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REVIEW

Molecular explanation of Wnt/βcatenin antagonist pyrvinium mediated calcium equilibrium changes in aging cardiovascular disorders

Khalid Saad Alharbi[1] · Yogendra Singh[2] · Obaid Afzal[3] · Abdulmalik Saleh Alfawaz Altamimi[3] · Imran Kazmi[4] · Fahad A. Al-Abbasi[4] · Sami I. Alzarea[1] · Dinesh Kumar Chellappan[5] · Sachin Kumar Singh[6,7] · Kamal Dua[7,8] · Gaurav Gupta[9,10,11]

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Abstract

The symptoms of ageing are somewhat different and can lead to the altered role of the cardiovascular system at the levels of genetic, biochemical, tissue, organ, and systems. Ageing is an autonomous cardiovascular risk factor. In the ageing rat heart, oxidative and inflammatory stress, immune cell infiltration, increasing myeloperoxidase function, elevated caspase-3 activity, and protein fibronectins were detected and associated with ageing and cardiovascular disease. The intracellular Ca2 + homeostasis disturbed in an older heart dramatically increases cardiomyopathy, atherosclerosis, stroke, ischemia, myocardial infarction, hypertrophy, remodelling, and hypertension. Evidence shows that suppression of Wnt/β signals prevents cardiovascular dysfunction, such as remodelling, high blood pressure, and excessive overload stress. However, one study has shown that the pharmacological disruption of Wnt-β-catenin by decreasing expression of α-smooth muscle actin, fibronectin and collagen I proteins attenuates angiotensin II mediated hypertension cardiac fibrosis. Thus, this review examined the impacts of calcium overload and age-related diseases, including cardiovascular. Energy dysregulation, calcium overloading, and mitochondrial dysfunction are the main activities causing cardiovascular disease linked with age. Therefore, the current study explores that age-associated cardiovascular disease has triggered the WNT/β-catenin pathway, and pharmacological inhibition can delay pathological changes by attenuating calcium dyshomeostasis.

Keywords Aging · Cardiovascular disease · Calcium · WNT/β-catenin

✉ Kamal Dua
kamalpharmacist02@gmail.com; Kamal.Dua@uts.edu.au

✉ Gaurav Gupta
gauravpharma25@gmail.com

[1] Department of Pharmacology, College of Pharmacy, Jouf University, Sakaka, Al-Jouf, Saudi Arabia

[2] Department of Pharmacology, Maharishi Arvind College of Pharmacy, Ambabari Circle, 302023 Ambabari, Jaipur, India

[3] Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam Bin Abdulaziz University, 11942 Al Kharj, Saudi Arabia

[4] Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

[5] Department of Life Sciences, School of Pharmacy, International Medical University, 57000 Kuala Lumpur, Malaysia

[6] School of Pharmaceutical Sciences, Lovely Professional University, 144411 Phagwara, Punjab, India

[7] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, 2007 Ultimo, NSW, Australia

[8] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, 2007 Ultimo, NSW, Australia

[9] School of Pharmacy, Suresh Gyan Vihar University, Jagatpura 302017, Mahal Road, Jaipur, India

[10] Department of Pharmacology, Saveetha Institute of Medical and Technical Sciences, Saveetha Dental College, Saveetha University, Chennai, India

[11] Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India

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Introduction

The loss in function associated with age is a physiological condition in all organs. Intrinsic cardiac ageing also increases the sensitivities of the heart to stress and adversely affects cardiac mortality and elderly morbidity. With age, the cardiac functions that guard against damage and heal injury grow gradually deficient, resulting in accentuated adverse remodelling and increased dysfunction. Moreover, ageing in individuals without CV disease is associated with various ECG changesatrial, arrhythmias, atrial fibrillation, super ventricular tachycardia, and ventricular rhythms with the ageing rise [1]. Ageing produces such modifications that slow down cellular responses that regulate the heartbeat in their entirety[2, 3]. The action potential, intermittent increase in cytosolic calcium, and rate of contraction are all extended, resulting in a prolongation of the heart's systole and diastole[4]. However, in cardiovascular pathologies such as hypertension, acceleration and early onset are noted[5, 6]. In the ageing rat heart, oxidative and inflammatory stress, immune cell infiltration, increasing myeloperoxidase function, elevated caspase-3 activity, and protein fibronectins were detected and associated with aging cardiovascular disease[7–10]. The intracellular Ca2 + homeostasis has been disturbed in an older heart dramatically increases cardiomyopathy, atherosclerosis, stroke, ischemia, myocardial infarction, hypertrophy, remodeling, and hypertension, which, While ageing is well understood to be a powerful risk factor of the cardiovascular system[11, 12], the mechanisms underlying the relationship between ageing and cardiovascular calcification are still not known. However, one study has shown that the pharmacological disruption of Wnt-β-catenin by decreasing expression of α-smooth muscle actin, fibronectin and collagen I proteins attenuates angiotensin II mediated hypertension cardiac fibrosis[13].

