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Innovative Utilization of Orange Peel Waste through Modified Citrus Pectin (MCP) as a Preventive Agent Against Atherosclerosis Progression via Galectin-3 (Gal-3) Inhibition: A Comprehensive Literature Review on In Vitro and In Vivo Study Designs

Lamirza RMF [1], Rivaldi DP [1], Hagil AR [1], Fauzan SN*[1], Dio Kurniawan [1]
[1] Biomedical Science Departement, Faculty of Medicine, Andalas University
e - mail : *2010347003_fauzan@student.unand.ac.id.

Abstract −Atherosclerosis is an arterial disease often associated with lipids and other metabolic alterations. Various factors are involved in developing atherosclerosis, including Galectin-3 (Gal-3). Pre-clinical studies have shown that Modified Citrus Pectin (MCP), a modified polysaccharide from citrus peels, has the potential of inhibiting Gal-3 and countering the development of atherosclerosis. Thus, this review aims to analyze the role of MCP on inhibiting and regulating Galectin-3 (Gal-3) as an alternative therapeutic target. We examined valid pre-clinical experimental study designs taken from the databases Science Direct, Taylor & Francis, PubMed, and Google Scholar, with publication dates ranging from 2014 to 2024. 15 research articles meet the established inclusion criteria. Our review found that Gal-3 levels rose during atherosclerosis development, triggering proteins that disturbs cardiovascular physiology. Additionally, Gal-3 targeted inhibition using MCP has shown to have therapeutic effects that alleviates hypertrophy and plaque's size. In essence, MCP emerges as a promising alternative therapy targeting Gal-3 in atherosclerosis progression.

Key words −**Atherosclerotic, *Gal-3, MCP,* Therapy, Regulation.**

I. INTRODUCTION

Atherosclerosis is an arterial disease often associated with lipids and other metabolic alterations and is a major cause of cardiovascular diseases. Atherosclerosis encompasses two conditions: Ischemic Heart Disease (IHD) and Cerebrovascular Disease (primarily ischemic stroke). Globally, IHD and stroke are the first and third leading causes of death, accounting for approximately 247.9 deaths per 100,000 people1. Additionally, IHD affects around 126 million individuals, or about 1.72% of the global population, and is projected to exceed 140 million individuals affected by IHD by the end of 2030[2].

Atherosclerosis is the narrowing and hardening of blood vessels caused by the buildup of plaques (atheroma) within the arterial walls. These plaques obstruct blood flow to the heart, leading to gradual blockages that can cause coronary heart disease (CHD). According to data from the 2018 Riset Kesehatan Dasar (Riskesdas), the number of coronary heart disease (CHD) patients has been increasing annually, with approximately 15 out of every 1,000 Indonesians, or about 2,784,964 people, suffering from heart disease. The 2018 Riskesdas also reported that the prevalence of heart disease based on doctor diagnoses in Indonesia is 1.5%, with the highest prevalence found in North Kalimantan Province at 2.2%, followed by the Special Region of Yogyakarta and Gorontalo, each with a prevalence of 2%[3].

Many risk factors can be sources of atherosclerosis, such as high cholesterol levels, diet, stress, smoking, and obesity[4]. High concentrations of plasma lipoproteins like VLDL, LDL, and IDL are also associated with atherogenesis. Low-density lipoproteins (LDL) are easily oxidized into oxidized low-density lipoproteins (oxLDL), which are absorbed by macrophage scavenger receptors without downregulation despite the increase of cholesterol content, leading to foam cell's death and the formation of necrotic lipid cores. Atherosclerotic plaques then accumulate vascular smooth muscle cells (VSMC) that migrate, proliferate, and synthesize extracellular matrix proteins, contributing to the narrowing of the lumen and the formation of a strong fibrous cap that supports plaque growth and stability[5].

Risk factors that influence atherosclerosis generally develop through inflammatory mechanisms within the arteries. One of the mechanisms affecting inflammation is the protein Galectin-3 (Gal-3).

