Heart Failure: An update on Pharmacotherapy

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Abstract:

Cardiovascular diseases especially heart failure (HF) are one of the biggest challenges for modern medicine. There is a strong need to develop a new therapy that can manage heart failure and also reduces its complications due to the increasing number of people suffering from this disease. In recent years, various efforts have been made for improving the primary outcome in HF patients. Several clinical studies have shown the potential of various agents in reducing mortality and morbidity thereby shifting the use of pharmacological approaches. Sacubitril/Valsartan combination, Tolvaptan has been recently approved by FDA. Further, balancing intracellular calcium concentration and potassium levels and correcting iron deficiency also present a viable option. Various Heart failure trials such as PARADIGM and PIONEER trial for Angiotensin-neprilysin inhibitors, VICTORIA trial for Vericiguat, CANVAS and EMPA-REG OUTCOME trial for sodium-glucose transport protein 2 (SGLT2) inhibitors and DECLARE-TIMI 58 trial for dapagliflozin are considered as landmark clinical trials for heart failure as these trials have shown reduction in death rate and hospitalizations due to heart failure. Rapid progress in gene therapy also provides great hope in this field and needs to be explored further. The present study summarizes the recent advances in the management of heart failure with reduced ejection fraction and the mechanism involved in the treatment approaches.

Keywords: Heart Failure, biomarkers, neprilysin inhibitor, potassium absorbents, vasopressin-2 receptor antagonist.

1.0 Introduction

Heart failure (HF) is a serious health problem affecting nearly 64 million people around the world (Savarese et al., 2023). Also, the rate of hospitalization and health cost is high (Hunt et al., 2005). Earlier studies conducted to estimate the occurence of HF were focussed on high-income nations, but occurence is expected to rise in lower and middle income countries in coming few decades due to the increased risk of population aging and the burden of risk factors for heart failure, such as high blood pressure (Yusuf et al., 2001). In 2017, Ischaemic heart disease accounted for the highest proportion of HF cases (26.5%), followed by hypertension (26.2%), chronic obstructive pulmonary disease (COPD) (23.4%), cardiomyopathy (6.5%), mitral valve disease (2.7%), other cardiovascular disorders (2.4%), cardiomyopathy due to alcoholic consumption (2.4%), non-rheumatic calcific aortic valve disease (2.3%), rheumatic heart disorder (1.8%) and myocarditis (1.7%) (Bragazzi et al., 2021). Although progress has been made in managing heart failure with various drugs including angiotensin receptor blockers, beta-

blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists are commonly used. However, outcomes remain suboptimal. As the cases of mortality are high, there is a need for newer management approaches that improve therapy outcomes and are safer (Kitai and Tang, 2015). The reason for high mortality rates may be the use of unfocused and impersonal therapies in a person and comorbidities (Correale et al., 2021). So, in the present manuscript, the authors have provided an update on recent advancements in managing or controlling symptoms of HF or post HF therapies useful in preventing the recurrence of HF and other related complications. These agents have reduced the mortality associated with the disease progression. Various novel target agents that have been recently identified along with their mechanism of action are discussed below.

2.0 Pathophysiology of Heart Failure

Patients suffering from HF may be classified into the following categories: patients with reduced ejection fraction (EF) (<40%) having systolic HF, patients with preserved ejection fraction (>50%) having diastolic HF or mid-range ejection fraction (40–49%) (Ponikowski et al., 2016).

Heart failure may occur due to structural or functional alterations in the heart, often worsened by various factors such as diabetes, hypertension, and congenital heart disease. However, the majority of HF cases are found to be due to myocardial infarction or CAD. Restrictive cardiomyopathies and constrictive pericarditis can both cause diastolic HF with poor ventricular filling (Ziaeian and Fonarow, 2016).

It is necessary to recognize the etiology of decompensated HF, as it is causes morbidity or mortality related to the disease. Uncontrolled hypertension, inappropriate drug therapy, dietary salt intake, and reduced physical activity contribute to decompensated heart failure, with uncontrolled hypertension being the second most common cause (Lind et al., 2021).

