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A Review on The Role of Apocynin in Cardiovascular Health - A Game Changer

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, often driven by oxidative stress, inflammation, and endothelial dysfunction. Apocynin, a naturally occurring methoxy-substituted catechol derived from *Picrorhiza kurroa*, has gained attention for its potent antioxidant and anti-inflammatory properties. This review evaluates the role of apocynin in cardiovascular health, highlighting its potential as a therapeutic agent. Relevant experimental, preclinical, and clinical studies were analyzed to assess its impact on oxidative stress, inflammation, platelet aggregation, endothelial function, and cardiovascular health. Apocynin has been shown to inhibit NADPH oxidase, thereby reducing the production of reactive oxygen species (ROS) and mitigating oxidative damage. Studies indicate that it helps maintain vascular integrity, prevents endothelial dysfunction, and modulates inflammatory pathways involved in atherosclerosis and thrombosis. Additionally, apocynin's role in regulating platelet activation and improving nitric oxide bioavailability suggests its potential in preventing ischemic events such as myocardial infarction and stroke. Apocynin exhibits promising cardioprotective properties by targeting key pathological mechanisms underlying cardiovascular diseases. Its ability to reduce oxidative stress, inflammation, and thrombolytic properties enables it as a potential game-changer in cardiovascular therapy. However, further clinical trials are needed to determine its efficacy, optimal dosage, and long-term safety in humans.

Keywords: Apocynin; NADPH oxidase inhibitor; cardioprotective thrombolytic; anti-platelet; cardiovascular diseases

Introduction

Apocynin (4′-hydroxy-3′-methoxyacetophenone), commonly known as acetovanillone, is a naturally occurring bioactive compound found in the roots of *Picrorhiza kurroa* Royle ex Benth. This perennial medicinal plant, native to the alpine Himalayan region, has been extensively used in Ayurvedic medicine across India and Sri Lanka. Traditional formulations incorporating *Picrorhiza kurroa* root extracts have been employed for centuries to manage various ailments, particularly those affecting the liver, heart, joints, and respiratory system [1, 2].

Figure 1: *Picrorhiza kurroa* Plant.

Pharmacology of Apocynin

Apocynin (4-hydroxy-3-methoxyacetophenone or acetovanillone) is a naturally occurring organic compound derived from the roots of an Alpine Himalayan medicinal plant [3]. It shares structural similarities with vanillin and is predominantly found in mountainous regions of India, Pakistan, Tibet, and Nepal. The compound has a molecular weight of 166.17 g/mol, emits a faint vanilla-like scent, melts at 115°C, and has a boiling point between 233-235°C. It is soluble in hot water, alcohol, benzene, and chloroform. Traditionally, apocynin has been an essential component of Ayurvedic medicine, where it has been used to address various health conditions, including those affecting the liver, heart, and lungs. When administered orally, apocynin is rapidly absorbed and eliminated, with its metabolites detected in feces and urine in forms such as ring-hydroxylated, demethylated, and glucuronide derivatives [4].

Anti-Inflammatory Properties

Apocynin is widely recognized for its potent anti-inflammatory effects, which are largely attributed to its ability to regulate oxidative stress and immune responses. Structurally, apocynin is a methoxy-substituted catechol that has garnered significant attention due to its ability to modulate oxidative stress and inflammation [5]. It is widely recognized as an inhibitor of NADPH oxidase, an enzyme complex responsible for generating reactive oxygen species (ROS) such as superoxide anions (O_2^-). Excessive ROS production is a major contributor to cellular damage, oxidative stress, and inflammation, all of which play a pivotal role in the pathogenesis of cardiovascular diseases [6].

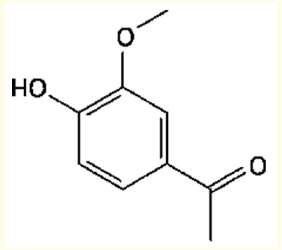

Figure 2: Structure of apocynin.

These effects have been demonstrated in various disease models, including cardiovascular diseases, neuroinflammation, and autoimmune disorders [7].

Inhibition of Pro-Inflammatory Cytokines

Apocynin effectively reduces the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, which are central mediators of inflammation. By inhibiting the activation of NF-κB and MAPK pathways, apocynin prevents excessive cytokine production and alleviates inflammation-associated tissue damage [8].

