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Review

The Role of Amino Acid Glycine on Cardiovascular Health and Its Beneficial Effects: A Narrative Review

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Abstract: Glycine, a simple amino acid, is not only essential due to its potential insufficiency in vivo, but also has significant metabolic functions. It serves as a crucial building block for proteins. At the same time, as a bioactive molecule, it regulates gene expression for cytoprotection, protein configuration and activity, and other critical biological processes, including glutathione synthesis. The intriguing, beneficial effects of glycine in medical applications have piqued the research community's interest in recent decades. This work delves into the compelling discoveries about the pivotal role of glycine in cardiovascular health and its intricate mechanisms of action for alleviating several medical conditions. Glycine's broad spectrum of impact spans numerous diseases, encompassing not only acute myocardial infarction, aortic dissection, and cardiac hypertrophy, but also transplant rejections of aortic allografts, insulin resistance, and endothelial dysfunction, thereby providing a comprehensive understanding of its medical applications.

Keywords: glycine; cardio-metabolic protection; cardio-metabolic diseases; cardiovascular health

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1. Introduction

Glycine is the simplest proteinogenic amino acid. Unlike other amino acids, it has a hydrogen atom as its side chain, which makes it the only achiral amino acid (Figure 1). As an alpha-amino acid, it belongs to the serine family [1]. Humans synthesize glycine from various sources, like glyoxylate, glucose (via serine), betaine, and likely threonine, as well as during the endogenous synthesis of L-carnitine [2]. Despite this, studies of several animal models have suggested that glycine may be conditionally essential, as the amount synthesized in the body may sometimes be insufficient to meet an organism's metabolic needs [3]. Therefore, it is necessary to have a dietary intake of approximately 1.5–3 g/day to stay healthy and to keep a physiological glycine plasma concentration ranging from 200 to 300 mol/L [4].

Glycine is vital for synthesizing biomolecules like creatine and purine nucleotides, making it a valuable nutrient for therapeutic use [1]. Studies have shown that it possesses anti-inflammatory properties, enhances insulin response, and stimulates glutathione biosynthesis, which is crucial for antioxidant protection in all tissues [4–6]. Also, there is evidence that glycine is necessary for reinforcing the extracellular matrix, and glycine dietary supplementation is very effective against viral infections [7]. Clinical research has suggested that glycine supplementation can have a positive impact on metabolic disorders associated with obesity, such as type 2 diabetes and nonalcoholic fatty liver disease, as

individuals with lower circulating glycine levels are more likely to develop these conditions [3]. Additionally, it has been found to increase blood levels to more than 900 µM without harmful side effects, providing cytoprotective benefits [8,9]. The glycine plasma concentration has also been found to impact the severity of schizophrenia symptoms [10,11]. In contrast, low levels of glycine and other amino acids in serum are often observed in children with autism compared to control groups [12]. Figure 2 outlines glycine's main positive impacts on cardiovascular health.

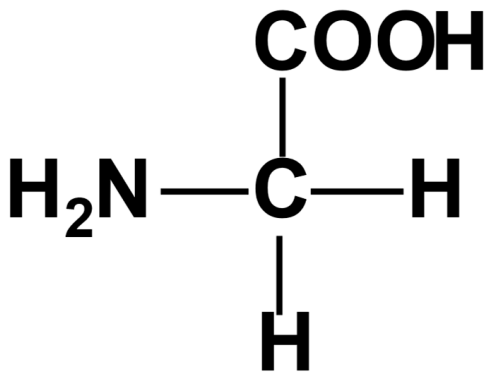

Figure 1. Chemical structure of glycine.

