TANG HUMANITAS MEDICINE

Review

Terminalia arjuna Bark and inotropic therapy for heart failure

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ABSTRACT

Heart disease that ultimately leads to heart failure (HF) has been the number one cause of death in the United States as well as in many other countries for over a century. Inotropic therapy utilizing cardiotonics to increase cardiac contractility remains a significant component of the management of HF. However, adverse effects of currently available cardiotonics have been compromising their therapeutic value and often lead to further myocardial dysfunction. Thus, discovery of safe cardiotonics remains a main challenge to improvement of inotropic therapy for HF. This review briefly summarized cellular mechanisms underlying the inotropic action of currently available cardiotonics, newly-developed carditonics and the bark of *Terminalia arjuna (TA)*, a tropical tree used in ayurvedic medicine. The potential of TA bark as a new cardiotonic in inotropic treatment for HF was also discussed.

Keywords inotropic therapy, heart failure, ayurvedic medicine, cardiotonic, naturoceutical, neutralceutical, contractility

INTRODUCTION

Heart disease accompanied by declined myocardial contractility or a defect in contractile function ultimately leads to heart failure (HF), which is still the number one cause of death of both men and women in the United States according to the Centers for Disease Control and Prevention of the United States. It is estimated over 5 million Americans currently have this condition, and the incidence of HF increases with advancing age. HF that can be caused by diverse cardiovascular disorders including coronary artery disease and hypertension leads to failure of the heart to pump blood for body needs. A primary goal of HF treatment has been to multi-dimensionally target alterations in function and structure of the heart to improve contractile function (Braunwald, 2008; Katz, 2008; Metra et al., 2001; Stevenson, 1998; Teerlink et al., 2009). Inotropic therapy utilizing cardiotonics to directly enhance cardiac contractile function, increase cardiac output and then alleviate symptoms, remains a significant component of the management of acute and chronic HF for decades (Braunwald, 2008; Campia et al., 2010; Felker and O'Connor, 2001; Hasenfuss and Teerlink, 2011; Katz, 2008; Stevenson, 1998; Teerlink et al., 2009; Toma and Starling, 2010). Based on mechanisms of action, current well-known cardiotonics have been classified into at least four classes: β-adrenergic agonists, phosphodiesterase inhibitors (PDI), cardiac glycosides and Ca^{2+} sensitizers (Felker and O'Connor, 2001; Hasenfuss and Teerlink, 2011; Stevenson, 1998; Toma and Starling, 2010). In addition to their specific inotropic actions, some classes of cardiotonics exert common signaling pathways to increase cardiac contractility and/or alter central nervous system and peripheral vasculature, i.e., hemodynamic effects. As a consequence, various adverse effects of current cardiotonics are common among these classes, posing a major challenge in inotropic therapy. Currently available cardiotonics in conjunction with hemodynamic therapies have been often found not to improve survival or shown to increase hospitalization and mortality in patients with HF (Braunwald, 2008; Felker and O'Connor, 2001; Metra, et al., 2011; Toma and Starling, 2010), closely associated with their adverse effects, including arrhythmogenesis (Stump et al., 2000), increasing myocardial oxygen demand and facilitating myocyte apoptosis (Felker and O'Connor, 2001). Thus, discovery of safe cardiotonics remains a main challenge to the improvement of inotropic therapy for HF. The history and development of therapeutics for HF in clinic trials have been described in a great detail in many excellent review articles. To limit the scope, this review is only to summarize cellular mechanisms of inotropic action of currently-known cardiotonic classes and to define the role of the bark of *Terminalia arjuna* (*TA*) in inotropic therapy for HF.

Mechanisms of action of current cardiotonics in inotropic therapy for HF

β-Adrenergic agonists

This class includes catecholamines such as epinephrine, norepinephrine and isoproterenol (ISO) that are known to act primarily to increase Ca^{2+} influx via sarcolemmal (SL) L-type Ca^{2+} channels mediated by a cAMP-PKA signaling pathway via activation of its G-protein-coupled receptors (Fig. 1) (Trautwein and Hescheler, 1990; Yatani and Brown, 1989). β-Adrenergic stimulation also phosphorylates sarcoplasmic reticular (SR) phospholamban (PLB), a negative regulator of SR Ca^{2+}-ATPase (SERCA2a), and troponin I (cTnI) of cardiac myofilaments (Layland et al., 2005). The resultant increases in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) and SR Ca^{2+} content lead to positive inotropy, while enhancement of SR Ca^{2+}uptake during the relaxation phase leads to a lusitropic effect. Similarly, dopamine (the immediate precursor of norepinephrine) and dobutamine (a synthetic catecholamine) exert a positive inotropic effect via activation of dopaminergic receptors (Ding et al., 2008) and/or β-adrenergic receptors (Toma and Starling, 2010; Wakita, 2007; Zhao et al., 1997). β-Adrenergic agonists also increase SR Ca^{2+}