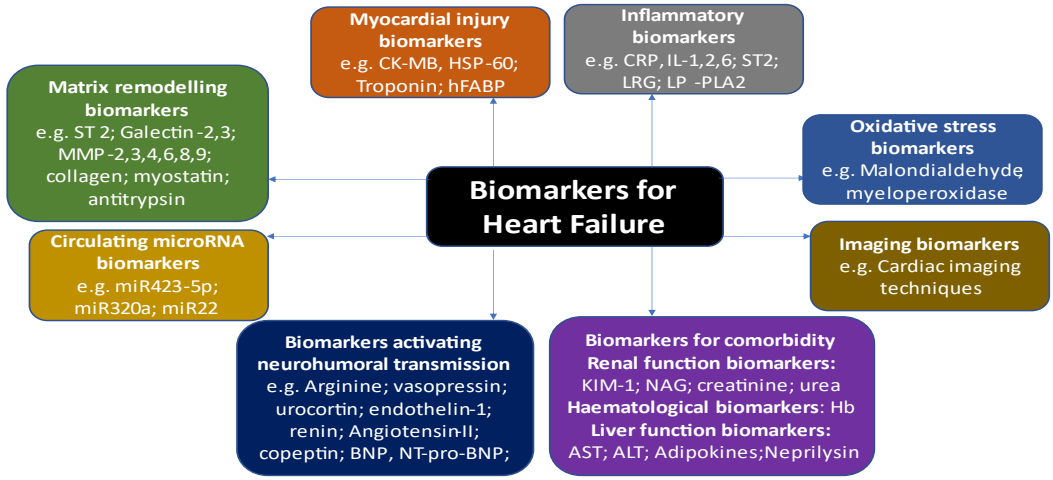
Initially, cardiac physiology tries to meet the systemic demand during the initial stage of heart failure by adapting via various compensatory mechanisms such as the Frank-Starling mechanism, adaptations to myocardial hypertrophy and contractility, and myocyte regeneration. As the wall stress increases, the myocardium compensates via eccentric cardiac remodelling, which further worsens the wall stress (Kemp and Conte, 2012).

Reduction in the cardiac output releases various hormones such as epinephrine, norepinephrine, and vasopressin due to stimulation of the neuroendocrine system which is further responsible for vasoconstriction that leads to increased afterload. Increased cyclic adenosine monophosphate (cAMP) is responsible for enhanced cytosolic calcium in the myocytes responsible for increased myocardial contractility. Increased myocardial contractility/ relaxation and afterload lead to an increase in oxygen demand of myocardial cells. Thus, the need for raised myocardial demand leads to myocardial cell death. Further, reduction in cardiac output and increased myocardial oxygen demand causes alteration in neurohumoral stimulation and altered hemodynamic and myocardial responses (Kemp and Conte, 2012). Reduceded myocardial relaxation and increased ventricular stiffness due to increased afterload, alters

myocardial hemodynamics and progresses to HF in patients having preserved EFHF (Obokata et al., 2020).

3.0 Biomarkers in Heart Failure

Biomarkers are designed to provide biological information and can be measured accurately and are reproducible and interpretable. Biomarkers should predict whether the patient is at risk of developing HF or confirm HF. Biomarkers serve as surrogate endpoints and help in the drug development process and provide a complete understanding of mechanisms involved in drug therapy. Initially, serum C-reactive protein assay was used in biomarker testing in HF (Braunwald et al., 1964). After the various biomarkers have been identified, B-type natriuretic peptides being the gold standard among all. (Strimbu and Tavel, 2010; Ibrahim et al., 2016). Biomarkers widely used in HF are described in Fig. 1.



ST2: Suppression of tumerogenicity; MMP: Matrix metalloptoteinase; hsp 60: Thermal Shock Protein 60; CRP: C-reactive protein; CK-MB: Creatinine kinase; Hfabp: Heart type fatty acid binding protein; BNP: Brain natriuretic peptide; NT-pro-BNP: N-terminal-pro-B-type natriuretic peptide; KIM-1: Kidney injury molecule-1; NAG: N-acetyl-β –glucosominidase

Fig. 1: Biomarkers in Heart Failure

4.0 Management of Heart failure

Various drugs that are recently been used in managing HF cases are described below:

4.1 Ivabradine

Alterations in heart rate is responsible for heart failure. Increased heart rate is an indicator of sympathetic nervous system activation and it worsens cardiovascular outcomes. Ivabradine, a selective inhibitor of I *f* current in the sino-atrial (SA) node, lowers heart rate and inhibits I*f* current of the SA node without affecting myocardial function, intracardiac conduction, and ventricular repolarization, thus proving to have a positive beneficial role in heart failure (Borer et al., 2003; Bel et al., 1986). The SHIFT trial, which was published in 2010, examined the beneficial effects of ivabradine. In this study, symptomatic HF patients with decreased ejection fraction (NYHA II-IV patients with LVEF of 35% and heart rate of 70 bpm) on guideline mediated medical therapy including β-blockers, angiotensin converting enzyme inhibitor, angiotensin receptor blocker and aldosterone antagonists were randomly administered ivabradine (7.5 mg twice daily) in comparison to placebo. After a follow-up period of around 23 months,

ivabradine reduced the composite primary endpoint of cardiovascular death or hospitalization for worsening HF by 18% (Swedberg et al., 2010). Generally, beta blockers are used for reduction in heart rate but there are incidences of increased adverse reactions with them (Metra et al., 2005; Butler et al., 2002; Komajda et al., 2003). Beta-blockers act on beta-adrenergic receptors and are responsible for a negative ionotropic effect, bronchial vasoconstriction. Calcium channel blockers also cause negative ionotropic effects, and hypotension by acting on the calcium channel located in the myocardium and smooth muscle.

4.2 Relaxin

Relaxin is known to have interaction with G protein coupled receptors that increase cyclic adenosine monophosphate production. Due to increase in cAMP, nitric oxide production also increases due to an increase in the expression of inducible and endothelial forms of nitric oxide synthases (Du et al., 2010; Conrad and Novak, 2004; Bani et al., 1983). Relaxin also increases the matrix metalloproteinase-2 expression that further activates endothelin-1 (Jeyabalan et al., 2003) and endothelin-B leading to nitric oxide generation (Conrad and Novak, 2004). Endothelin-B receptor activation leads to relaxin-stimulated increased kidney blood flow (Jeyabalan et al., 2003). So, relaxin is responsible for increasing cardiac output, arterial and kidney blood flow (Jeyabalan et al., 2007). Various studies have indicated the production of relaxin by blood vessels and failing myocardium (Samuel et al., 2006; Novak et al., 2006).

4.3 Sacubitril/Valsartan

In the current scenario, blocking the renin-angiotensin aldosterone system (RAAS) is the mainstay treatment approach for heart failure. Recent studies have shown the effectiveness of combination therapy of RAAS blockade (Valsartan) and neprilysin inhibitor (Sacubitril) (McMurray et al., 2014). Neprilysin, a zinc-dependent neutral endopeptidase enzyme, leads to the breakdown of various vasoactive peptides including natriuretic peptides, neprilysin, bradykinin, adrenomedullin and angiotensin II (Daniels and Maisel, 2007). In July 2015, the Food and Drug Administration (FDA) approved the Sacubitril/Valsartan combination for use in individuals with chronic, stable, asymptomatic heart failure and patients having left ventricular ejection fraction < 40% (McMurray et al., 2014).

PIONEER-HF clinical trial demonstrated that sacubitril/valsartan admininistration resulted in reduced N-terminal-pro-brain natriuretic peptide (NT-proBNP), HF re-hospitalization, transplant listing, and ventricular assist device implantation (Velazquez et al., 2019). ESC Heart Failure Association (HFA) Clinical Practice Update stated that for patients hospitalized with HF or decompensated chronic HF, starting sacubitril/valsartan instead of ACE inhibitor can be considered to decrease the risk of adverse events and lead to easier HF management (Seferovic et al., 2019).

4.4 Mineralocorticoid receptor antagonist (MRA)

Aldosterone is an critical marker of heart failure that causes salt, water retention, endothelial dysfunction, hypertrophy in ventricles, and fibrosis in the myocardium (Struthers and MacDonald, 2004). So, inhibiting RAAS by employing MRAs including eplerenone and

spironolactone may provide benefit in heart failure in symptomatic patients (NYHA class III and IV) patients in an EMPHASIS-HF study conducted in 2011 (Zannad et al., 2011).