Reduction of Neutrophil and Macrophage Activation

During inflammation, neutrophils and macrophages produce large amounts of ROS, contributing to tissue damage. Apocynin selectively inhibits NOX in these immune cells without impairing their phagocytic function, allowing them to effectively clear pathogens while minimizing oxidative stress-induced damage [9].

Prevention of Endothelial Dysfunction

Chronic inflammation contributes to endothelial dysfunction, a key factor in the progression of cardiovascular diseases. Apocynin helps maintain endothelial health by reducing ROS levels, improving NO bioavailability, and preventing vascular inflammation. This results in enhanced vasodilation reduced arterial stiffness, and lower risk of atherosclerosis [10, 11].

Protection against Neuroinflammation

Emerging studies suggest that apocynin may also provide neuroprotective effects by reducing oxidative stress and inflammation in the central nervous system. Its ability to inhibit microglial activation and reduce neuroinflammatory cytokines makes it a promising candidate for conditions such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis [12].

One of apocynin's remarkable properties is its selective inhibition of NADPH oxidase activity while preserving the phagocytic function of neutrophils and macrophages. This ensures that while ROS production is controlled, the immune system's ability to eliminate pathogens remains unaffected [13]. Experimental studies in various cellular and animal models have consistently demonstrated apocynin's strong anti-inflammatory effects, highlighting its potential as a therapeutic agent for conditions driven by chronic inflammation and oxidative stress [14].

Apocynin in Thrombosis and Cardiovascular Health

Thrombosis, the formation of blood clots within blood vessels, is a major risk factor for several life-threatening cardiovascular disorders, including deep vein thrombosis (DVT), myocardial infarction (heart attack), ischemic stroke, and pulmonary embolism [15]. The excessive activation of platelets, endothelial dysfunction, and oxidative stress are key drivers of thrombotic events.

Apocynin has shown promising potential in mitigating thrombosis-related complications through its dual action as an NADPH oxidase inhibitor and a ROS scavenger. By reducing oxidative stress, it helps in maintaining endothelial integrity, preventing platelet hyperactivation, and modulating megakaryopoiesis—the process responsible for platelet production. Dysregulated megakaryopoiesis, often triggered by chronic stress and inflammation, has been implicated in abnormal platelet function, increasing the risk of clot formation [16].

Research suggests that apocynin's antioxidative and anti-inflammatory properties may contribute to improving vascular health, reducing arterial stiffness, and protecting against atherosclerosis, a condition characterized by plaque buildup in arteries [17]. Additionally, by regulating hydrogen peroxide levels, apocynin helps in preserving endothelial nitric oxide (NO) bioavailability, which is essential for vasodilation and overall cardiovascular function [18].

Apocynin in preventing abnormal Megakaryopoiesis and platelet activation

Sandrini et al. conducted a study investigating the role of apocynin in preventing abnormal megakaryopoiesis and platelet activation induced by chronic stress in mice. Their findings revealed that exposure to four days of forced swimming stress (FSS) led to elevated oxidative stress markers, such as increased plasma malondialdehyde levels, and a higher predisposition to arterial thrombosis. Notably, treatment with apocynin effectively prevented these adverse changes [19].

Furthermore, FSS disrupted normal megakaryopoiesis, resulting in an increased number and maturation of bone marrow megakaryocytes (MKs), along with alterations in circulating platelets. Specifically, the study observed a greater presence of large and reticulated platelets exhibiting significant functional activation following FSS. Apocynin administration reduced the overall MK count and inhibited their ability to generate reactive oxygen species (ROS) without affecting the percentage of CD42d+ cells. Additionally, it mitigated platelet hyperactivation in stressed mice [20].

Apocynin appears to have a strong protective effect against the development of a prothrombotic phenotype triggered by environmental stress. This protective action is likely due to its ability to influence multiple cell types and tissues, including megakaryocytes, the bone marrow environment, platelets, and blood vessel walls. Notably, chronic stress leads to an upregulation of NOX1 expression in bone marrow cells, including megakaryocytes, but Apocynin treatment significantly reduces these elevated levels. Furthermore, Apocynin inhibits platelet activation and enhances vascular and endothelial function by limiting ROS production. It achieves this by preventing the interaction of NOXO1 and p47phox with p22phox, reducing Rho kinase activity, and acting as a radical scavenger. Additionally, Apocynin may influence platelet function through an alternative, yet unidentified, mechanism [21].