Furthermore, other research has been undertaken on the function of WNT5A in the macrophage activation mechanism and has been shown to induce WNT5A mRNA expression in human cardiovascular macrophages derived from monocytes[14]. Furthermore, by interfering with FZD5, WNT5A caused a more sustained NF-kB activation and a different expression of pro-inflammatory cytokines[15, 16]. Thus, this review examined the impacts on calcium overload and age-related diseases, including cardiovascular disease. Energy dysregulation, calcium overloading, and mitochondrial dysfunction are the main activities causing cardiovascular disease linked with age. Therefore, the current study explores that age-associated cardiovascular disease has triggered the WNT/β-catenin pathway, and pharmacological inhibition can delay pathological changes by attenuating calcium dyshomeostasis.

Selection of literature review

Articles were obtained by manual filtering linked reference lists in Springer, Science Web, Pub Med, Proquest, Embase, ScienceDirect, Mendeley, and Cochrane. During the literature review, some keywords were used, such as "Aging and cardiac oxidative disturbance," "Molecular Wnt antagonist pyrvinium mediated impairment of immune and inflammatory cytokines," "Basics of systole and diastole in normal heart," "Involvement of mitochondrial dysfunction and cell damage," "Aging mediated calcium dyshomeostasis," "Biological activity of Wnt-β-catenin in ageing heart," "Potential of Wnt-β-catenin antagonist Pyrvinium pamoate mediated cardiovascular protection," This article is directed at those interested in English publications. In addition, bibliographies are indexed with journals that aren't part of the original search can be done.

Wnt/beta-catenin pathway

In 1982, when Nusse and Varmus studied the carcinogenic mechanism of mouse breast tumour viruses (MMTV), they discovered a Wnt / beta-catenin pathway component. Insertion of the provirus at the "integration site" is considered a carcinogenic process, and INT1 is the first gene to be found in this pathway. Through parallel work in Drosophila and developmental biology, the INT1 gene was a homolog of the wingless segment polarity gene in Drosophila. Consequently, it was discovered that human INT1 is highly similar to mouse INT1, indicating that this pathway is highly conserved throughout the body. Further tumour scans of the MMTV provirus insertion site revealed many other active genes, including INT2, INT3, and INT4, associated with alternative developmental genetic pathways [17, 18]. INT2 belongs to the FGF family (the INT2 protein is identical to the FGF-3 protein), and INT3 is a member of the NOTCH gene family (the INT3 protein is similar to NOTCH4, where the neurogenic gene is found). As the "INT" nomenclature became inappropriate and misleading, it was decided to construct a hybrid name, "WNT" (for wing-based integration sites), to represent genes in the INT1 / Wingless family. INT1 (now WNT1) is one of the original members [19–21].

WNT (the translation product of the WNT gene) is a cysteine-rich glycoprotein that can be secreted into the extracellular matrix by cells so that receptor-mediated signal transduction is close to the cell. There are at least 19 glycoproteins that are secreted (350–400 amino acids in length) in the WNT family of proteins, which are highly conserved in various animals, from invertebrates to mammals. Wnt binds to the cysteine-rich domain of frizzled receptors on the cell surface (GPCR member) [22, 23]. This can activate

