


Figure (3) Antioxidant, anti-inflammatory, antiapoptotic and antifibrotic effect of pinocembrin in cardioprotective action

ACTION IN CARDIAC HYPERTROPHY

When the heart is subjected to an increased workload, the compensatory mechanism employed by the organ to adapt to this situation results in cardiac hypertrophy (Frank Lloyd Dini, 2019). Angiotensin II action triggers Rho A signaling pathway leading to cardiac hypertrophic condition. ROCK is therefore targeted in ameliorating cardiac hypertrophy, cardiac remodeling, and oxidative stress by suppressing endothelial nitic oxide synthase expression. RhoA, a GTP binding protein through its Rho associated kinase (ROCK) pathway controls cardiovascular system by regulating cellular motility, adhesion, proliferation, migration and apoptosis. When bound with GDP, Rho A will be in the inactive form and replacing GDP with GTP makes Rho A into active state and GTP bound Rho A then binds with ROCK, making the latter into the active state. Rho A/ROCK pathway upregulates VCAM -1 and ICAM-1 expression on endothelial cells inducing inflammatory responses and leukocyte infiltration (Cai Anping, 2016). Pinocembrin has shown blocking this Rho A/ROCK pathway studied in angiotensin II induced aortic constriction rat models (Li LI, 2013). Pinocembrin also suppresses the expression of pro-inflammatory vascular adhesion molecules ICAM-1, VCAM-1 and E-selectin expressions through its anti-inflammatory effects (Qiang Su, 2018).

Vasorelaxant injury is one of the main issues in developing cardiovascular diseases, mainly mediated through endothelium dependent NO/cGMP signaling pathway (Dan Wu, 2015). Vasodilation process also relies on endothelium independent mechanisms involving Ca^{2+} channel and K^{+} channels (Yu Yan, 2015). Pinocembrin induces aortic ring relaxation in rats either through endothelium dependent pathway or endothelium independent pathways (Xia- Ming Zhu, 2007).

CONCLUSION

A natural flavonoid Pinocembrin shows cardioprotective action primarily through its antioxidant, anti-inflammatory, antiapoptotic, vasodilation and antifibrotic effects, even though there are not much studies done on its cardioprotective action. Since the compound has shown therapeutic effects through regulating different

signaling pathways, more studies on cardiomyocytes should be done to elucidate its potent effect as a cardio-protecting agent. This review suggests more in vitro and in vivo studies using pinocembrin in different cardiovascular disease conditions.

REFERENCES

Allen Patrick Burke, M. (2021, April). Pathology of Acute Myocardial Infarction. *Drugs and diseases.*

Al-Salam, S. H. (2015, August). Acute myocardial infarction and myocardial ischemia-reperfusion injury: a comparison. *International journal of clinical and experimental pathology, 8*(8), 8786–8796.

Ambrose, M. S. (2018, September). Understanding myocardial infarction. *F1000Research, 7*. doi:10.12688/f1000research.15096.1

Anna Johansson, I. D. (2021, June). Modifiable and non-modifiable risk factores for atherothrombotic ischemic strokeamong subjects in malmo diet and cancer study. *Nutrients, 13 (6)*(1952). doi:10.3390/nu13061952

Antonio Cuadrado, A. I. (2019, January). Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases. *Nature Reviews Drug Discovery, 18*, 295-317. Retrieved from https://doi.org/10.1038/s41573-018-0008-x

Anusorn Lungkaphin, A. P. (2015, June). Pinocembrin reduces cardiac arrythmias and infarct size in rats subjected to acute myocardial ischemia/reperfusion. *Applied physiology, nutrition and metabolism, 40*(10). Retrieved from https://doi.org/10.1139/apnm-2015-0108

Asad Ullah, S. M. (2020). Important flavanoids and their role as therapeuyic agent. *Molecules, 25*(22). Retrieved from https://doi.org/10.3390/molecules25225243

Azhar Rasul, F. M. (2013). Pinocembrin: a novel natural compound with versatile pharmacological and biological activities. *BioMed Research International, 2013*(379850). doi: 10.1155/2013/379850

Bong Gyu Kim, H. L.-H. (2014). Biosynthesis of pinocembrin from glucose using engineered Escherichia coli. *Journal of Microbiology and biotechnology, 24*(11), 1536-1541.