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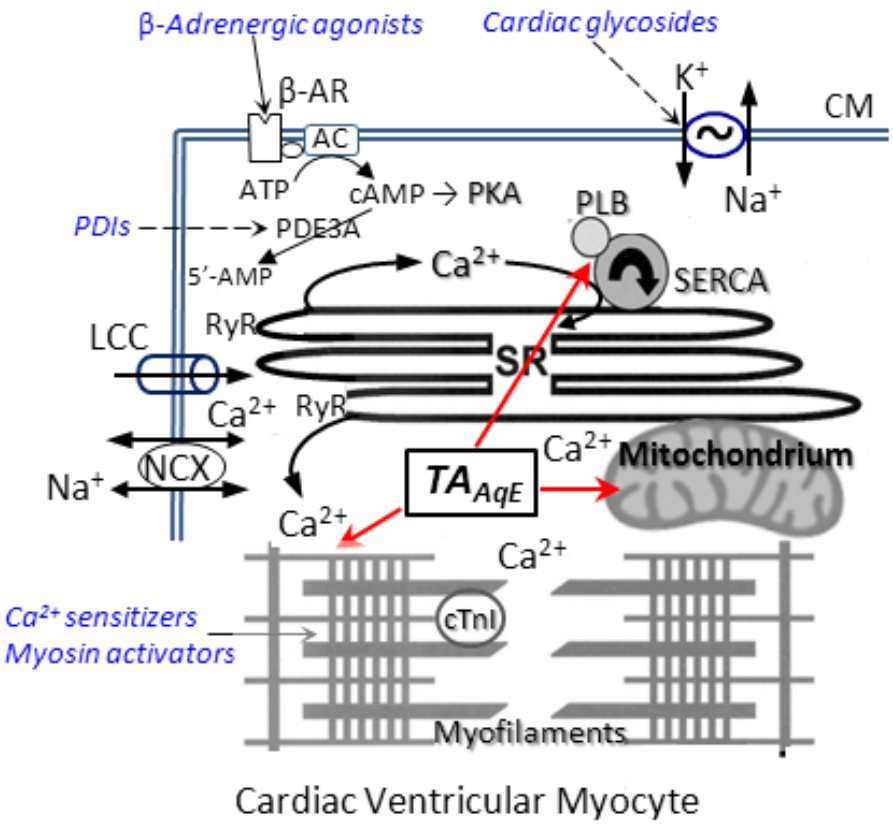

Fig. 1. Possible mechanisms for cardiotonic actions of TA_{AqE} on AVM by enhancing Ca^{2+} handling. TA_{AqE} increases contraction of AVM, probably by 1) increasing SR Ca^{2+} by SERCA, 2) enhancing Ca^{2+} sensitivity of myofilaments, and 3) minimizing oxidative stress of mitochondria. AC, adenyl cyclase; β-AR, β-adrenoreceptor; CM, cell membrane; PKA, protein kinase A; LCC, L-type Ca^{2+} channel; NCX, Na^+/Ca^{2+} exchanger; PLB, phospholamban, Dashlines indicate inhibition.

leak in cardiomyocytes (Curran et al., 2007; Lehnart et al., 2009), resulting in Ca^{2+} overload, which is closely associated with catecholaminergic ventricular tachycardia and arrhythmias (Lehnart et al., 2009; Nam et al., 2005; Stump et al., 2000; Verkerk et al., 2001), aftercontractions (Tweedie et al., 2000) and mitochondrial Ca^{2+} overload (Maack et al., 2006). This increases the risk of worsening HF and mortality because of known high sympathetic tone in HF (Colucci et al., 2000; Joseph and Gilbert, 1998; Lehnart et al., 2009). It is also known that β-adrenergic agonists exert positive inotropy concomitantly with increased heart rate at the expense of myocardial energy by increasing oxygen consumption (Teerlink et al., 2009) in the absence of a proportionate increase in energy supply. Moreover, studies showed that long-term β-adrenergic stimulation causes left ventricular dysfunction and hypertrophy (Osadchii et al., 2007; Shizukuda et al., 1998), due probably to promotion of myocyte apoptosis (Colucci et al., 2000; Communal et al., 1998; Osadchii et al., 2007; Shizukuda et al., 1998). These adverse effects are consistent with increased mortality in patients with advanced HF (O'Connor et al., 1999; Teerlink et al., 2009; Tomita et al., 2003).