Galectin-3 is a β-galactoside-binding protein from the lectin family that has pleiotropic regulatory activities and plays a role in various physiological cellular functions, such as cell growth, proliferation, apoptosis, differentiation, and cell adhesion[6]. In acute inflammatory response, Gal-3 acts as a promoter of monocyte/macrophage chemotaxis, reacting with oxLDL to form foam cells that then accumulate into plaques.

The Gal-3 inflammatory risk factor could be inhibited to prevent atherosclerosis. One of the inhibitors is known as Modified Citrus Pectin (MCP). Several preclinical studies have been conducted to examine the mechanisms of inhibition and regulation of atherosclerosis by MCP both in vitro and in vivo. MCP acts as a competitor of Gal-3 in binding with receptors expressed in monocytes, macrophages, and endothelial cells, which plays a role in atherosclerosis through vascular smooth muscle cells, arterial endothelial damage leading to lipid infiltration in the blood vessels, and acting as a promoter of monocytes or macrophages. Additionally, the inhibitory effects of MCP have been shown in several studies to reduce the potential risk and severity of atherosclerosis. Therefore, based on the preclinical studies conducted on the effects of MCP on atherosclerosis, we present this literature review to analyze the role of Gal-3 inhibition with MCP administration as an alternative therapy for atherosclerosis.

II. RESEARCH METHODS

A. Research Strategy

This literature review discusses the competitive inhibition response of Modified Citrus Pectin (MCP) in the occurrence of atherosclerosis in both in vivo and in vitro studies, viewed from preclinical aspects, was conducted based on the PRISMA guidelines. This review includes studies sourced from the journal databases Science Direct, Taylor & Francis, PubMed, and Google Scholar, with publication dates ranging from 2014 to 2024.

The literature search utilizes Boolean operators with the keywords [“*Galectin-3*” *or* “*LGALS3*” *and* “*markers*” *and* “*therapy*” *and* “*atherosclerosis*”]. The search process was structured as a flowchart, as shown in Figure 1. A total of 6,477 articles were identified during the initial identification stage. These articles were then screened based on established criteria, and duplicates were removed, resulting in 15 valid and reliable journals.

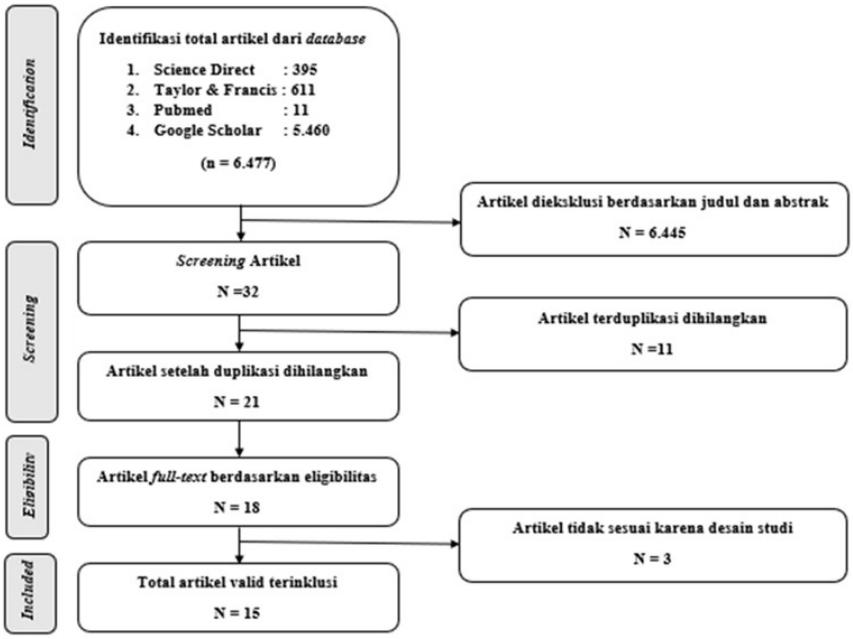

Fig. 1 Article Search Flowchart.