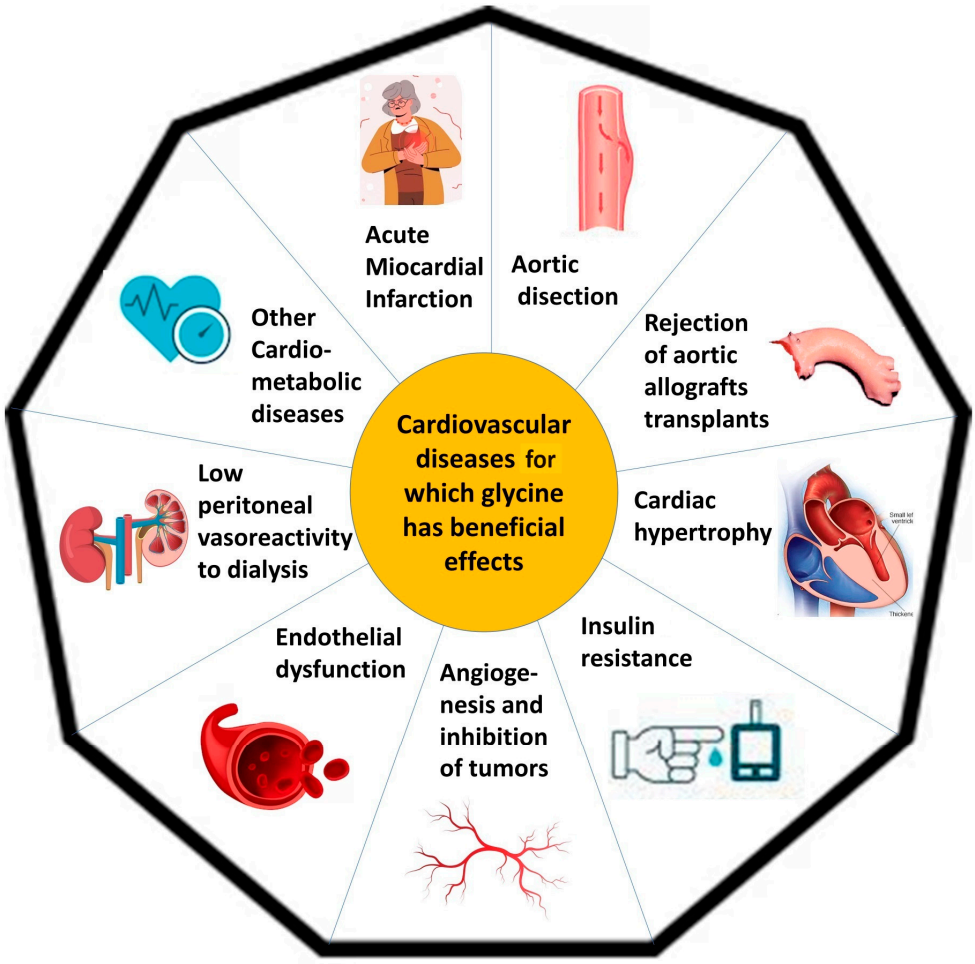

Figure 2. Glycine's main positive impacts on cardiovascular health.

While glycine has numerous effects on overall health, this work will highlight its significance in promoting cardiovascular health. Notably, there are no comprehensive review articles summarizing the beneficial effects of glycine on cardiovascular diseases or its mechanisms of action.

2. Methodology

This study presents a comprehensive analysis of glycine's positive impact on cardiovascular health and its therapeutic potential for managing symptoms of cardiovascular conditions. The authors extensively reviewed the relevant research articles, utilizing reputable databases, such as Google Scholar. The search concluded on 18 March 2024, and only articles presenting reliable and measurable results were included in this analysis. A summary of glycine's mechanisms of action can be found in Table 1.

Table 1. Mechanisms of action of glycine for the improvement of symptoms of different cardiovascular diseases.