Bushra Nisar, A. S. (2017). Comparison of medicinally important natural products versus synthetic drus: a short commentary. *Natural Products Chemistry & Research, 6*(2). doi:10.4172/2329-6836.1000308

Cai Anping, L. L. (2016, January). Pathophysiological effects of RhoA and Rho-associated kinase on cardiovascular system. *Journal of Hypertension, 34*(1), 1-3. doi:10.1097/HJH.0000000000000768

Casey L Sayre, S. A. (2015). Pre-clinical pharmacokinetics and pharmacodynamic charecterization of selected chiral flavonoids: Pinocembrin and pinostrobin. *J Pharm Pharm Sci, 18*(4), 368-395. Retrieved from www.cspsCanada.org

Cinthia C S Menezesda Silviera, D. A. (2021). Propolis: a useful agent on psychatric and neurological disorders? a focus on CAPE and pinocembrin components. *Medical research reviews, 41*(2). Retrieved from https://doi.org/10.1002/med.21757

Cinthia C. S, M. d. (2021). Propolis: A useful agent on psychiatric and neurological disorders? A focus on CAPE and pinocembrin components. *Medicinal research review, 41*(2), 1195-1215. Retrieved from Cinthia C. S. Menezes da Silveira,Diandra A

Dan Wu, Q. H. (2015). Vasorelaxant Effect of a New Hydrogen Sulfide-Nitric Oxide Conjugated Donor in Isolated Rat Aortic Rings through cGMP Pathway. *Oxidative medicine and cellular longevity, 2016*. Retrieved from https://doi.org/10.1155/2016/7075682

Dariush Mozaffarian, P. W. (2008, June). Lifestyle risk factors for cardiovascular diseases. *Circulation, 117*(23), 3031-3038.

Elizabeth Wilkins, L. W. (Ed.). (2017). Europian cardiovascular statistics 2017 edition. (pp. 1-192). Belgium: Europian heart network. Retrieved from www.ehnheart.org

Euler, G. (2015, March). Good and bad sides of TGFβ-signaling in myocardial infarction. *Frontiers Physiology, 6*(66). Retrieved from https://doi.org/10.3389/fphys.2015.00006

Frank Lloyd Dini, G. G. (2019). Left Ventricular Mass and Thickness: Why Does It Matter?,. *Heart Failure Clinics,, 15*(2), 159-166. Retrieved from https://doi.org/10.1016/j.hfc.2018.12.013.

Guoying Cao, P. Y. (2015, June). Pharmacokinetics, safety and tolerability of single and multiple doses of piocembrin injection administered intravenously in healthy subjects. *Journal of ethnopharmacology, 168*, 31-36. Retrieved from https://doi.org/10.1016/j.jep.2015.03.041

Hamza Hanieh, V. I. (2017, November). Pinocembrin, a novel histidinr decarboxylase inhibitor with anti-allergic potential in in vitro. *Euripian journal of pharmacology, 814*, 178-186. Retrieved from https://doi.org/10.1016/j.ejphar.2017.08.012

Jialal, U. S. (2006, August). Oxidative stress and atherosclerosis. *Pathophysiology, 13*(3), 129-142.

Jose Angel Alonso-Piñeiro, A. G.-R.-G. (2021, September). Nrf2 and Heme Oxygenase-1 Involvement in Atherosclerosis Related Oxidative Stress. *Antioxidants, 10*(9). Retrieved from https://doi.org/10.3390/antiox10091463

Junjun Wu, G. D. (2013, March). Metabolic enginnering for Escherichia coli for (2S)- pinocembrin production from glucose by a modular metabolic strategy. *Metabolic Engineering, 16*, 48-55. Retrieved from https://doi.org/10.1016/j.ymben.2012.11.009.

Kliebenstein, M. E. (2020, September). Plant secondary metabolites as defences, regulators and primary metabolites: The blurred functional trichotomy. *Plant Physiology, 184*(1), 39-52. doi: 10.1104/pp.20.00433

Kristian Thygesen, J. S. (2007, November). Universal Definition of Myocardial Infarction. *Journal of the American college of cardiology, 50*(22), 2173–2195.