They concluded that apocynin plays a crucial role in restoring physiological megakaryopoiesis and platelet function, thereby counteracting the harmful effects of chronic stress on thrombosis and preventing thrombosis associated with excessive corticosterone secretion (ECS) [22].

Apocynin on cardiac injury in type 4 CardioRenal Syndrome (CRS)

The heart and kidneys maintain a dynamic and interdependent relationship, where impairment in one organ often triggers dysfunction in the other. This reciprocal interaction creates a vicious cycle of progressive structural and functional deterioration, collectively known as cardiorenal syndrome (CRS)[23]. Among the different subtypes of CRS, Type 4—referred to as chronic renocardiac syndrome—specifically describes cardiovascular dysfunction that arises as a consequence of chronic kidney disease (CKD). The pathophysiology of this condition is multifactorial, involving hemodynamic alterations, neurohormonal activation, and oxidative stress, all of which contribute to the worsening of both cardiac and renal function.

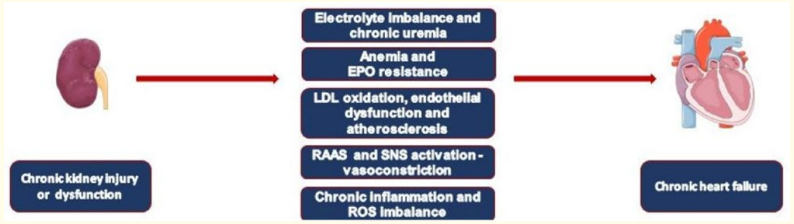

Figure 3: Mechanism of type IV cardiorenal syndrome.

Oxidative stress plays a pivotal role in the pathogenesis of type 4 CRS, acting as a key driver of tissue damage in both the heart and kidneys. It occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms, leading to cellular injury. In CKD, oxidative stress is a well-recognized pathological feature and can be monitored through specific biomarkers, including malondialdehyde (MDA), which reflects lipid peroxidation, superoxide dismutase (SOD), an enzymatic antioxidant, asymmetric dimethylarginine, and advanced oxidation protein products. The accumulation of these oxidative stress markers contributes to endothelial dysfunction, inflammation, and fibrosis, further aggravating cardiovascular complications associated with CKD.

Another major contributor to oxidative stress in CKD is the overactivation of the renin-angiotensin-aldosterone system (RAAS). Patients with CKD often exhibit significantly elevated levels of angiotensin II (Ang II), a vasoconstrictive peptide that promotes oxidative stress by stimulating NADPH oxidase activity. This leads to excessive ROS production, exacerbating vascular inflammation, endothelial dysfunction, and myocardial remodeling. The persistent activation of RAAS, coupled with increased oxidative stress, accelerates cardiovascular damage, making it a key therapeutic target in the management of type 4 CRS.

Apocynin, a naturally derived compound, has gained attention for its ability to modulate oxidative stress by inhibiting NADPH oxidase, an enzyme complex responsible for ROS generation. Unlike other antioxidants, apocynin specifically targets the assembly of NADPH oxidase subunits, effectively reducing ROS production without disrupting normal cellular functions.

Liu et al. conducted a study to examine the effects of apocynin on cardiac injury in patients with type 4 CardioRenal Syndrome (CRS). The study included 17 patients in the interventional group who received apocynin treatment and 16 patients in the control group. Their findings revealed that apocynin alleviated cardiac injury in type 4 CRS by inhibiting NOX-dependent oxidative stress, which in turn suppressed the activation of the ERK1/2 pathway and reduced the upregulation of Fibroblast Growth Factor-2 (FGF-2). These results provided additional evidence supporting the cardioprotective effects of antioxidant therapy and highlighted the role of FGF-2 in the pathophysiology of type 4 CRS [23].