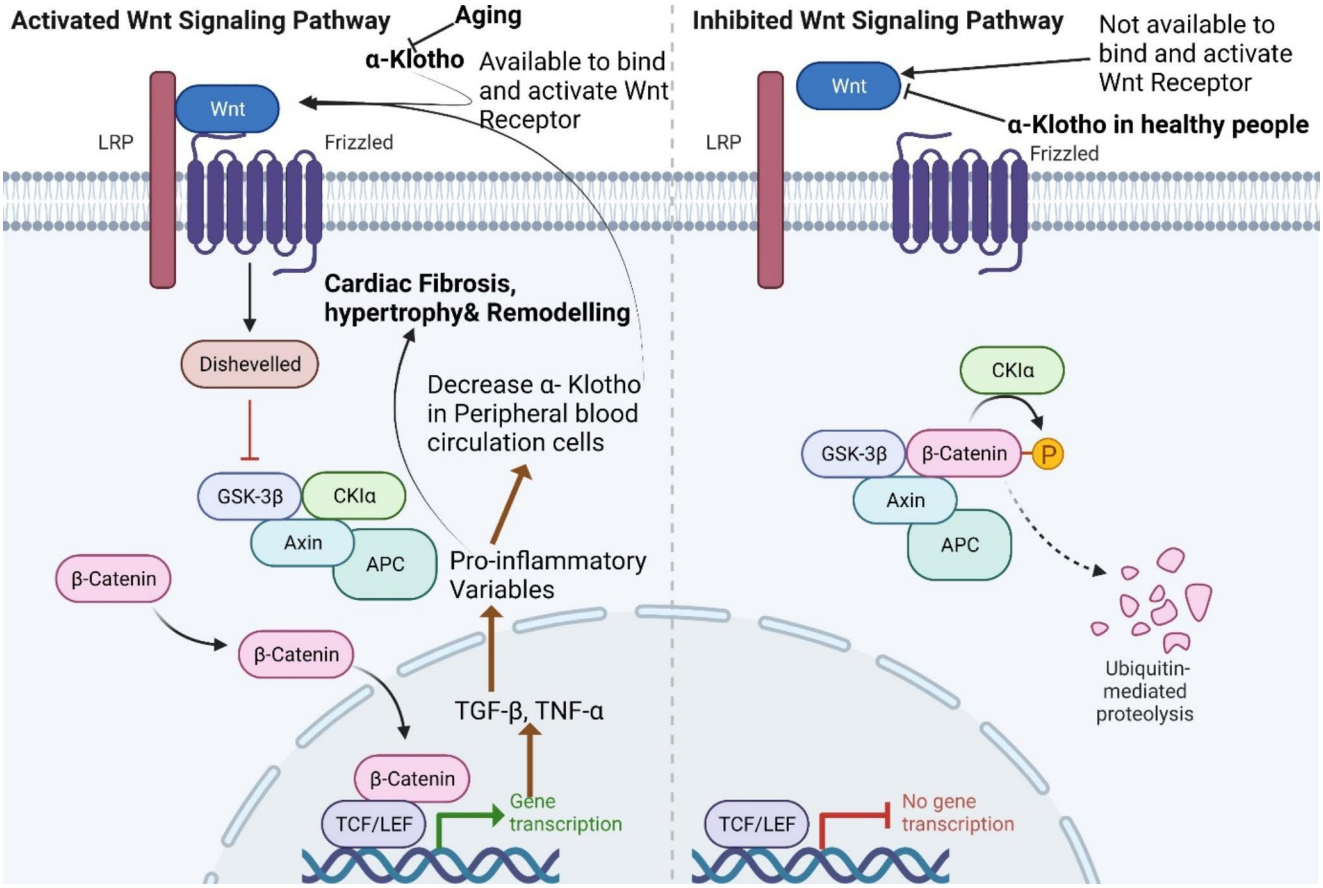

Fig. 1 Critical mechanical roles of Wnt-β-catenin pathways in cardiovascular diseases

cytokine-catenin T / lymphatic enhancer factor 1 (TCF / Lef1) by destroying the -catenin degradation complex (a tertiary complex composed of venom, adenomatous polyposis (APC), CK1, and GSK3). It is a transcription complex that mediates classic WNT-induced transcription. When B-catenin moves into the nucleus and interacts with TCF / Lef1, the TCF / Lef1 transcription complex is activated. Beta-catenin can also exist in many subcellular locations, including where the cytoplasm is tightly regulated. By collecting the sites of cell-cell interaction, β-catenin can also promote inter-cell adhesion (i.e., adhesion and attachment) [24, 25]. The Wnt/catenin signalling pathway is shown in Fig. 1. WNT can elicit alternative responses through mechanisms other than activating the classical WNT-induced transcription -catenin-TCF / Lef1 complex. These mechanisms are collectively referred to as non-classical pathways. Canonical and non-canonical pathways are combined into the optimized Wnt pathway. Various inputs have been integrated at the Wnt receptor binding level and later intracellular response stage [26, 27].