B. Study Inclusion and Exclusion Criteria

The inclusion criteria for the literature review were structured using the PICOS framework, summarized in Table 1. Summary results of literature studies from included articles are displayed in the supplementary data.

Table 1. Inclusion criteria for the literature review based on the PICOS framework

Criterias	Inclusion
Problems	The increasing and widespread development of atherosclerosis is influenced by Galectin-3
Intervation	The role of Modified Citrus Pectin (MCP) in suppressing the progression of atherosclerosis through Galectin-3 inhibition
Comparasion	The potential use of MCP in reducing Galectin-3 levels in atherosclerosis groups compared to control groups
Outcome	MCP as a novel therapy in diseases related to the development of atherosclerosis
Study Design	Preclinical studies encompassing both in vivo and in vitro research published within the last 10 years

III. RESULTS AND DISCUSSION

Role of Gal-3 in the Pathogenesis of Cardiovascular Atherosclerosis

Atherosclerosis is a pathological condition that is a major cause of coronary artery disease, stroke, and peripheral vascular disease, resulting from a series of complex processes with pathogenesis that starts with endothelial dysfunction. Various stimuli can trigger this dysfunction. One factor involved in the pathogenesis of atherosclerosis is Galectin-3 (Gal-3). Gal-3 is a member of the β-galactoside-binding lectin family with pleiotropic regulatory activity and various physiological cellular functions, including involvement in inflammation, tissue fibrosis, and angiogenesis. Identifying Gal-3 as a pro-inflammatory molecule that facilitates inflammatory responses through interaction with cell surface receptors and extracellular matrix (ECM) proteins enhances our understanding of the complexity of Gal-3's role in pathological conditions. Additionally, Gal-3 contributes to the regulation of acute and chronic inflammation, as well as tissue fibrogenesis. Its role in cardiac remodeling and dysfunction, as well as its involvement in inflammation and fibrosis related to aortic valve conditions, provides further insight into its potential as a therapeutic target in managing complex cardiovascular conditions such as heart failures[7].

Analysis from Matilla *et al.* study in 2023 demonstrated the role of Gal-3 in the inflammatory, angiogenic, and calcification processes of atherosclerotic plaques in patients with aortic stenosis, as illustrated in Figure 2.

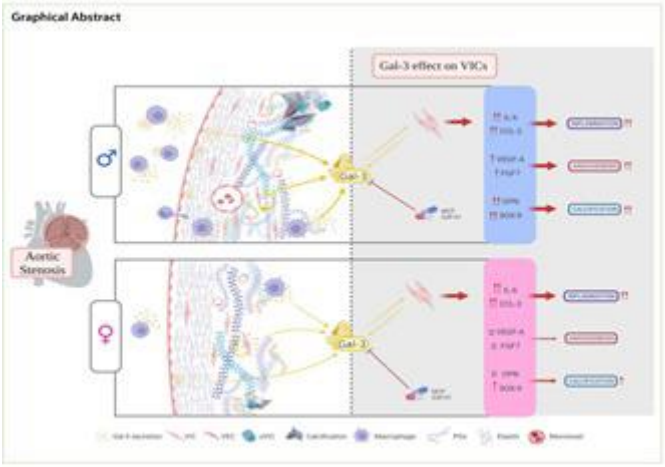

Fig 2. The mechanism of Gal-3's effect on aortic stenosis[8].