4.5 Potassium absorbents

With the use of RAAS blockers and MRAs, Risk of electrolyte disturbance particularly hyperkalemia in patients having kidney disease increases with the use of RAAS and mineralocorticoid receptor blockers. Various clinical trials for the evaluation of the efficacy of RAAS blockers were stopped prematurely due to unexpected outcomes of hyperkalemia (ONTARGET Investigators et al., 2008; Fried et al., 2013). So, there is a need for therapy that can effectively manage hyperkalemia along with RAAS blockade. Recently, two novel potassium absorbent compounds, namely, patiromer calcium and zirconium silicate, promote loss of potassium through the alimentary and digestive tract. These agents are yet not FDA-approved but have shown safety and effectiveness in the latest clinical trials. Patiromer, an orally administered polymer, binds to potassium and is exchanged with calcium in the alimentary and digestive tract and promotes the excretion of potassium through faeces and thus reduces plasma potassium levels (Weir et al., 2015). An inorganic crystal, Zirconium silicate, retains potassium in the intestine (Stavros et al., 2014) and exchanges it with sodium and hydrogen.

4.6 V**asopressin-2 receptor antagonist**

Tolvaptan is approved by FDA for hyponatremia. Tolvaptan has proven to improve the congestion of acute decompensated heart failure, thereby reducing the need for loop diuretics and improving renal function (Felker et al., 2017; Starling and Young, 2017). However, Tolvaptan has not shown significant improvement in dyspnoea, hospital stay, worsening heart failure, or post-discharge consequences (Konstam et al., 2017).

4.7 Potassium channel blocker

Levosimendan is responsible for causing vasodilatation by inhibiting the adenosine triphosphate (ATP) dependent potassium (K^+) channel and also increases cardiac contractility by promoting calcium sensitivity. Levosimendan has a longer half-life. In a clinical study, levosimendan provided symptom relief but also presented the risk of hypotension and cardiac arrhythmias (Packer et al., 2017), so, there is a need for further studies to evaluate the efficacy of Levosimendan.

4.8 Sodium-glucose cotransporter inhibitors (SGLTis)

Recently, sodium-glucose cotransporter inhibitors (SGLTis), dapagliflozin and empagliflozin have proven to be effective in the management of heart failure (McMurray et al., 2019; Packer et al., 2020; Bhatt et al., 2020; Zinman et al., 2015; Perkovic et al., 2018; Perkovic et al., 2019; Wiviott et al., 2019). A study comparing dapagliflozin with placebo reported that dapagliflozin significantly reduced hospitalization due to HF and death rate (McMurray et al., 2019). In another study comparing the efficacy of empagliflozin with placebo, empagliflozin has shown a reduction in primary endpoint related to mortality and hospitalization due to heart failure but no significant effect was seen on cardiovascular morbidity/mortality. Empagliflozin has also shown improvement in secondary endpoints such as first and recurrent hospitalizations, reduction in glomerular filtration rate, and renal outcome (Packer et al., 2020).

The CANVAS and EMPA-REG OUTCOME clinical trials demonstrated the potential of SGLT2i on reducing the cardiovascular deaths. CANVAS found that canagliflozin decreased the risk of mortality from cardiovascular incidents, myocardial infarction (MI) and stroke in comparison to placebo but increased the risk of lower limb amputation (Neal et al., 2017). The EMPA-REG OUTCOME clinical trial also bolstered the benefit of empagliflozin on cardiovascular outcomes (Zinman et al., 2015).

SGLT2i shows a diuretic osmotic effect (Hallow et al., 2018; Griffin et al., 2020; Mordi et al., 2020) that may lead to stable blood flow and increases the effect of loop diuretics without causing electrolytes imbalance and activating RAAS. SGLTi may also possess metabolic, (Ferrannini et al., 2016), anti-inflammatory, and antifibrotic effects (Heerspink et al., 2019) and improved myocardial energy utilization stimulated by the increase in blood volume and oxygen level(Inzucchi et al., 2018; Ferrannini et al., 2016). SGLT2i causes an rise in sodium levels in the distal tubule by inhibiting glucose and sodium (Na^+) reabsorption. Ultimately, tubuloglomerular feedback is blocked leading to inhibition of the RAAS activation (Gronda et al., 2020; DeFronzo et al., 2017) and providing nephroprotection in individuals suffering from heart failure and kidney disease (Heerspink et al., 2020).