Glycine levels in plasma and risk of acute myocardial infarction	Glycine-dependent reactions with lipid metabolism and cholesterol transport catabolize excess S-adenosylmethionine by its remethylation into sarcosine via the enzyme glycine-*N*-methyltransferase (GNMT) [5].
	Attenuates myocardial fibrosis by modulating the signal transducer and activator of the transcription 3/Nuclear Factor-κB/transforming growth factor-β axis [6].
	Inhibition of myocardial apoptosis in rats and suppression of phosphorylated p38 mitogen-activated protein kinase and c-Jun NH2-terminal kinase [13].
Glycine levels in plasma and aortic conditions	Glycine deficiency inhibits glutathione formation in bone marrow-derived macrophages. At the same time, glycine-based treatment induces de novo glutathione biosynthesis and mitigates atherosclerosis through antioxidant effects mediated by the induction of glutathione biosynthesis [13].
	Minimizes chronic rejection of aortic transplants by reducing the immune response and, in part, minimizing the proliferation and migration of smooth muscle cells [14].
	Works at the level of NINJ1, an executioner of plasma membrane rupture in pyroptosis, necrosis, and post-apoptosis lysis [15].
The role of glycine in angiogenesis and the inhibition of tumors	Acts on PI3K/Akt/mTOR signaling: low doses of glycine (10 mM) promote angiogenesis, whereas high doses (400 mM) cause anti-angiogenesis [16].
	It attenuates cerebrovascular remodeling in rats after stroke via glycine receptor alpha 2 and vascular endothelial growth factor receptor 2 [8].
	An increase in intracellular glycine causes the endothelial growth factor to activate the glycine transporter 1 (GlyT1), which is directly bound to the voltage-dependent anion channel 1 (VDAC1) on the mitochondrial outer membrane, inhibiting its opening [9].
	Glycine increases intracellular Ca^{2+} concentration. Also, it significantly diminishes the serum-stimulated proliferation and migration of endothelial cells by activating a glycine-gated chloride channel [10].
	Glycine decreases GlyR-dependent, VEGF-A-mediated, angiogenic signaling in human hepatocellular carcinoma [11].

Table 1. *Cont.*

Dietary glycine supplementation for endothelial dysfunction	It improves endothelial function in aged rats by enhancing eNOS expression and reducing the role of superoxide anion and contractile prostanoids, which increase nitric oxide bioavailability [12].
Effects of glycine on pathologic cardiac hypertrophy	Glycine could antagonize Ang II stimulated release of transforming growth factor-β and endothelin-1 by cardiomyocytes, preventing an over-production of collagens in rat fibroblasts [17].
Glycine and low peritoneal vasoreactivity to dialysis solutions	Vasoreactivity to peritoneal dialysis solution is entirely restored by glycine supplementation, thanks to its antioxidant effects, which mitigate oxidative stress [18].
Correlation between glycine, insulin resistance, and other cardio-metabolic diseases	Glycine intake (1% in drinking water) decreases plasma-free fatty acids, adipose cell size, and blood pressure in sucrose-fed rats [19].
	Glycine could have effects against dietary fructose [20] via activation of glycine-gated chloride channels.
	Supplementing with glycine and N-acetylcysteine in older adults improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, physical function, and aging hallmarks [21].
	It improves the symptoms of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis by enhancing fatty acid oxidation and glutathione synthesis and modulating the gut microbiomes [22].

3. Beneficial Effects of Glycine on Cardiovascular Diseases

3.1. Glycine Levels in Plasma and Risk of Acute Myocardial Infarction

Acute myocardial infarction occurs when the heart muscle suffers necrosis due to the acute obstruction of a coronary artery. The symptoms include chest discomfort, nausea, and sweating, which can be diagnosed through electrocardiography (ECG) and serologic markers. In the US, approximately 1 million myocardial infarctions occur each year [14]. A study conducted by Ding et al. involving 4109 participants who underwent coronary angiography for suspected stable angina pectoris found that plasma glycine was associated with a lower risk of AMI [5]. Women generally had higher plasma glycine levels than men, related to a favorable lipid profile and a lower prevalence of obesity, hypertension, and diabetes mellitus. The study also found that plasma glycine was inversely associated with the risk of AMI, particularly in those with higher apolipoprotein B, low-density lipoprotein cholesterol, or apolipoprotein A-1 levels. The researchers concluded that plasma glycine was inversely associated with the risk of AMI in patients with suspected stable angina pectoris. This relationship demonstrates the role of glycine-dependent reactions in lipid metabolism and cholesterol transport. Specifically, glycine is used to catabolize excess S-adenosylmethionine via the enzyme glycine-*N*-methyltransferase (GNMT), and its remethylation into sarcosine, which has been linked to the regulation of apolipoprotein (apo) B mRNA expression and very low-density lipoprotein formation in the liver.