Ageing and cardiovascular diseases

Per year, cardiovascular disease claims 4 million lives in Europe and is also one of the leading causes of death in the world. The incidence of CVD such as atherosclerosis, myocardial infarction, cardiac fibrosis, ischemic injury, hypertrophy, hypertension, and stroke is increasing, accounting for 39.6% of all age-related diseases. Ageing reduces the effectiveness of homeostasis control, leading to tissue damage and increased morbidity and mortality [28, 29]. The complex regulatory interactions between cells, tissues, and systems change with age. The heart and smooth muscle cells mediate voluntary regulation of heart and blood vessel function. The contractility, excitability, elasticity, integrity, and conductivity of these cells are essential for cardiovascular function [30]. The senescence of cardiomyocytes and vascular smooth muscle cells is related to the gradual loss of physiological processes. Ageing cells can let other cells know how they behave inside. Before losing heart and blood vessel function, ageing destroys nutritional and metabolic signalling pathways at the cellular level [31, 32].

Steenman and Lande (2017) recently found a link between population ageing and CVD rates. These scholars

believe that the ageing of the human heart will produce a mechanism similar to heart disease. Physical, physiological, cellular, and molecular modifications are common features of cardiac ageing. Understanding cardiac ageing can help solve heart disease's physical and physiological problems and improve the treatment of cardiovascular disease. Several reports have been on the conduction of neurohormonal signals and the morphological improvement of diastolic function, contractile function, and electrical function caused by ageing [33, 34]. This study is based on cardiac ageing and the autonomic and epigenetic changes that underpin certain CVDs. The process and elasticity of the heart and arteries are often hampered by cardiovascular function anatomical changes caused by ageing [35, 36]. In humans, ageing is associated with diastolic dysfunction, fibrosis, and left ventricular hypertrophy leading to decreased diastolic filling and ejection fraction of cardiac output. Although the underlying mechanism is not yet fully understood, studies have linked cardiomyocyte apoptosis and vascular stiffness to structural and functional changes caused by age [37, 38].

Due to myocardial hypertrophy caused by ageing and other physiological stimuli, the functional requirements of the heart are maintained in a compensatory way. However, hypertrophy can turn into a neurological disease if the heart is tired. Increased myocardial cell volume, asymmetric development of the ventricular septum, and change in heart shape are characteristics of left ventricular wall thickening. These changes can reduce or increase the efficiency of the heart's contraction [39, 40].

In preclinical and clinical studies, biochemical variation is related to cardiac hypertrophy. Through the Ras / Raf / MEK / ERK signalling pathway, extracellular signal-regulated kinase 1/2 (ERK1 / 2) is essential in the production of cardiac hypertrophy. Furthermore, cardiac hypertrophy has been associated with downstream regulators (such as protein kinase B, Akt, mTOR, etc.). According to the study by Manne et al. [41], the regulation of ERK1 / 2 and Akt signalling pathways was previously related to cardiomyocyte hypertrophy. Therefore, these signal transduction pathways tend to regulate ageing-related cardiac hypertrophy.

Cardiac hypertrophy is related to the massive consumption of myocardial cells in the microscopic stage. Previous studies have shown that apoptosis can reduce the number of ventricular myocytes with age. According to Olivetti et al., the left ventricle of older men loses about 45 million cardiomyocytes each year. Although there is a lack of cardiomyocytes that grow with age, studies have shown that the number of ventricular myocytes increases. As a result, it is proposed that age-related muscle cell depletion will augment the mechanical load imposed on the remaining muscle cells, leading to compensatory hypertrophy [42, 43].

Along with decreasing the number of cardiomyocytes, stiffening of peripheral blood vessels can also lead to progressive hypertrophy of the elderly heart. The lack of elasticity of the aorta increases the mechanical load on the heart and accelerates heart failure. In addition, hemodynamic overload caused by ageing-related arteriosclerosis exacerbates hypertrophy of myocardial cells in the left ventricle and increases collagen deposition in myocardial tissue. As a result, hypertrophy tends to be an adaptive response to physiological changes caused by ageing in the cardiovascular system to maintain cardiac activity [44].

Atherosclerosis and heart disease are related to the accumulation of epicardial fatty tissue and calcification of the aortic valve leaflets, all caused by ageing. Cardiac fibroblast proliferation is also seen in aged hearts. Collagen aggregation before atrial fibrillation and ventricular fibrosis in the elderly may result from this proliferation. For many years, myocardial fibrosis caused by ageing has been studied in humans, rodents, dogs, and sheep [45, 46].