Kyuhwa Seo, J. H. (2014). The Antioxidant Effects of Isorhamnetin Contribute to Inhibit COX-2 Expression in Response to Inflammation: A Potential Role of HO-1. *Inflammation, 37*, 712-722. Retrieved from https://doi.org/10.1007/s10753-013-9789-6

Li LI, H.-G. Y.-Y. (2013, May). Rho kinase inhibition activity of pinocembrin in rat aortic rings contracted by angiotensin II. *Chinese Journal of Natural Medicines, 11*(3), 258-263. Retrieved from https://doi.org/10.1016/S1875-5364(13)60025-4.

Li-li Shi, B.-n. C. (2011). The characteristics of therapeutic effect of pinocembrin in transient global brain ischemia/reperfusion rats. *Life Sciences, 88*(11-12), 521-528. Retrieved from https://doi.org/10.1016/j.lfs.2011.01.011.

Mahmoud Rafieian-Kopaei, M. S. (2014, August). Atherosclerosis: Process, Indicators, Risk Factors and New Hopes. *Int J Preventive Medicine, 5*(8), 927-946.

Mandal, S. K. (2009). Antiproliferative effects of honey and its polyphenols : a review. *BioMed Research International, 2009*, 13. Retrieved from https://doi.org/10.1155/2009/830616

Marber, M. A. (2002, March). Na+/h+exchange inhibitors for cardioprotective therapy: progress, problems and prospects. *Journal of the American College of Cardiology , 39*(5), 747-753. Retrieved from https://doi.org/10.1016/S0735-1097(02)01693-5

Marcos Roberto de Oliveira, G. d. (2018). Pinocembrin Suppresses H2O2-Induced Mitochondrial Dysfunction by a Mechanism Dependent on the Nrf2/HO-1 Axis in SH-SY5Y Cells. *Molecular Neurobiology, 55*, 989–1003 . Retrieved from https://doi.org/10.1007/s12035-016-0380-7

Marwa M Said, S. S. (2018, March-April). Antifibrotic mechanism of pinocembrin : Impact on oxidative stress, Inflammation and TGF-beta/ Smad inhibition in rats. *Annals of hepatology, 17*(2), 307-317. doi:DOI:10.5604/01.3001.0010.8661

MitsuhiroYokoyama. (2004, April). Oxidant stress and atherosclerosis. *Current Opinion in Pharmacology, 4*(2), 110-115. Retrieved from https://doi.org/10.1016/j.coph.2003.12.004

Nonhlakanipho F Sangweni, M. M. (2020, August). The prophylactic effect of pinocembrin against doxorubicin-induced cardiotoxicity in an in vitro H9c2 cell model. *Frontiers in pharmacy, 11*(1172), 13. Retrieved from https://doi.org/10.3389/fphar.2020.01172

Peng Zhang, J. X. (2018, July). Effects of Pinocembrin Pretreatment on Connexin 43 (Cx43) Protein Expression After Rat Myocardial Ischemia-Reperfusion and Cardiac Arrhythmia. *Medical Science monitor, 24*, 5008-5014. Retrieved from https://doi.org/10.12659/MSM.909162

Phillip J.Tully, J. S. (2011). Anxiety, depression, and stress as risk factors for atrial fibrillation after cardiac surgery. *Heart & Lung, 40*(1), 4-11. Retrieved from https://doi.org/10.1016/j.hrtlng.2009.12.010

Qian Ran, X. C. (2022, May). Pinocembrin Decreases Atrial Fibrillation Susceptibility in a Rodent Model of Depression. *Front. Cardiovasc. Med, 9*. Retrieved from https://doi.org/10.3389/fcvm.2022.766477

Qiang Su, Y. S. (2018, November). Pinocembrin protects endothelial cells from oxidized LDL- induced injury. *Cytokines, 111*, 475-480.

Qing Zhang, J. L. (2021, December). Activation of Nrf2/HO-1 signaling: An important molecular mechanism of herbal medicine in the treatment of atherosclerosis via the protection of vascular endothelial cells from oxidative stress. *Journal of Advanced Research, 34*, 43-63. Retrieved from https://doi.org/10.1016/j.jare.2021.06.023

Rana, R. T. (2015, September-October). Plant secondary metabolites: a review. *International journal of engineering research and general science, 4*(5), 661-670.