4.9 Vasodilators and inotropes

Endothelial dysfunction and generation of reactive oxygen species (ROS) in chronic HF decreases the production of guanylate cyclase, cyclic GMP (cGMP) and nitric oxide (Follman et al., 2017). Increased cGMP inhibits calcium entry into vascular smooth muscles and activate K^+ channel, causing hyperpolarization, and activates cGMP-mediated protein kinase, which is responsible for activation of myosin light chain phosphatase. So, raised cGMP has a variety of beneficial effects, including vasodilation, antithrombotic, antiinflammatory, and antiproliferative activities (Stasch et al., 2011). Vericiguat, a vasodilator, and oral guanylate cyclase stimulator modulate the nitric oxide (NO)-guanylyl monophosphate (GMP)- phosphodiesterase signaling cascade by activating guanylyl cyclase (Emdin et al., 2020). In a clinical study, vericiguat administered in HF patients (NYHA class II-IV) having <45% ejection fraction, has been found to significantly decrease hospitalization or cardiovascular mortality despite of risk of hypotension and syncope (Armstrong et al., 2020).

VICTORIA clinical trial assessed the safety and efficacy of vericiguat in chronic HF cases with decreased EF. The trial included 5,050 patients (having chronic HF; NYHA class II-IV; EF of 45%) over the age of 18 on guideline mediated medical therapy. The patients were randomly assigned to either vericiguat (10 mg daily) or a placebo. Primary outcome was a composite endpoint of mortality due to cardiovascular reasons or hospitalization. After 10.8 months follow-up period, Vericiguat showed a significant difference in the primary composite end point of mortality due to cardiovascular causes or HF hospitalization (Armstrong et al., 2020).

Omecamtiv mecarbil and danicamtiv, myotropic or myosin activators, directly activate myosin in the heart by increasing myosin pull on actin during depolarization. This action is independent of calcium (Psotka et al., 2019; Malik et al., 2011). Omecamtiv mecarbil raises

ventricular systole duration, systolic ejection time, and aortic flow without the need for higher oxygen utilization (Malik et al., 2011).

Omecamtiv mecarbil and danicamtiv improve myocardial contractility by promoting the myosin-actin complex, without affecting Ca^{2+} homeostasis, and increasing left ventricular systole function without improving arrhythmogenesis (Shen et al., 2010; Psotka and Teerlink, 2017; Szentandrassy et al., 2016). The bioavailability of Omecamtiv mecarbil is higher and comparatively it is safer in HF with reduced ejection fraction (Teerlink et al., 2016). Although the drug has not been found to improve dyspnoea but has increased systolic ejection fraction and reduced natriuretic peptide tests (Swenson et al., 2017; Teerlink et al., 2016; Kaplinsky and Mallarkey, 2018) proving it to be safe in acute heart failure.

4.10 Iron deficiency correction

The occurence of acute decompensated HF can be reduced by administering Ferric carboxymaltose to correct iron deficiency as iron deficiency is very common in patients with HF (Ponikowski et al., 2020; Rocha et al., 2018). Reduced iron absorption, haematic loss, inflammation, anaemia and hemopoiesis impairment and iron storage lead to iron deficient state (Ghafourian et al., 2020; Jankowska et al., 2010). Iron is an important element of mitochondrial electron transport proteins involved in ATP generation (Mracek et al., 2017), so iron deficiency may lead to abnormality in myocardial and skeletal muscle functions (Hoes et al., 2018; Dziegala et al., 2018). Various studies have indicated that correction of iron deficiency by administering Ferric carboxymaltose may show improvement in the patient's life quality (Anker et al., 2009; Ponikowski et al., 2015). Administration of intravenous Ferric carboxymaltose reduces hospitalizations after heart failure exacerbations suggesting the need to administer Ferric carboxymaltose before hospital discharge to prevent reoccurrence (Anker et al., 2018; Iacoviello et al., 2021).

The EFFECT-HF clinical study compared the effectiveness of ferric carboxymaltose (FCM) on the exercise capacity to standard care. Ferric carboxymaltose was found to be linked with enhanced consumption of oxygen after 24 weeks treatment (van Veldhuisen et al., 2017). FERRIC-HF II clinical trial assessed the effect of iron repletion with iron isomaltoside on phosphocreatine recovery half-time at submaximal exercise in patients having symptomatic HF with reduced ejection fraction. Iron isomaltoside replacement was linked with less phosphocreatine time, indicating better mitochondrial oxidative functioning (Charles-Edwards et al., 2019).