Li et al. discovered that glycine can lessen myocardial fibrosis in rats who have suffered from myocardial infarction by modulating the signal transducer and activator of the transcription 3/Nuclear Factor-κB/transforming growth factor-β axis [6]. In their study, rats were given either saline solution or glycine (0.5 mg/g bodyweight) for seven days. The glycine-treated group showed a significant decrease in the expression of signal transducer and activator of transcription 3 (STAT3), tumor necrosis factor-α, and transforming growth factor-β (TGF-β), compared to the model group. In another experiment by Zhong et al., rats were administered glycine intraperitoneally (0.5 mg/g body weight), reducing myocardial ischemia–reperfusion injury [9]. Glycine achieved this by inhibiting myocardial apoptosis (cardiomyocytes) and suppressing phosphorylated p38 mitogen-activated protein kinase and c-Jun NH2-terminal kinase.

3.2. Glycine Levels in Plasma and Aortic Conditions

The aorta, which is responsible for transporting oxygen-rich blood throughout the body, is susceptible to a range of disorders, including aortic aneurysms (abdominal, thoracic, thoracoabdominal), aortic arch aneurysms, aortic arch syndrome, aortic insufficiency, aortic intramural hematoma, aortic occlusive disease, aortic penetrating ulcer, aortic valvular disease (including aortic stenosis), aortitis, bicuspid aortic valve, congenital and hereditary aortic defects (including Marfan syndrome), degenerative aortic disease, mycotic aortic aneurysm, pseudoaneurysm, traumatic aortic injury, and type A and type B aortic dissections [23]. On average, an estimated 200 million blood liters are transported through the aorta over a lifetime [24].

A study by Wang et al. examined 33 human subjects, including 11 coronary heart disease (CHD) patients without aortic lesions, 11 with acute aortic dissection (AD), and 11 with chronic AD [25]. Using liquid chromatography and mass spectrometry (LC-MS/MS), the researchers identified amino acids, like glycine, in plasma. They found that the contents of glycine and other amino acids were significantly different in acute AD patients compared to CHD patients, with levels declining in acute AD patients. These findings suggest that the amino acid profile could serve as a biomarker for AD, providing a novel and non-invasive method for objective diagnosis.

Chao de la Barca et al. conducted a targeted metabolomics study on an experimental aortic aneurysm model generated by a high-cholesterol diet and angiotensin II in Ldlr−/− mice [26]. The study revealed significant hyperlipidemia in the blood, with decreased concentrations of glutamine, glycine, taurine, and carnitine, and increased concentrations of branched amino acids (BCAA). The BCAA/glycine and BCAA/glutamine ratios were found to discriminate between aneurysmatic and non-aneurysmatic mice with excellent sensitivity and specificity. Another study by Rom et al. revealed that glycine deficiency inhibits glutathione formation in bone marrow-derived macrophages through metabolic flux and carbon tracing experiments. On the other hand, glycine-based treatment induces de novo glutathione biosynthesis, suggesting a glycine-based therapy could mitigate atherosclerosis through its antioxidant effects mediated by the induction of glutathione biosynthesis [13].

Additionally, glycine has shown promise in combating the chronic rejection of aortic allograft transplants. Yin et al. conducted a study revealing that a glycine-rich diet can reduce the histopathological changes associated with chronic rejection in Lewis recipients of Fisher-344 abdominal aortic allografts [27]. During the study, patients were given diets containing either 5% glycine plus 15% casein or 20% as a control for ten weeks. The team evaluated the vascular lesions of aortic isografts and allografts with image analysis and cell counting. The findings indicated that dietary glycine can minimize the histopathological modifications of chronic rejection by reducing the immune response and limiting the proliferation and migration of smooth muscle cells. Glycine's protective ability against hypoxia–reoxygenation injury in the liver can also inactivate hepatic resident macrophages and exhibit immunosuppressive properties in vitro. In separate research, Borges et al. discovered that glycine can work at the level of NINJ1, a recently identified executor of plasma membrane rupture in pyroptosis, necrosis, and post-apoptosis lysis. NINJ1 is believed to cluster within the plasma membrane to cause cell rupture [15].