Phosphodiesterase inhibitors (PDIs)

PDIs, especially inhibitors of PDE3A (the major isoform in the heart) such as milrinone, enoximone and amrinone, elevate cellular cAMP by inhibiting the degradation of cAMP. Thus, PDIs enhance L-type Ca^{2+} channels (Akita et al., 1994; Hatem et al., 2010) and exert positive inotropic (Endoh, 1995; Rendig and Amsterdam, 1994) and lusitropic effects on cardiomyocytes (Holubarsch et al., 1994; Yano et al., 2000) via the cAMP-PKA pathway. Consequently, PDI therapy shares many adverse effects of catecholamine therapy, e.g., arrhythmia and sudden death (Packer et al., 1991; Stump et al., 2000; Teerlink, 2009; Toma and Starling, 2010). Moreover, the down-regulation of PDE3A observed in human failing hearts was suggested to cause the progression of HF (Ding et al., 2005). This study showed that both ISO and angiotensin II induce down-regulation of PDE3A gene expression and promote cardiomyocyte apoptosis, which was mimicked by PDIs (Ding et al., 2005). The PDI-induced myocyte apoptosis could account for the increased morbidity and mortality observed in long-term PDI-treated patients with chronic HF (Nony et al., 1994; Packer et al., 1991; Teerlink et al., 2009; Toma and Starling, 2010).

Cardiac glycosides

Cardiac glycoside therapy is of potential value to patients with symptoms and signs of congestive HF (Katz, 2008; Teerlink et al., 2009). Digitalis glycosides, such as digoxin, digitoxin, and ouabain, have been used as therapeutic cardiotonics in treating HF for centuries (Teerlink et al., 2009). The positive inotropic action of glycosides arises from inhibition of the SL Na^+/K^+ pump, which causes an increase in $[Na^+]_i$, thereby increasing $[Ca^{2+}]_i$ (Wier and Hess, 1984) via reversal of the normal operating mode of SL Na^+/Ca^{2+} exchange (NCX) (Fig. 1). Consequently, cardiac glycosides enhance myocyte contractility (Lee, 1985; Wier and Hess, 1984) and cardiac performance but have no effect on cardiac output (Lucke et al., 1994) likely due to their effect on peripheral vasculature and neurohormonal systems (Medford, 1993). Ouabain has also been shown to increase Ca^{2+} influx via SL Ca^{2+} channels (Le Grand et al., 1990) and digitoxin-forming Ca^{2+} channels (Arispe et al., 2008), and enhance Ca^{2+} release channels (RyR2) (McGarry and Williams, 1993; Ruch et al., 2003; Sagawa et al., 2002). In contrast to ISO, ouabain has no effect on SERCA2a or on relaxation of contraction (Brixius, et al., 1997; Holubarsch et al., 1994; Rendig and Amsterdam, 1994). These effects could account for ouabain-induced increases in diastolic $[Ca^{2+}]_i$ in the human heart (Brixius et al., 1997) and cardiotoxicity, including arrhythmias (Lederer and Tsien, 1976; Marban et al., 1986; Stump et al., 2000), SL damage (Korge and Langer, 1998), and impaired

mitochondria (Maack et al., 2006). Digoxin toxicity is one of the most commonly encountered adverse drug reactions due to the narrow range between therapeutically effective doses and toxic doses in patients with HF (e.g., the FDA has recalled Digitek® (2008)) and is associated with the increased incidence of breast cancer among post-menopausal women with heart disease (Ahern et al., 2008). In contrast to the above-mentioned cardiotonics, digitalis glycoside therapy does not increase morbidity and mortality in HF patients also undergoing hemodynamic therapy (Ahmed et al., 2006; Felker and O'Connor, 2001); however, it has no beneficial effect on survival (Hasenfuss and Teerlink, 2011; The Digitalis Investigation Group, 1997).