4.11 Transthyretin stabilizers

Accumulation of misfolded transthyretin monomer into amyloid protein and its deposition causes tissue dysfunction (Ruberg et al., 2019). Infiltration of amyloid fibrils in the myocardium may lead to heart failure by altering myocardial contractility. Around 12% of HF cases with normal EF account for transthyretin amyloid cardiomyopathy (González-López et al., 2015). Before the use of transthyretin stabilizers, management of transthyretin amyloidosis with cardiomyopathy provided only symptomatic relief.

Tafamidis (Transthyretin stabilizer) binds to the thyroxine-binding site of the transthyretin (Bulawa et al., 2012). Tafamidis has indicated a decreased risk of cardiovascular hospitalizations and mortality in transthyretin amyloidosis with cardiomyopathy (Maurer et al., 2018). Delay in the worsening of heart failure symptoms and improvement in reducing exercise capability was seen in the tafamidis group in the early 6 months, and improvement in mortality cases was observed after 18 months of treatment.

Patisiran (RNA therapeutics) is a small RNA molecule that is encapsulated in a liposome. Patisiran targets transthyretin mRNA sequence in 3′ untranslated region and suppresses gene expression through RNA mediated silencing complex (Fire et al., 1998; Coelho et al., 2013). Patisiran (0.3 mg/kg weekly for 3 weeks) has shown a reduction in blood transthyretin concentration by 81% and provided relief in neuropathy in patients with transthyretin amyloidosis (Adams et al., 2018). Patisiran has shown a reduction in the mean difference in wall thickness in ventricles and left ventricular end-diastolic volume (Minamisawa et al., 2019; Solomon et al., 2019).

In 2019, Tafamidis has already been approved by FDA for the management of both, wildtype and hereditary cases of transthyretin amyloidosis with cardiomyopathy whereas, in 2018, patisiran got approval for hereditary transthyretin amyloidosis with polyneuropathy. Thus, Tafamidis may act as a preferred agent in the management of amyloid cardiomyopathy (Buckley and Shah, 2019).

4.12 Chymase inhibitor

Chymase, a serine protease, is released from the mast cells and cardiomyocytes during tissue damage (Takai and Jin, 2016; Ahmad et al., 2011). Chymase causes activation of locally acting fibrotic factors including angiotensin II, transforming growth factor (TGF) β, and matrix metalloproteinases (MMP) that are responsible for adverse effects occurring after the attack of heart failure (Dell'Italia et al., 2018). Fulacimstat, a chymase inhibitor, improves cardiac remodelling and decreases left ventricular dysfunction after a heart attack (Düngen et al., 2019).

4.13 Na+-H+ exchanger-1 inhibitor (NHE-1i)

Na+-H+ exchanger-1 may also act as a potential target for the managing heart failure. Administering cariporide, an NHE-1 inhibitor has shown improvement in hypertrophy and heart failure and also reduced cell death in cardiomyocytes (Kim et al., 2016). Cariporide has also shown antiarrhythmic effects (Baartscheer et al., 2008).

4.14 GLP-1 receptor agonists

The GLP-1 receptor agonist, liraglutide, may also play a critical role in improving inflammation in the heart. Liraglutide has also shown improvement in IL-1β mediated ROS generation and NADPH oxidase levels. Further, liraglutide has also shown a reduction in ATP generation and preservation of cardiomyocytes against IL-1β mediated decreased mitochondrial membrane potential (Zhang et al., 2020).

5.0 Role of Antioxidants in Heart failure

Oxidative stress is the major pathophysiological factor in the development and progression of HF (van der Pol et al., 2019). Both, an rise in oxidative stress and suppression of

innate anti-oxidant defense mechanisms that leads to heart failure. Reduction in major components of antioxidant defense mechanisms such as superoxide dismutase, catalase, glutathione peroxidase, nicotinamide adenine dinucleotide, and glutathione are responsible for HF which has been confirmed from various animal studies (Khaper et al., 2003).