3.3. The Role of Glycine in Angiogenesis and the Inhibition of Tumors

Angiogenesis is the natural process of creating new blood vessels. It involves the movement, expansion, and specialization of endothelial cells on the inner walls of blood vessels. Chemical signals in the body, like the vascular endothelial growth factor (VEGF), regulate this process. Usually, these signals maintain a delicate balance, creating blood vessels only when necessary, such as during growth or recovery. However, when this balance is disrupted, excessive blood vessel growth can occur, leading to abnormal conditions or diseases, such as cancer [28].

According to previous research, glycine may play a role in angiogenesis, with its impact varying based on the dosage. A recent study by Tsuji-Tamura et al. focused on the PI3K/Akt/mTOR signaling pathway, its correlation with vascular development, and how it interacts with glycine. In this way, the study discovered that low glycine doses positively affect angiogenesis in transgenic zebrafish Tg(fli1a: Myr-mCherry)^{ncv1} embryos, by expressing fluorescent proteins in vascular endothelial cells. In contrast, high doses have an anti-angiogenic effect. The study also found that low glycine concentrations (10 mM) boosted vascular elongation. Conversely, high glycine concentrations (400 mM) reduced vascular development, which was exacerbated when combined with PI3K/Akt/mTOR signaling inhibitors [16]. In a separate study, Chen et al. found that glycine can potentially reduce cerebrovascular remodeling in rats after a stroke by targeting glycine receptor alpha 2 and vascular endothelial growth factor receptor 2, achieved through VEGFR2/pSTAT3 signaling [8].

Moreover, glycine has been found to offer potential benefits to individuals with ischemic conditions, such as atherosclerosis. Specifically, it has been shown to aid in therapeutic angiogenesis, the restoration of blood flow, and the rescue of ischemic tissue, as detailed in the research conducted by Gou et al. This study explored the mechanisms behind glycine's ability to promote angiogenesis both in vivo and in vitro. The findings revealed that the activation of glycine transporter 1 (GlyT1) by the endothelial growth factor led to an increase in intracellular glycine, which then directly bound to the voltage-dependent anion channel 1 on the mitochondrial outer membrane, ultimately inhibiting its opening [9].

Some studies have suggested that dietary glycine is related to tumor growth inhibition. The vascular endothelial growth factor (VEGF) contributes to cancer progression, creating new blood vessels and increasing intracellular Ca^{2+} levels. However, Yamashina et al. discovered that glycine can dampen the increase in intracellular Ca^{2+} concentration. Additionally, they observed that activating a glycine-gated chloride channel could significantly reduce the serum-induced proliferation and migration of endothelial cells. As a result, they believe that glycine may help treat inflammation and prevent and treat carcinoma [10].

Meanwhile, Bruns et al. demonstrated that glycine decreases GlyR-dependent, VEGF-A-mediated, angiogenic signaling in human hepatocellular carcinoma [11]. This study treated HepG2 and Huh7 cells with glycine-free DMEM supplemented with 0, 0.01, 0.1, 1.0, 2.0, 5.0, and 10 mM glycine. As a result, they suggested that glycine might be a promising additive to chemotherapy treatment strategies for highly vascularized tumors.

3.4. Dietary Glycine Supplementation for Endothelial Dysfunction

Endothelial dysfunction is a non-obstructive coronary artery disease (CAD) with no blockages in the heart's arteries. Still, large blood vessels on the heart's surface constrict instead of dilating [29]. Brawley et al. conducted a study to test the hypothesis that dietary glycine repletion could reverse endothelial dysfunction in protein-restricted pregnant rat dams using wire myography. The study found that the adequate provision of glycine, a conditionally essential amino acid during pregnancy, could be involved in the vascular adaptations to pregnancy and protect the fetus from abnormal programming of the cardiovascular system [30].