As we age, we find that glycosaminoglycans, glycoproteins, integrins, proteoglycans, and collagen are more abundant in the heart's extracellular matrix. According to the research, the collagen content rose from 1 to 2 per cent to 2–4 per cent in the left ventricle of mice. Compared with the younger participants, the autopsy of the elderly showed higher levels of type I collagen and lower levels of type III collagen. Type I collagen has higher tensile strength, while type III collagen has more stretchability [47–49]. As a result, a higher proportion of type I collagen can cause left ventricular stiffness and affect the biomechanical function of the heart. Additionally, changes in the extracellular matrix surrounding muscle cells or myofibril bundles make it difficult to transmit electrical signals, leading to arrhythmia.

Post-transcriptional events are related to the increase in collagen with age. High collagen levels are determined. Autophagy regulates the destruction of bacterial lysosomes, aging, or the weakening of proteins and organelles to protect cells. During baseline and hemodynamic stress, autophagy of the heart is essential to prevent systemic and functional abnormalities. On the other hand, as we age, the autophagy mechanism becomes fragile, leading to ineffective heart function. As a result, as people age, their ability to regenerate and break down weakened intracellular substances decreases, leading to changes in structure and function [50, 51]. mTOR complex 1 inhibits autophagy through the protein kinase serine/threonine. Excessive Akt activation is linked to reduced cardiac autophagy and ageing. Inhibition of autophagy reduces life expectancy and worsens cardiomyopathy associated with ageing. In elderly mice, rapamycin-induced autophagy (rapamycin as an mTOR inhibitor) improved ejection fraction and reduced ventricular hypertrophy [52].

Cellular calcium in aging and cardiovascular disorder

The SERCA2a isoform allows the storage and release of Ca2 + ions in the SR in cardiac tissue. During systole, the action potential induces a small Ca2 + influx through sarcolemmal L-type Ca2 + channels. This influx starts with a large Ca2 + release from stores SR Ca2 + through the Ca2 + release channel or ryanodine receptor[53]. Ca2 + then binds to troponin C, which begins the cross-bridge movement of myofibrils and leads to the formation and contraction of force. For cardiac relaxation, fast removal of Ca2 + in SR or extracellular lumen is necessary. In cardiac tissue, SR Ca2+-ATPase (70-80% Ca2 + in higher mammalian species and human myocardial syndrome) is the major facilitation of this mechanism in the diastole process, and sarcolemmal Na+, Ca2+ (20-30%) and slower Ca2 + transport mechanisms are less common[54]. In SR, Ca2 + mainly binds to the binding SR Ca2 + protein calsequestrin[55] and other Ca2 + binding proteins, for example, calreticulin and the protein-rich in histidine[56, 57]. Ca2 + is stored by the tridine and junction proteins near the Ca2 + release pathway, which is more likely to allow quicker Ca2 + availability close to the ryanodine receptor on the early systole[58–60]. More recently, a new protein known as junctate consists of junctine and aspartyla-β-hydroxylase combined sequences which may also affect the kinetics of SR release[61, 62]. Therefore, SERCA2a is the key player in restoring and terminating diastolic Ca2 + stimulation of power.

In an older heart, age-related mitochondrial changes include decreased sarcoplasm Ca2 + uptake and decreased buffering capability against reactive oxygen (ROS) molecules, resulting in compromised metabolism, increased heart susceptibility, and cardiac stress. On the immune side, neutrophils are subject to delayed apoptosis during ageing. The release of immature bone marrow neutrophils results from neutrophil dysfunction combined with excessive ROS, cell invasion, and activation events throughout the organ dysfunction[63–66]. While the opening of the L-type calcium channels, followed by the release of further stored calcium ions from the sarcoplasmic reticulum that initiate myocyte shorter, plays an integral part in cardiomyocyte contractility[67]. During pathology, however, the intracellular calcium levels become too high, which can trigger cell death with the activation of calcium-regulated calpain that causes damage to the cell membrane and DNA[68, 69]. Recently, a longevity-associated-variant of BPIFB4 has been associated to the regulation of eNOS in vascular tissue through the regulation of calcium modulation [70]. In addition, it has also been shown that its overexpression can exert beneficial cardiovascular effect both in diabetic and atherosclerotic condition [71, 72]. Research showed that reduced sarcoplasmic calcium uptake leads to mishandling of calcium and contractile cardiomyocyte defects in aging[73], a reduction in phospholamban phosphorylation, and a ~ 50% rise in Na+/Ca2 + interchange amounts. Rodent studies that have applied gene therapy or exercise conditioning to enhance SERCA2 have shown that these treatments' impaired relaxation and Ca2 + sequestration can be minimized with the age of these treatments. A recently conducted research has also shown that [Ca2+]SR in thoracic muscles declines with age up to 1/10 of the young fly's and proves the small but substantial decline in expression of SERCA. Though this shift could help deteriorate [Ca2+]SR in old flies, the reduction in the SERCA seems insufficient to justify the significant decline in [Ca2+]SR.