Various studies have shown that exogenous antioxidant supplementation with antioxidants such as Vitamin A, C, and E, and folic acid, reduces cardiovascular events and reduces oxidative stress (Stephens et al., 1996; Singh et al., 1996). However, a meta-analysis of 50 clinical studies involving 294478 participants suggested that exogenous antioxidant supplementation did not reduce the risk of cardiovascular complications (Myung et al., 2013). Various clinical studies have shown that boosting GSH levels improve antioxidant activity and thus provides an improvement in HF (van der Pol et al., 2019).

Antioxidants may also be useful in improving heart function. Resveratrol treatment has been found to reduce galectin-3 levels. Galectin-3 is secreted from macrophages that play a keyt role in fibrosis and inflammation. Resveratrol treatment also reduces interleukins 1 and 6 levels and may improve heart function in patients with HF with reduced EF (Gal et al., 2020).

6.0 Role of Herbal medicines in Heart Failure

Various challenges are routinely encountered with drug therapy in managing heart failure (Yancy et al., 2017) and there is no particular therapy that may improve morbidity or mortality in HF, particularly patients with preserved EF heart failure (Felker et al., 2010; Tamargo et al., 2011). Various drugs have been developed focusing on left ventricular ejection fraction but comorbidities limit their usage (Dickstein et al., 2008; Tamargo and Lopez-Sendon, 2011). As the role of herbs in preventing cardiovascular disorders has been explored, their usage in managing heart disorders have been increased (Li et al., 2015).

Allium sativum has been widely used for managing various diseases particularly cardiovascular disorders (Turner, 1990). Allicin (2-propenyl-2-propene-thiosulfinate or diallyl thiosulfinate) is the odoriferous main constituent of garlic responsible for cardiovascular activity (Sendl, 1995). Further, *Berberis vulgaris* (Parsaee et al., 2006; Fatehi-Hassanabad et al., 2005; Sa et al., 2006), *Cerasus avium* (Sina, 2010), *Berberis integerrima* (Sharifi et al., 2013; Mahdavi et al., 2016), *Apium graveolens* (Zhang et al., 2000; Tashakori-Sabzevar et al., 2016; Ko et al., 1991), *Peganum harmala* (Berrougui et al., 2006; Shi et al., 2001; Astulla et al., 2008), Citrus *aurantifolia swings* (Souza et al., 2011; Akhtar, 2013), *Citrus aurantium* (Kang et al., 2016; Huang et al., 2001), *Centella asiatica* (Intharachatorn and Srisawat, 2020; Huo et al., 2016; Kumar et al., 2015) and *Curcuma longa* (Tang et al., 2009; Zhang et al., 2010; Yao et al., 2004) are some of the herbal natural products that may exert a therapeutic role in managing heart failure.

7.0 Future perspectives

There is a strong need to identify a therapy that may provide complete relief in heart failure. Other possible approaches that may act as potential drug targets may include type-2 ryanodine receptors (RyR2) and their associated accessory proteins. RyR2 acts on the sarcoplasmic reticulum and generates Ca2+ transients within the cardiomyocytes. So, RyR2

normal functioning is important for normal timing and force production in cardiomyocytes. Impairment in RyR2 function alters Ca^{2+} handling and may lead to heart failure (Connell et al., 2020). Striated preferentially expressed protein kinase (SPEG) is also responsible for normal Ca^{2+} handling in cardiomyocytes. Alterations in SPEG have also been related to heart failure and atrial fibrillation, hence its role is needed to be explored further (Campbell et al., 2020).

Gene therapy may be employed in the management of heart failure (Fargnoli et al., 2017). cysteine-rich secretory protein LCCL domain containing 1 gene is over-expressed in heart failure. Downregulation of the signalling cascade after knocking out CRISPLD1 implied benefit in heart failure (Khadjeh et al., 2020). Cardiac bridging integrator 1 gene therapy has also shown benefits in stabilizing cardiomyocyte membrane, thus, may pave the way to find new drugs that may offer benefits in heart failure pharmacotherapeutics (Liu et al., 2020). Further, the use of PP1 inhibitor (regulator of SERCA2a gene), S100A1 (calcium sensor), and upregulation of β receptor also provide hope in managing heart failure (Williams et al., 2004).

8.0 Conclusion

Although the existing therapies are not completely effective in managing heart failure, there is still a need for newer agents which can lessen the burden of disease and provide improvement. This article has summarized the progress of newer therapeutic agents that may be used as standard therapies for heart failure in near future.

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