The distribution of Gal-3 within cells depends on its ability to interact with various components of the extracellular matrix (ECM), such as laminin, elastin, and fibronectin. These interactions facilitate cell-ECM adhesion and transendothelial migration. Additionally, Gal-3 plays a crucial role in mediating the interaction between neutrophils and monocytes with endothelial cells, both directly and indirectly. This process is influenced by the release of reactive species and proteolytic enzymes induced by neutrophil and monocyte adhesion, which can lead to endothelial erosion, endothelial cell dysfunction, increased vessel permeability, leukocyte accumulation in atherosclerotic areas. The expression of major adhesion molecules, such as β2-integrin on the surface of neutrophils, plays a key role in recruiting and transmigrating neutrophils and monocytes. Gal-3 strengthens adhesion by binding to endothelial cell surfaces and also potentially enhances cell adhesion through interactions with Mac-2 binding proteins. Additionally, Gal-3 acts as a receptor for advanced glycosylation end-product clearance and mediates macrophage-led endocytosis of oxidized low-density lipoprotein (LDL), which can facilitate foam cell formation and amplify subsequent inflammation. Thus, the distribution of Gal-3 on cell surfaces and in the extracellular environment can influence the initiation and progression of atherosclerosis by regulating leukocyte accumulation and activation[9].

Several studies have highlighted that oxidized low-density lipoprotein (LDL) triggers endothelial cell injury by altering the expression of pro-inflammatory genes. From accumulating evidence, it is known that Gal-3 exacerbates LDL-induced endothelial injury by stimulating inflammation. LDL itself induces endothelial dysfunction, ultimately increasing the expression of atherogenic signaling molecules. This subsequently facilitates monocyte adhesion to arterial endothelium and monocyte penetration into the intima layer. Scientific studies support findings that Gal-3 is specifically localized in macrophages and foam cells, core elements of atherosclerotic plaques. Gal-3 accumulates significantly and exclusively within the intimal plaques, with its distribution co-located with macrophage sites within the plaque. The process of macrophage differentiation into foam cells after LDL uptake also indicates Gal-3 involvement. This suggests that Gal-3 facilitates lipoprotein uptake by foam cells, thereby exacerbating atherosclerosis progression. Therefore, research supports the hypothesis that Gal-3 worsens the progression of atherosclerotic plaques through increased lipoprotein endocytosis and disruption of lipid metabolism.

The Mechanism of Modified Citrus Pectin (MCP)

Modified Citrus Pectin (MCP) is a polysaccharide derived from citrus peels that has been modified. MCP has been shown to have anti-inflammatory and anti-fibrotic effects in various cardiovascular diseases due to its ability to inhibit the effects of Gal-3. MCP is a modification of Citrus Pectin (CP) achieved through acid or alkaline treatment. The study conducted by Zhang *et al.*, in 2016 outlined a method for

modifying CP into MCP using acid-base treatment. First, CP was dissolved in distilled water (1.5%), and the pH of this solution was raised to pH 10.0 using 3M NaOH. The solution was allowed to stand for 1 hour before adjusting the pH to 3.0 using 3M HCl and then incubated overnight at room temperature. After incubation, the pH of the solution was adjusted to pH 6.3. Subsequently, MCP was precipitated by adding 95% ethanol to achieve 70% (v/v), followed by recovery through centrifugation, washing with acetone, and air drying[10].

Another study conducted by Lim *et al.*, in 2014 concluded that when pectin is digested by the body, it is broken down into constituent monosaccharides such as arabinose and xylose in the large intestine. These monosaccharides are then fermented by gut microflora, producing short-chain fatty acids (SCFAs) which are believed to influence the effectiveness of pectin, including arabinose and its metabolite butyrate. Additionally, the study demonstrated that consuming pectin can protect the heart from ischemic attacks, with implications for explaining the role of dietary fiber in reducing the risk of coronary heart disease (CHD)[11].

Regulation of MCP in Inhibiting Gal-3 Expression

Several studies confirm that Gal-3 plays a central role as a contributing factor in various cardiovascular diseases, including atherosclerosis. Gal-3 has been shown to be involved in the pathogenesis of atherosclerosis by triggering inflammation, fibrogenesis, and cardiac remodeling[12]. This phenomenon is supported by the ease of Gal-3 expression in monocytes, macrophages, and endothelial cells during atherosclerotic plaque formation[9]. These findings are reinforced by several in vivo and in vitro (pre-clinical) studies demonstrating a significant increase due to Gal-3 expression in atherosclerosis.