Furthermore, increased expressions of RyR in older flies were also minimal and not significant[74]. Therefore, we assume that an increase in cytosolic calcium may result from an increase in leakage activity. In addition, the verapamil inhibition of the L-type calcium channel prevents an increase in the amount of dystrophin, actin, and myosin protein and thus increases it[75]. Finally, calcium dyshomeostasis causes a hyperinflammatory state and triggers myocardial damage by the enzyme caspase-3[7]. In addition to, calcium overload can notably cause mPTP openings in cardiomyocytes, causing caspases and contractile abnormalities to be activated [76, 77].

Aging mediated aggravation of Wnt/β-Catenin

Wnt/ß-catenin signalling has many physiological functions, including the growth of embryos, damage repair, and tissue homeostatic control [78, 79]. However, Wnt signalling in the adult heart is minimally exposed. Still, it upregulates in ageing [71] that directed to different heart conditions such as myocardial ischemic damage, persistent pressure overload, and cardiac dysfunction due to hypertension [80, 81]. Primary events in ageing-induced heart dysfunction are energy dysregulation, calcium overcharge, and mitochondrial dysfunction.

Binding to its plasma membrane receptors (Frizzled or FZD), several intercellular transducers can be activated canonically or non-canonically, including the two main transducers β-catenin and Ca2+, respectively. The effect of the Axin complex consisting of the scaffolding Axine protein, the adenomatotic polyposis coli tumour suppressor (APC), casein kinase 1 (CK1), and glycogen synthase kinase three is continuously degraded in the absence of Wnt (GSK3)[82]. CK1 and GSK3 phosphorylate sequentially the amino end of the region of the β-catenin, which results in β-catenin detection by the subunit of β-Trcp, the

subunit of the E3 ubiquitin ligase, and subsequent β catenin and proteasomal degradation. This continuous β-catenin removal stops β-catenin from accessing the nucleus. The target genes of Wnt will thus be suppressed by the protein family T cell factor-limited factor (TCF/LEF). When a Wnt-Ligand binds to a 7-pass Friczled (Fz) receptor and its LRP-related co-receptor, low-density lipoprotein receptor (LRP6) or nearby relative LRP, the Wnt/β-catenin pathway is activated. The development of a probable Wnt-Fz-LRP6 complex and the recruitment of the Dishevelled (Dvl) scaffolding protein leads to phosphorylation and activation of LRP6 and recruitment of the Axin complex to the receptors. These events cause Axin-mediated β-Catenin phosphorylation to be inhibited and thus β-catenin stabilized, which accumulates and travels into the nucleus to form complexes with TCF/LEF and triggers the expression of the Wnt goal gene [83].

The signature trait of an ageing heart is cardiomyocyte hypertrophy. Stabilizing β-catenin has previously been shown to favour myocyte development and be required for cardiac pathological hypertrophy [84]. The cardiomyocyte-specific conditional deletion of exon 3 from the β-catenin gene subsequently activated the signalling of Wnt in cardiac myocide in vivo, which makes β-catenin resistant to GSK-3β–mediated phosphorylation/degradation and results in β-catenin stabilization [85]. Despite this vulnerability, Wnt/β-catenin signalling plays a vital role in developing cardiovascular disease [86]. In contrast to previous studies, Wnt activation in cardiomyocytes has been suggested to result from an attenuated response to hypertrophic stimuli and failure to undergo adaptive remodelling under stressed conditions. Lithium, an inhibitor of GSK 3β and thus an activator of Wnt signalling, was also shown to induce endothelial cell senescence [87, 88].