Several experimental studies have highlighted the protective effects of apocynin on both the heart and kidneys. By reducing oxidative stress, it helps maintain endothelial function, prevents excessive inflammation, and mitigates fibrosis—key factors implicated in the progression of type 4 CRS. Furthermore, apocynin has been shown to counteract the detrimental effects of Ang II, thereby limiting RAAS-induced cardiovascular and renal damage [24].

Apocynin and atherosclerosis

Atherosclerosis is a long-term inflammatory condition arising from imbalances in lipid metabolism and immune system responses. The formation of atherosclerotic plaques is primarily driven by inflammation, which is influenced by oxidized lipoproteins, oxidative stress, and shear stress. Research into apocynin's immunomodulatory effects has provided insights into its role in endothelial cells, revealing that its mechanism of action closely resembles that observed in phagocytic cells [25].

Studies on animal models have shown that administering 4 mg/kg of apocynin significantly reduces vascular inflammation, though this effect appears to be independent of NOX activity, suggesting an alternative mode of action that is not reliant on ROS. Additionally, apocynin mitigates platelet-endothelial interactions by downregulating endothelial adhesion molecules, thereby reducing platelet adhesion and plaque growth. Its immunoregulatory properties also contribute to the inhibition of platelet aggregation by downregulating thromboxane A2 (TxA2) synthesis. However, the precise mechanism by which apocynin disrupts endothelial-platelet interactions remains unclear [25].

In later stages of atherosclerosis, apocynin demonstrates a ROS-dependent mode of action. Initially, it lowers ROS production, followed by vascular remodeling through the reduction of intimal thickness and cell proliferation. Furthermore, by enhancing nitric oxide (NO) production, apocynin not only promotes endothelial vasodilation but also helps inhibit LDL oxidation, thereby slowing down the progression of atherosclerosis [25].

Superoxide radicals generated by NOX enzymes contribute to increased intimal thickness and cell proliferation, key factors in vascular remodeling. Animal studies suggest that apocynin exerts a regulatory effect on arterial remodeling in the early stages of atherosclerosis. Moreover, its ability to reduce H_2O_2 production highlights its anti-atherogenic potential, particularly in the presence of serum low-density lipoprotein (LDL) in endothelial cells. Given its antioxidant activity through NOX suppression, apocynin may serve as a protective agent against the onset of atherosclerosis [25].

Experimental research using a hypercholesterolemic mouse model of atherosclerosis demonstrated that apocynin, when administered at 500 mg/L in drinking water over 17-18 weeks, slowed the formation of atherosclerotic plaques by inhibiting NOX activity. In peritoneal macrophages of atherosclerosis-prone apoE−/− mice, apocynin was found to prevent atherosclerosis progression by reducing oxidized LDL-mediated ROS production, inhibiting the expression of pro-inflammatory mediators such as MCP-1, IL-6, and granulocyte/macrophage colony-stimulating factor, as well as limiting cell proliferation [25].

Additionally, apocynin reduced NADH-induced superoxide anion production in both rat and human arteries while increasing NO bioavailability, thereby improving endothelium-dependent vasodilation. In studies on myocardial ischemia/reperfusion (I/R) injury, apocynin was shown to lower inflammatory markers such as myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), toll-like receptor 4 (TLR4), and asymmetric dimethylarginine (ADMA), suggesting a protective role against oxidative stress and inflammation in myocardial tissue.

Apocynin also affects vascular smooth muscle cells by inhibiting redox-sensitive kinases, including p38-mitogen-activated protein kinase (MAPK), protein kinase B (Akt), and extracellular signal-regulated kinase 1/2 (ERK1/2), by reducing intracellular hydrogen peroxide and menadione, a radical generator.

Moreover, an in vivo study on rat ventricular myocytes highlighted the dual role of apocynin. Its primary function involves modulating the L-type calcium channel (Ica,L), which regulates muscle contractility. Through redox-related mechanisms, apocynin decreases H_2O_2 and glutathione (GSH) levels, ultimately inhibiting Ica,L activity. However, in a secondary role, apocynin has also been observed to act as a prooxidant, leading to H_2O_2 production, which can enhance Ica,L function in ventricular myocytes [26].