Ca^{2+} sensitizers

Levosimendan, a novel calcium sensitizer, was shown to bind to cardiac troponin C (TnC) and stabilize the Ca^{2+}-TnC conformation (Edes et al., 1995; Sorsa et al., 2001), thereby enhancing contractility without altering $[Ca^{2+}]_i$ or increasing myocardial oxygen consumption (Banfor et al., 2008; Edes et al., 1995; Gheorghiade et al., 2005). Contrarily, levosimendan was shown to cause an increase in cytosolic $[Ca^{2+}]_i$ of isolated hearts before or after ischemia (Chen et al., 2003). Furthermore, levosimendan-induced vasodilation via opening of ATP-sensitive K^+ channels (Gheorghiade et al., 2005) makes it an excellent choice in short-term treatment of patients with acute HF, especially associated with acute myocardial infarction. In the levosimendan treatment group, improvement of ventricular performance in patients with HF was attributable primarily to hemodynamic improvement rather than direct inotropy of levosimendan (Adamopoulos et al., 2006; Delaney et al., 2010). However, long-term peripheral vasodilation could result in hypotension, a known limitation of the use of levosimendan. Moreover, a study comparing cardiotonics reported that levosimendan in combination with PDE3 inhibition elicits inotropic and adverse effects similar to those induced by PDIs (Chen et al., 2003). Ongoing clinical trials also showed that levosimendan improves cardiac performance and hemodynamics but not survival (Delaney et al., 2010). In contrast, other Ca^{2+} sensitizers such as pimobendan with an activity of PDE inhibition were found to increase mortality (Felker and O'Connor, 2001; Stevenson, 1998). Thus, the benefit of long-term treatment of HF with Ca^{2+} sensitizers remains unclear.

Newly-developed cardiotonics

Istaroxime, a new class of non-cardiac glycoside cardiotonics or known as SERCA activators, is identified to inhibit the Na^+/K^+ pump and stimulate SERCA2 activity. While istaroxime and digoxin both increase diastolic Ca^{2+}, SR Ca^{2+} content and the rate of cytosolic Ca^{2+} decay in normal ventricular myocytes, only istaroxime increases SERCA activity without significantly affecting SR Ca^{2+} leak in myocytes isolated from normal hearts (Rocchetti et al., 2005) and failing hearts (Micheletti et al., 2007; Rocchetti et al., 2008). Consequently, istaroxime was able to recover the declined SR function in myocytes isolated from failing hearts (Rocchetti et al., 2008). The istaroxime-induced increase in SERCA2a activity was suggested to result from modulation of the interaction between SERCA2a and phospholamban (Micheletti et al., 2007). These studies also showed that istaroxime facilitates the rate of myocyte relaxation and cytosolic Ca^{2+} decay, i.e., a lusitropic effect as observed with β-adrenergic agonists and PDIs. However, istaroxime-induced increase in diastolic Ca^{2+} (Rocchetti et al., 2005) is the major concern as above-described for cardiac glycosides. In HORIZON trial, istaroxime increased cardiac index and systolic blood pressure, and decreased LV end-diastolic volume (Hasenfuss and Teerlink, 2011). Meanwhile, istaroxime decreased heart rate with no change in left ventricular ejection fraction; thus, its benefit to HF patients during long-term treatment remains unclear.

Omecamtive mecarbil (or CK-1827452), another new class of cardiotonics known as cardiac myosin activators, was shown to directly accelerate the rate of the rate-limiting step of myosin cross-bridge formation, thereby increasing the duration and magnitude of myocyte contraction without altering Ca^{2+} transients and kinetics of contraction (Malik et al., 2011). Both animal studies and clinical trials on subjects with systolic HF showed that treatments with omecamtive mecarbil for 24 - 72 h increases concentration-dependently left ventricular ejection time and stroke volume, and decreases heart rate with no effect on the maximum rate of developed pressure and myocardial oxygen consumption (Cleland et al., 2011; Shen et al., 2010). The degree of increased stroke volume induced by omecamtive mecarbil is greater than that of decreased heart rate, thereby resulting in a small increase in cardiac output. Although treatment for 24 h with omecamtive mecarbil did not alter the coronary blood flow (Shen et al., 2010), one noticeable concern for the increased systolic ejection time induced by omecamtive mecarbil was to induce coronary hypoperfusion with shortened ventricular filling time during diastole. Thus, during long-term treatments, omecamtive mecarbil could potentially induce further myocardial ischemia/damage. While omecamtive mecarbil appears to be a new promising cardiotonic for patients with systolic HF, its therapeutic value to HF patients with diastolic dysfunction remains questionable. Currently, omecamtive mecarbil is advanced to the Phase II clinical trial, and its long-term effect remains to be determined.