Furthermore, β-catenin genetic ablation of the second heart field has been shown to cause loss of second heart field tissues and to cause massive accumulation of Isl1 + progenitor and inhibition of further differentiation of these cells into mature cardiomyocytes stabilizing of β-catenin of the second heartfield[89, 90]. Thus, Wnt signalling facilitates the expansion of Isl1 + cardiac progenitor cells and prevents further differentiation into mature cardiac cell forms. In addition, deletion of Wnt inhibitory factor 1, WIF1, causes more inflammatory monocytes and extreme negative remodelling, while WIF1 overexpression, which is unique to the cardiomyocyte, reduces monocyte response and enhances cardiac efficiency [91].

Role of Wnt/β-Catenin antagonist pyrvinium in aging cardiovascular disorders

During ageing, cardiac dysfunction progression includes oxygen dysmetabolism, hypovolemia, acidosis, reactive oxygen production, chronic inflame-reactive immune function, and mitochondrial and cardiomyocyte necrosis. The results from several studies in the present review, the ageing rat cardiac tissue, showed elevated transcriptional concentrations of Wnt-coupled subunit β-catenin, which suggested that the pathway should be increased during ageing. Although extracellular levels of calcium decrease in age, the amount of intracellular calcium is still high. Defects cause excessive rises in intracellular calcium levels in the uptake and release process from sarcoplasmic reticules and excessive calcium inflow of the membranal channels. These increased intracellular calcium levels activate a variety of calcium-dependent proteases in the cell and cause the permeability transition pore in the mitochondria to open. Furthermore, calcium levels in the apex region of the endocardium and epicardium tissue in cardiomyocytes are also increased, leading to oxidative stress and opening of the mPTP[92]. Additionally, inflammatory cytokines are released, and suppressive immune cells infiltrate the cell, initiating cell death cascades. Further, activating the canonically active Wnt pathway will adversely influence cardiac outcomes and its function in cardiac hypertrophy, fibrosis and ischemia injury [93, 94]. The Wnt subtype protein Wnt-5a is located in cardiomyocytes and activates lymphocytes and monocytes to release IL-1, IL-6, and IL-8[95, 96]. New points of action have been disclosed for new drug goals for small molecular weight compounds in recent breakthroughs in Wnt signalling research. In addition, SFRPs that are endogenous inhibitors of the Wnt pathway can defend the MI injury by modulating the inflammatory response. Other studies have shown that blocking Wnt/β-catenin signalling prevents unwanted remodelling or improves cardiac function in a myocardial disease model of animals[97–99]. We recently found an FDA-approved medicament, pyrvinium. This compound is registered as an anti-helminthic drug, which works by binding and activating CK1α as a potent inhibitor of Wnt signalling [100]. The serine/threonine kinases CK1α family is evolutive conserved in eukaryotes and is linked to various cell processes, including cell cycle, apoptosis, and signalling of Wnt[101]. Since Thorne et al.[102] has shown that pyrvinium pamoate was strongly targeting β-catenin signalling by activating casein kinase 1. New pathways were indicated to function on Pyrvinium pamoate in various cancer cell lines, defining Pyrvinium pamoate as a novel anti-cancer drug targeting hypoglycemic and hypoxic mitochondrial respiration conditions[103]. However, findings indicate that administration of the Wnt