Run-Min Guo Wen-Ming Xu Jian-Cong Lin et al. (2013, June). Activation of the p38 MAPK/NF-κB pathway contributes to doxorubicin-induced inflammation and cytotoxicity in H9c2 cardiac cells. *Molecular medicine reports, 8*(2), 603-608. Retrieved from https://doi.org/10.3892/mmr.2013.1554

Sadaf Mushtaq, B. H. (2018, May). Natural products as reservoirs of novel therapeutic agents. *Excli journal, 17*, 420-451. doi: 10.17179/excli2018-1174

Satish Ramkumar, A. R. (2016, November). Statin therapy: review of safety and potential side effects. *Acta cardiologica Sinica, 32*(6), 631-639. doi:10.6515/ACS20160611A

Susanna Fiorelli, B. P. (2019). Activation of Nrf2/HO-1 Pathway and Human Atherosclerotic Plaque Vulnerability: An In Vitro and In Vivo Study. *Cells, 8*(4). Retrieved from https://doi.org/10.3390/cells8040356

Tianxin Ye, C. Z. (2019, December). Pinocembrin attenuates autonomic dysfunction and atrial fibrillation susceptibility via inhibition of the NF-κB/TNF-α pathway in a rat model of myocardial infarction. *International immunopharmacology, 77*. Retrieved from https://doi.org/10.1016/j.intimp.2019.105926

Tianxin Ye, C. Z. (2020, November). Pinocembrin Decreases Ventricular Fibrillation Susceptibility in a Rat Model of Depression. *Front. Pharmacol., 11*. Retrieved from https://doi.org/10.3389/fphar.2020.547966

Weijia Cao, W. M. (2016). Enhanced pinocembrin production in Escherichia coli by regulating cinnamic acid metabolism. *Scientific reports, 6*(32640). Retrieved from https://doi.org/10.1038/srep32640

Weijia Cao, W. M. (2016, April). Improved pinocembrin production in Escherichia coli. *Journal of industrial microbiology and biotechnology, 43*(4), 557-566. Retrieved from https://doi.org/10.1007/s10295-015-1725-3

Xia- Ming Zhu, L.-H. F.-J. (2007, March). Endothelium dependent and independent relaxation induced by pinocembrin in rat aortic rings. *Vascular pharmacology, 46*(3), 160-165. Retrieved from https://doi.org/10.1016/j.vph.2006.09.003

Xiaohua Jin, Q. L. (2015). Pinocembrin Attenuates 6-OHDA-induced Neuronal Cell Death Through Nrf2/ARE Pathway in SH-SY5Y Cells. *Cellular and Molecular Neurobiology , 35*, 323–333. Retrieved from https://doi.org/10.1007/s10571-014-0128-8

Xiaoli Chen, W. W. (2022). Pinocembrin mediates antiarrhythmic effects in rats with isoproterenol-induced cardiac remodeling. *European Journal of Pharmacology, 920*.

Xiuhuan Chen, w. W. (2021). Pinocembrin ameliorates post-infarct heart failure through activation of Nrf2/HO-1 activation pathway. *Molecular medicine, 27*(100), 12.

Yanjun Zheng, G. W. (2020). Xardioprotective natural compound pinocembrin attinuates acute ischemic myocardial injury via enhancing glycolysis. *2020*, 13. Retrieved from https://doi.org/10.1155/2020/4850328

Yu Yan, Y.-c. C.-h. (2015). Brazilin isolated from the heartwood of Caesalpinia sappan L induces endothelium -dependent and -independent relaxation of the rat aortic rings. *acta pharmacologica sinica, 36*, 1318–1326. Retrieved from https://doi.org/10.1038/aps.2015.113

Zhi-Cong Zou, J.-J. F.-Y. (2021). Pinocembrin-7-Methylether Protects SH-SY5Y Cells Against 6-Hydroxydopamine-Induced Neurotoxicity via Modulating Nrf2 Induction Through AKT and ERK Pathways. *Neurotoxicity Research , 39*, 1323–1337. Retrieved from https://doi.org/10.1007/s12640-021-00376-4