Potential therapeutic applications and future perspectives

Given its wide-ranging pharmacological activities, apocynin presents itself as a promising natural compound for cardiovascular health. Its ability to regulate oxidative stress, prevent excessive platelet activation, and protect vascular function makes it a potential candidate for developing novel therapeutic strategies against cardiovascular diseases, including hypertension, atherosclerosis, and ischemic heart disease [18].

NADPH Oxidase Inhibition

Apocynin exerts its effects by selectively inhibiting NOX activity, thereby reducing superoxide anion (O_2^-) and hydrogen peroxide

(H_2O_2) production. Unlike direct NOX inhibitors, apocynin prevents the assembly of the active enzyme complex by interfering with the translocation of the p47phox subunit, which is crucial for NOX activation. This results in a decrease in oxidative stress without completely shutting down physiological ROS production, which is essential for normal cellular signaling [12, 19].

Regulation of Nitric Oxide (NO) Bioavailability

Oxidative stress leads to the inactivation of nitric oxide (NO), a vital vasodilator that maintains endothelial function and prevents platelet aggregation. By reducing ROS levels, apocynin preserves NO bioavailability, thereby promoting vasodilation and improving cardiovascular health. This mechanism plays a significant role in preventing conditions such as hypertension, atherosclerosis, and thrombosis [20].

Modulation of the NF-κB Pathway

The nuclear factor kappa B (NF-κB) pathway is a key regulator of inflammation. Under oxidative stress conditions, NF-κB is activated, leading to the transcription of pro-inflammatory genes that produce cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β). Apocynin has been shown to inhibit NF-κB activation, thereby suppressing the production of these inflammatory mediators and reducing inflammation-associated damage [21].

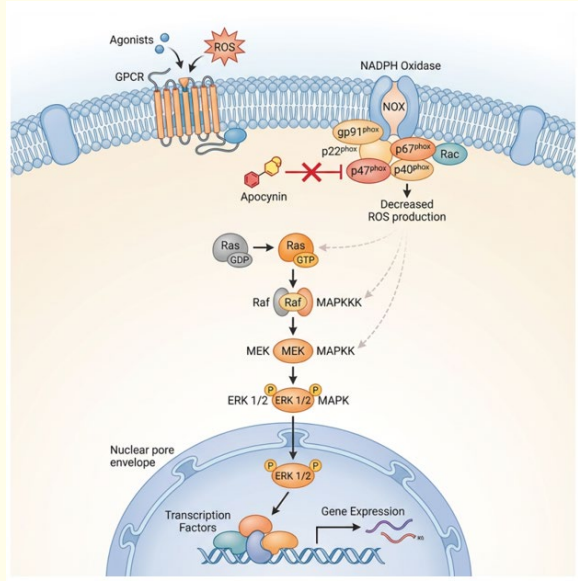

Figure 4: Molecular mechanism of apocynin in MAPK Signaling pathway illustrating the Inhibition of NADPH Oxidase (NOX) assembly.

Suppression of MAPK/ERK Signaling

The mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) pathways are involved in inflammatory signaling and oxidative stress responses. Apocynin has been found to downregulate these pathways, preventing inflammatory gene expression and reducing cellular damage caused by chronic inflammation [21, 27].

Despite its potential, further clinical studies are necessary to determine the optimal dosage, bioavailability, and long-term effects of apocynin in human subjects. The development of targeted drug delivery systems, such as nanoparticle-based formulations, may enhance its efficacy and therapeutic benefits.

Conclusion

Apocynin demonstrates significant potential as a cardioprotective agent by addressing critical pathological mechanisms involved in cardiovascular diseases. Its multifaceted ability to mitigate oxidative stress, suppress inflammation, and prevent thrombosis makes it a promising candidate for therapeutic intervention in cardiovascular health. This review has explored its role in cardiovascular disease management by analyzing experimental, preclinical, and clinical studies that highlight its impact on reducing oxidative damage, regulating platelet function, improving endothelial integrity, and modulating inflammatory pathways. While the current evidence supports its beneficial effects, further comprehensive clinical trials are essential to establish its efficacy, determine the optimal dosage, and assess its long-term safety profile in human populations.

Declaration

All the authors have read and approved the manuscript.

Conflict of Interest

There is no conflict of interest.

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