In contrast, Gómez-Zamudio et al. discovered that oral glycine treatment improved vascular endothelial function in aged rats. The researchers analyzed aortic rings with intact

or denuded endothelium from untreated or glycine-treated male Sprague Dawley rats at 5 and 15 months of age. They studied their reaction to phenylephrine by incubating them with NG-nitro-l-arginine methyl ester (l-NAME), superoxide dismutase (SOD), indomethacin, SC-560, and NS-398. The study found that endothelial modulation of the contraction by phenylephrine was decreased in the aortic rings of the aged rats, and glycine augmented the sensitivity to phenylephrine in the presence of l-NAME and SOD. The amino acid also reduced the contraction by incubation with indomethacin, SC-560, and NS-398. Glycine increased the mRNA expression of eNOS and decreased the expression of COX-2 and TNF-α. Additionally, glycine improved the endothelial function in the aged rats, possibly by enhancing eNOS expression and reducing the role of superoxide anion and contractile prostanoids that increase nitric oxide bioavailability [12].

3.5. Effects of Glycine on Pathologic Cardiac Hypertrophy

Cardiac hypertrophy occurs when the heart muscle thickens, making it difficult to pump blood [31]. This thickening is an adaptive response to hemodynamic stress and is believed to enhance cardiac performance while reducing ventricular wall tension and oxygen consumption [32]. To combat this condition, Lu et al. discovered that pre-treatment with glycine significantly attenuated murine cardiac hypertrophy induced by transverse aortic constriction or angiotensin II (Ang II) administration. Interestingly, they also found that this cardioprotective effect disappeared when the rats' endogenous glycine receptor α2 was knocked down. Glycine also prevented the over-production of collagens in rat fibroblasts by antagonizing the Ang II stimulated release of transforming growth factor β and endothelin-1 by cardiomyocytes [17]. This study highlighted the potential of glycine as a novel cardioprotector against pressure overload-induced cardiac hypertrophy and could help prevent heart failure.

3.6. Glycine and Low Peritoneal Vasoreactivity to Dialysis Solutions

Chronic renal failure (CRF) is a widespread public health concern among the elderly population worldwide, primarily caused by damaged kidneys. As a result of compromised renal function, toxins and excess water accumulate in the body [33]. To combat this, dialysis is a form of renal replacement therapy that removes waste and excess water from the blood [34]. A study by Zakaria and Kandi investigated the peritoneal dialysis solution (PDS)-mediated vasoreactivity of four intestinal visceral arterioles of varying orders in weaned, adult, and elderly rats using in vivo intravital microscopy. Their objective was to confirm subordinate vasoreactivity to PDS in elderly rats and to restore vasoreactivity through glycine supplementation, while establishing age as an independent risk factor for endothelial cell dysfunction. The researchers discovered that peritoneal microvascular vasoreactivity to PDS exposure was remarkably reduced in elderly rats, possibly due to oxidative stress. However, subordinate vasoreactivity was entirely restored by adding glycine to PDS, which has antioxidant effects. Furthermore, the study found that glycine can increase peritoneal vasoreactivity to dialysis solutions in older adults [18].

3.7. Correlation between Glycine, Insulin Resistance, and Other Cardio-Metabolic Diseases

Insulin resistance (IR) is a clinical condition that affects the glucose uptake ability of tissues sensitive to insulin, such as skeletal and cardiac muscle, adipose tissue, and the liver. This reduction in insulin's biological effect compared to that in healthy individuals alters insulin signaling pathways and leads to cardio-metabolic disorders. These disorders include obesity, dyslipidemia, low-grade inflammation, endothelial dysfunction, and hypertension, all of which are predisposing factors for atherosclerosis and cardiovascular disease [35]. The latter is a general term for conditions affecting the heart or blood vessels, often caused by a build-up of fatty deposits inside the arteries (atherosclerosis) and an increased risk of blood clots. Cardiovascular disease is one of the leading causes of death and disability in countries such as the UK [36].