The mechanism of the relationship between the downregulation of Gal-3 and the progression of atherosclerosis is demonstrated by in vitro research conducted by Sadaba *et al*., in 2016. The study showed that administration of MCP can reduce the secretion of IL-6 and IL-1β, as well as the levels of Gal-3 protein. The decrease in Gal-3 is accompanied by a reduction in fibronectin protein levels. Additionally, Valvular Interstitial Cell Line (VICs) treated with MCP showed a decrease in calcification markers. MCP reduces the levels of BMP-2, BMP-4, SOX-9, and Runx2, which are pro-inflammatory and pro-calcification proteins, thereby significantly suppressing inflammation potential in arterial valves ($P<0.05$)[13].

Studies by *Xu et al*., in 2020 conducted in vivo also demonstrated that MCP administration can downregulate Gal-3 by reducing mRNA and protein levels of Gal-3 in fibrotic heart tissues, thereby significantly ($P<0.05$) improving cardiac dysfunction by inhibiting the reduction of left ventricular end-systolic diameter, left ventricular end-diastolic diameter, stroke volume, cardiac output, ejection fraction, and fractional shortening. In this study, it was also found that MCP prevents the activation of the TLR4/MyD88/NF-κB signaling pathway, which is a potential pro-inflammatory pathway, reduces myocardial injury, collagen deposition, and decreases Gal-3 expression in Isoproterenol (ISO)-induced rats[7]. Mo *et al*., also demonstrated in their research using infrared (IR) injury treatment that MCP significantly reduces cardiac dysfunction and improves myocardial injury[14]. This study is further supported by an in vivo study in 2021 by Li *et al*., which demonstrated that cardiac hypertrophy decreased due to the effect of MCP, evidenced by its ability to lower the elevation of Gal-3 expression in Wistar rats[15]. Martinez *et al.*, in 2015 also stated that MCP can inhibit Gal-3, prevent inflammation and hypertension, thereby normalizing blood pressure levels in aldosterone-induced rats[16].

In 2024, Wang *et al*. conducted an in vivo study using Sprague-Dawley rats subjected to arterial cuff placement, high-fat diet, and sham surgery. The results showed that after treatment with MCP, there was a significant reduction in luminal narrowing and the intima-to-lumen area ratio. Furthermore, compared to the CUFF + HFD group, the MCP group exhibited lower blood flow in the penile vessels during erection and lower rectal temperature ratio, while the penis-to-rectum temperature ratio was also lower. These findings highlight a potential relationship between atherogenic erectile dysfunction development and vascular remodeling influenced by cuff placement and high-fat diet. During the erection phase, such vascular remodeling may hinder adequate blood supply to the penile vessels, which MCP treatment can potentially ameliorate. Additionally, the study noted that MCP could inhibit the upregulation of Gal-3, Toll-like receptor 4 (TLR4), and myeloid differentiation primary response protein 88 (MyD88), which could

increase the risk of inflammation and fibrosis in the penile corpus cavernosum. Treatment with Gal-3 inhibitor modified citrus pectin (MCP) successfully normalized the decrease in intracavernosal pressure, endothelial nitric oxide synthase expression, smooth muscle content, and reduced inflammation and fibrosis. This Gal-3 inhibitor proves effective in reducing inflammation, endothelial injury, and fibrosis in the penile corpus cavernosum through the TLR4/MyD88/NF-κB pathway[17].