Bark of *Terminalia arjuna* (*TA*) as a cardiotonic

The bark of *TA*, a well-known ayurvedic botanical with active organic constituents such as tannins, triterpenoid saponins, flavonoids, gallic acid, ellagic acid, oligomeric proanthocyanidins, and phytosterols, has been used for centuries in ayurvedic medicine as a cardiotonic and diuretic for treatment of various cardiovascular disorders, including HF (Jain et al., 2009; Miller, 1998) . Studies using crude powder of *TA* bark showed attenuation of ischemia/reperfusion-induced myocardial injury by reducing oxidative stress (Gauthaman et al., 2001). Studies using *TA* bark extracted with organic solvents (defined as organic extracts) showed that such extracts exert a variety of biological activities, including reduction in blood pressure (Nammi et al., 2003), negative inotropy and chronotropy (Radhakrishnan et al., 1993), reduction of ISO-induced myocardial injury (Karthikeyan et al., 2003), induction of cell apoptosis (Kuo et al., 2005; Sivalokanathan et al., 2006), and growth suppression of human cell lines (Nagpal et al., 2000) and insect larva (Singh et al., 2004). Some cardioprotective effects of organic extracts (e.g., triterpenoids) of *TA* bark were attributed to antioxidant properties (Ali et al., 2003; Jain et al., 2009; Karthikeyan et al., 2003; Pawar and Bhutani, 2005). Two studies using constituents of *TA* bark extracted in water (defined as aqueous extracts) showed positive inotropic effects on rat atria (Radhakrishnan et al., 1993), and reduction in blood pressure, and bradycardia in the rat (Singh et al., 1982). Both studies suggested that *TA* bark acts on the nervous system. Thus, the direct cardiac effect and underlying mechanisms of action of *TA* bark remain undefined.

A clinical trial of *TA* bark in India evaluated the effect of administration of *TA* bark prepared as a mixture of alcoholic and aqueous extracts to 136 patients with severe refractory HF (Class IV New York Heart Association [NYHA]) and unresponsiveness to conventional therapy (i.e., cardiac glycosides, maximally tolerable diuretics including vasodilators

and spironolactone, an aldosterone blocker) (Bharani et al., 1995). This *TA* adjuvant therapy resulted in increases in systolic blood pressure, stroke volume index and left ventricular ejection fraction concomitantly with a decrease in diastolic pressure, improvement in symptoms and signs of HF, and quality of life, compared with patients taking placebo (Class III vs. IV NYHA). Moreover, no adverse effect was found in patients treated with *TA* adjuvant therapy. In another clinical trial, the similar mixture of *TA* bark extract was found to be as effective as isosorbide mononitrate (ISMN, a vasodilator) in treating patients with myocardial ischemia and chronic stable angina (Class II-III NYHA) (Bharani et al., 2002). Both *TA* therapy and ISMN therapy resulted in improvement in treadmill exercise performance and a decrease in the frequency of angina, compared to placebo therapy. A more recent study reported that *TA* adjuvant therapy (500 mg *TA* bark powder with anti-ischemic treatment following American Heart Association guidelines) induced significant improvement in diastolic dysfunction and ischemic mitral regurgitation, with a mild side effect of gastritis, in patients with acute myocardial infarction (Dwivedi et al., 2005). Such compelling clinical data of *TA* bark highlight the need for better understanding of mechanisms of direct cardiac action of this botanical.

Recently, we have focused on defining cellular mechanisms of cardiac action of the aqueous extract of *TA* bark (TA_{AqE}), similar to that used in traditional therapy and clinical trials. We used adult ventricular myocytes (AVM) isolated from rat hearts to examine the direct inotropic effect of TA_{AqE} on single heart cells and compared the results with that of some organic extracts of *TA* bark, ISO and ouabain (Oberoi et al., 2011). We found that TA_{AqE} displays a positive inotropic effect on contraction (or cell shortening, CS) of AVM in a concentration-dependent manner (in the range from 0.05 to 50 µg/ml). In addition to inotropy, at the concentration of 5 µg/ml, TA_{AqE} causes a significant reduction (by 41%) in the decay time during myocyte relaxation by increasing the maximal rate of relaxation, i.e., a positive lusitropic effect. In contrast to TA_{AqE}, organic extracts of *TA* bark (prepared sequentially with hexane, ethyl acetate and chloroform), at concentrations from 9 to 95 µg/ml, exerted arrhythmogenic effects with no or inconsistent inotropy.