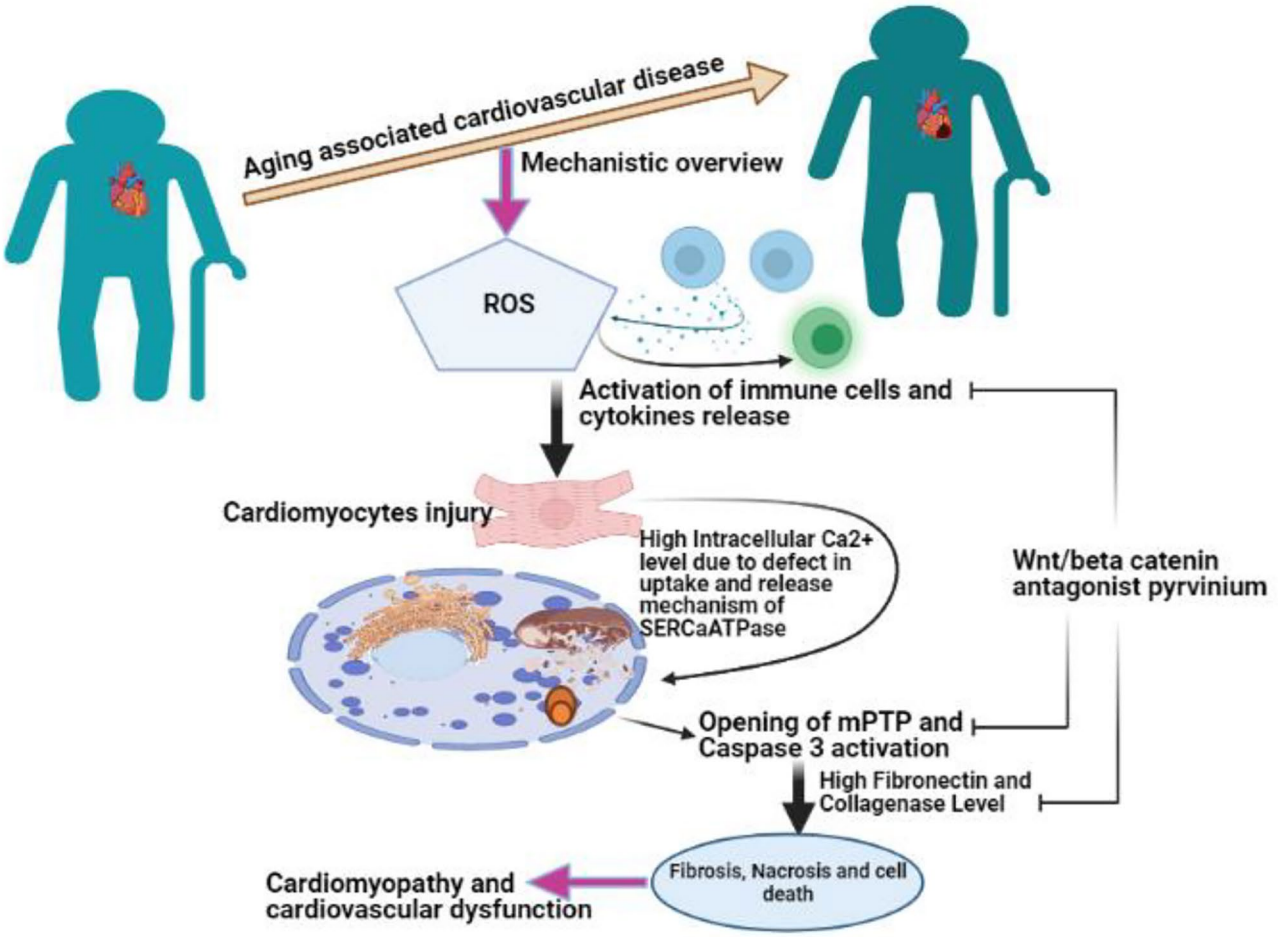

Fig. 2 Molecular explanation of WNT/β-catenin antagonist pyrvinium mediated changes in aging cardiovascular disorders

antagonist pyrvinium impaired renal immune cell migration, inhibited the release of pro-inflammatory cytokines and decreased MPO functionality. Recently, the therapeutic benefits of pyrvinium pamoate in two different types of myocardial remodelling have been demonstrated[100, 104]. The upregulating amount of fibronectin, a cardiac profibrotic protein and fibrosis in the myocardium was attenuated by both the before and after treatment of pyrvinium. In LV apex regions and the entire heart, calcium dyshomeostasis was prevented by pretreatments with Wnt/β-catenin antagonistic substances, and the opening of mitochondrial mPTP was reduced (Fig. 2) [105, 106].

Conclusion

We are exceedingly restricted in our current knowledge about the importance of Wnt in ageing-associated cardiac dysfunction. However, the finding that structural factors trigger Wnt signalling in the serum of old animals and encourage aging-related phänotypes in at least some tissues indicates that the aged heart is also a focus of Wnt's research. Furthermore, various studies have identified that the augmented Wnt pathway causes ageing-associated cardiac problems. We thus infer that pre-treatment with pyrvinium successfully eliminates ageing mediated heart malfunction and injury by correcting dyshomeostasis, fibronectin protein levels, and improvements in mitochondrial dysfunction. Moreover, these changes have been linked with decreased oxidative/inflammatory distress, inhibition of caspase-3, and cardiac immune cell infiltration suppression. Therefore, Wnt pathway inhibition is a new therapeutic approach for developing elderly cardiac diseases.

Author contribution KSA, and YS contributed to the study conception and design; IK, DKC and FAA wrote a manuscript; SIA, OA, and ASA prepared figures; SKS, GG, and KD supervised and corrected the manuscript. All authors have read and approved the final manuscript.

Data availability Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no interest dispute.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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