In 2022, Gehlken *et al*. conducted a study aiming to investigate the inhibitory effects of Gal-3 both in vivo and in vitro. They utilized a C57BL/6J mouse model induced with subcutaneous infusion of angiotensin II to simulate cardiac fibrosis. Ang II infusion significantly increased fibrosis formation signals by 4-5 times and elevated the number of CD45+ cells in the left ventricular tissue. In their in vivo experiments, treatment with MCP provided strong evidence of its therapeutic potential in reducing cardiac fibrosis. Furthermore, in their in vitro assays, researchers isolated monocytes from buffy coats. MCP demonstrated significant inhibition of Gal-3-induced monocyte chemotaxis, highlighting MCP's potential role in inhibiting the movement of monocytes that trigger inflammatory processes[18]. This pattern was also observed in a previous study by Wan et al. in 2021 using Sprague-Dawley rats, which found that MCP effectively inhibited fibrosis and collagen accumulation induced by Gal-3[19]. Both studies are supported by research conducted by Li *et al.* in 2019, stating that MCP comparatively improved ischemic heart failure by reducing Gal-3 regulation, thereby decreasing myocardial fibrosis, delaying ventricular remodeling, and preventing heart failure[20]. Collectively, these three studies conclude that MCP significantly contributes to reducing cardiac fibrosis and preserving heart function, both in vivo and in vitro contexts. These findings highlight MCP's potential as a therapeutic agent for addressing cardiac fibrosis and preventing heart failure through the mechanism of Gal-3 inhibition.

Based on various previous studies, MCP has been shown to play a crucial role in the characteristics of atherosclerosis. Its crucial role is evidenced by significant reductions in inflammation, fibrogenesis, and cardiac remodeling by inhibiting Gal-3, which triggers these factors and impacts the occurrence of atherosclerosis. The use of MCP thus holds the potential to become an effective new therapeutic model in the treatment of atherosclerosis.

The Potential of MCP as an Alternative Therapeutic Agent for Atherosclerotic Cardiovascular Diseases

Gal-3 plays a crucial role in inflammation, calcification, and angiogenesis processes involved in the development of atherosclerosis and various other cardiovascular diseases, based on preclinical research[8]. Therefore, several interventions and therapies have been developed to lower Gal-3 levels, one of which is the use of Modified Citrus Pectin (MCP). MCP is a molecule frequently studied as a specific ligand for Gal-3[18]. MCP shows high potential as an alternative therapy for atherosclerosis.

The preclinical studies involving in vitro and in vivo research have revealed the role of MCP in cardiovascular atherosclerosis therapy. Sadaba *et al.*, in 2016, and Martinez *et al.*, in 2019, demonstrated that MCP significantly ($P<0.05$) reduces the activity and levels of Gal-3, contributing to inflammation reduction and osteogenic differentiation. Additionally, Gal-3 inhibition has been shown to mitigate inflammation and cardiac fibrosis in experimental hyperaldosteronism, irrespective of high blood pressure levels[13,21]. A similar pattern was observed in the 2017 study by Ibarrola *et al.*, where MCP treatment prevented the increase in Gal-3, fibrosis, inflammation, and calcification in the aortic valve (AV), thereby inhibiting remodeling in rats under pressure overload (PO) conditions[22]. Analysis of the relationship between heart dysfunction and Gal-3 downregulation via MCP administration in male Wistar rat heart tissue induced by Isoproterenol (ISO) was conducted by Xu *et al.*, in 2020. The findings from Xu *et al.*'s study in 2020 are depicted in Figure 2.

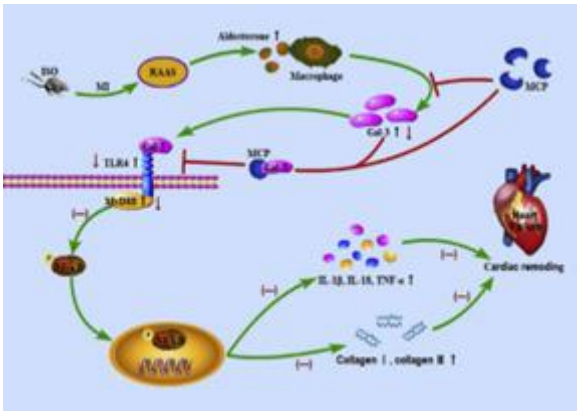

Fig 3. The mechanism of MCP in Isoproterenol-induced Myocardial Inflammation and Myocardial Fibrosis[7].