Recent research by Wittemans et al. investigated the mechanisms related to glycine and cardio-metabolic diseases using genetic approaches. The study conducted a meta-analysis of genome-wide association studies for glycine in 80,003 participants and found that glycine is genetically associated with lower coronary heart disease (CHD) risk, partly driven by blood pressure. The study also reported a solid inverse genetic effect of hyperinsulinemia on glycine, indicating a protective effect of glycine on CHD and a glycine-lowering effect on insulin resistance [37].

A recent study proposed by Do Prado et al. examined the potential correlation between circulating glycine levels and the biomarkers of cardiovascular disease (CVD) in children diagnosed with obesity. Upon analyzing the data, the researchers found a notable correlation between glycine and various parameters, such as visceral fat, insulin resistance, and adiponectin, resulting in additional evidence of the link between glycine and CVD [38].

According to one study, including glycine in the diet of sucrose-fed rats for four weeks reduced plasma-free fatty acids, adipose cell size, and blood pressure [19]. The researchers noted a significant decrease in high blood pressure among the rats who consumed 1% glycine in their 30% sucrose drinking water. Additionally, the rats treated with glycine had lower levels of plasma triglycerides, intra-abdominal fat, and adipose cell size compared to those who did not receive treatment. Glycine intake also led to a significant reduction in nonesterified fatty acids in the rats' plasma.

Furthermore, glycine has the potential to combat dietary fructose by activating glycine-gated chloride channels in various types of cells. Research on rodents has identified glycine's anti-inflammatory, immunomodulatory, cytoprotective, platelet-stabilizing, and antiangiogenic effects [20].

On the other hand, supplementing with glycine/*N*-acetylcysteine has been shown to improve glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, aging hallmarks, metabolic defects, muscle strength, cognitive decline, and body composition [39]. A clinical trial by Kumar et al. involving older and young adults found that glycine/N-acetylcysteine supplementation improved glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, and physical function in older adults [21]. Additionally, amino acids like glycine have proven effective for improving the symptoms of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) by promoting fatty acid oxidation, enhancing glutathione synthesis, and modulating the gut microbiome [22]. These findings suggest the potential of glycine as a treatment for these conditions.

4. Limitations

The scope of this review is confined to the current understanding and trends of the role of glycine in cardiovascular and related ailments, with a particular emphasis on its advantageous effects. It should be noted that certain studies discussed were conducted on rats, and further research is required to ascertain if comparable outcomes can be achieved in humans.

5. Conclusions

Glycine is an amino acid that plays a crucial role in various metabolic functions, including those related to cardiovascular health and several diseases. When administered appropriately, glycine has therapeutic potential for treating cardiovascular illnesses and can be a biomarker for monitoring and preventing such diseases. Research has shown that glycine operates through several processes, including lipid metabolism and cholesterol transport, myocardial fibrosis attenuation, the inhibition of myocardial apoptosis in rats, de novo glutathione biosynthesis induction, atherosclerosis mitigation through its antioxidant effects, chronic rejection minimization of aortic transplants, and activation of the voltage-dependent anion channel 1 (VDAC1) on the mitochondrial outer membrane, inhibiting its opening. Glycine also decreases the serum-stimulated proliferation and migration of endothelial cells, attenuates cerebrovascular remodeling in rats after strokes, completely

restores vasoreactivity to the peritoneal dialysis solution, and has effects against dietary fructose. Additionally, it improves the symptoms of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in older adults and modulates the gut microbiome. Glycine significantly improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, physical function, and aging hallmarks in older adults, suggesting new therapeutic applications for this amino acid.

6. Perspectives

Medical research has great potential to uncover new therapeutic uses of glycine for various diseases, including cardiovascular and psychiatric conditions. Further studies are needed to understand better how glycine works in different medical contexts. Additionally, implementing blood glycine monitoring as an auxiliary tool for disease diagnosis and control could be beneficial. To achieve this, new methodologies and instrumental techniques must be developed to quantify blood glycine, surpassing conventional processes' limitations. These new methods should also be quick, portable, and usable at the point of care.

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