The model of myocardial fibrosis (MF) in rats, ISO activates the Renin-Angiotensin-Aldosterone System (RAAS), thereby increasing plasma aldosterone levels. Aldosterone induces myocardial inflammation and fibrosis by activating the mineralocorticoid receptor (MR). Gal-3 mediates ventricular dysfunction and remodeling caused by ISO, while Gal-3 inhibitor (MCP) and MR antagonist (potassium canrenoate) can reverse myocardial inflammation and fibrosis. Aldosterone also triggers Gal-3 secretion via the MR/PI3K/AKT/NF-κB signaling pathway in macrophages, contributing to cardiovascular fibrosis. MR antagonists such as eplerenone and SPI reduce Gal-3 expression and decrease markers of fibrosis and inflammation in rat models of left ventricular systolic dysfunction post-acute myocardial infarction. Gal-3 also acts as an endogenous paracrine ligand for TLR4, inducing pro-inflammatory responses, and mediating pro-inflammatory and pro-apoptotic effects on chondrocyte injury. Pharmacological blockade of Gal-3 with MCP improves ISO-induced cardiac injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway[7].

In vivo research using C57BL/6J apoE -/- mouse model discussed the mechanism of MCP in reducing atherosclerotic lesions. In 2017, Lu *et al*. found that MCP treatment for 4 weeks significantly reduced the size of aortic lesions, brachiocephalic artery (BCA) lesions, and aortic root compared to the model group, as shown by Movat staining. Scanning Electron Microscopy (SEM) analysis revealed significant damage to the endothelial structure in the model group, whereas the MCP-treated group only showed mild endothelial structure relaxation, with the surface of the atherosclerotic plaque remaining intact[7]. Therefore, the use of MCP as a therapeutic agent for atherosclerotic cardiovascular diseases is supported by preclinical studies and demonstrated promising results in reducing atherosclerotic lesions by inhibiting leukocyte adhesion to endothelial cells. Research has also shown that MCP significantly reduces the activity and levels of Gal-3, which contributes to reducing inflammation and osteogenic differentiation. Thus, MCP may represent a promising therapeutic strategy as an alternative treatment for cardiovascular atherosclerosis in the future.

IV. CONCLUSION

Galectin-3 (Gal-3), as a member of the β-galactoside-binding lectin family, plays a key role in the pathogenesis of atherosclerosis. The distribution of Gal-3 in various cellular compartments, including the nucleus, cell surface, and extracellular environment, significantly impacts the initiation and progression of this disease. Gal-3 is involved in regulating cell adhesion, transendothelial migration, and critical cellular interactions in the process of atherosclerosis. Additionally, Gal-3's role in mediating the clearance of low-density lipoprotein (LDL) modified by macrophages strengthens foam cell formation and associated inflammation. The potential of Gal-3 as a therapeutic target in managing complex cardiovascular conditions such as atherosclerosis and heart failure is becoming increasingly evident.

Studies also indicate that downregulation of Gal-3 by Modified Citrus Pectin (MCP), both in vivo and in vitro research, significantly reduces the expression of proteins activated by Gal-3, such as IL-6, IL-

1 β, BMP-2, BMP-4, SOX-9, and Runx2, all of which play roles in pro-inflammatory, pro-calcification, and pro-fibrosis processes. MCP has also been shown to reduce inflammation, endothelial injury, and fibrosis by inhibiting Gal-3 through the TLR4/MyD88/NF-κB pathway, thereby significantly reducing the risk of atherosclerosis.

The development of MCP through pH modification of citrus pectin (CP) has affirmed that MCP holds significant potential as a therapeutic agent for cardiovascular atherosclerosis. Besides inhibiting leukocyte adhesion to endothelial cells, MCP has also shown promising results in both in vitro and in vivo studies, demonstrating a reduction in the severity of atherosclerosis. This confirms that MCP could be an effective alternative therapy for atherosclerosis, providing consistent positive responses in treating this disease.

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