In comparison with ISO (100 nM) and ouabain (1 mM) that induce inotropy to a similar degree, TA_{AqE} (at 50 µg/ml) causes a decrease in the decay time of CS relaxation, positive lusitropy, as ISO, and increase in the rise time of myocyte contraction as ouabain (Oberoi et al., 2011). These results suggest that TA_{AqE} exert a cardiotonic action distinct from that elicited by ISO and ouabain but share certain mechanisms with each agent. More importantly, under this condition, both ISO and ouabain, but not TA_{AqE}, often cause lethal arrhythmias that cause cell death.

Possible mechanisms for cardiotonic action of TA_{AqE}

The cardiotonic effect of TA_{AqE} (i.e., positive inotropy and positive lusitropy) suggests an enhancement in SR Ca^{2+} handling. The TA_{AqE}-induced lusitropy is similar to that induced by ISO, which is known to facilitate SR Ca^{2+} uptake. This is supported by our finding that TA_{AqE} enhances caffeine-elicited contraction (Oberoi et al., 2011), indicative of TA_{AqE} enhancing SR Ca^{2+} uptake during relaxation so to increase SR Ca^{2+} content. The lusitropic effect of TA_{AqE} appears to be also comparable to that of istaroxime (a SERCA2a activator). On the other hand, TA_{AqE} and ouabain induce an increase in the rise time of myocyte contraction, but not the maximum rate, of contraction, probably resulting from an increase in Ca^{2+} sensitivity of myofilaments. Such prolonged contraction phase induced by TA_{AqE} is also similar to that of omecamtive mecarbil (a cardiac myosin activator). More importantly, unlike ISO and ouabain, TA_{AqE} does not elicit arrhythmia, a major adverse effect of above-mentioned current cardiotonics. This supports our suggestion that TA_{AqE} acts primarily on cardiac SR and myofilaments rather than alters membrane transport mechanisms such as L-type Ca^{2+} channels, which is enhanced by ISO and ouabain, and/or Na^{+}-dependent transports, which is enhanced by ouabain (Fig. 1). Such unique mechanisms of TA_{AqE}-induced inotropy and lusitropy enable TA_{AqE} to stabilize intracellular Ca^{2+} handling and minimize a change in the duration of each contraction cycle, thereby preventing Ca^{2+} overload and genesis of arrhythmia. This finding is also consistent with no side effects of *TA* bark application observed in clinic trials (Bharani et al., 1995).

In addition, *TA* bark contains many triterpenoids and flavonoids that possess numerous antioxidant capacity (Jain et al., 2009; Miller, 1998;). Accordingly, *TA* bark has been shown to improve or prevent oxidative stress of the heart by augmentation of endogenous antioxidant enzymes under ischemic/reperfusion conditions (Gauthaman et al., 2001). Therefore, it is logical to hypothesize the action site of *TA* bark at the cellular level is the mitochondria (Fig. 1) that play a pivotal role in bioenergetics and oxidative homeostasis in physiology and pathophysiology of the heart. Furthermore, it is well known that the cAMP-PKA pathway-mediated positive inotropy (e.g., by β-adrenergic agonists) is accompanied by an increase in myocardial oxygen consumption, i.e., increased mitochondrial workload, thereby leading to an increase in oxidative stress. *TA* bark (including crude power, alcoholic extract and TA_{AqE}) was shown to counteract the action of norepinephrine and ISO-induced myocardial injury, an anti-adrenergic action (Karthikeyan et al., 2003; Singh et al., 1982). Thus, we hypothesize that TA_{AqE} minimizes oxidative stress of mitochondria of AVM during exerting positive inotropy. Taken together, the direct cardiac effect of TA_{AqE}, not *TA* organic extracts, is consistent with the therapeutic property of *TA* bark used in ayurvedic medicine and in clinic trials. Thus, it is suggestive that TA_{AqE} is a promising, safe cardiotonic. Further characterization of mechanisms for *in vivo* actions of TA_{AqE} on normal and abnormal hearts is under investigation.

CONCLUSION

HF is a multifactorial symptom with mechanical and mitochondrial dysfunction, and Ca^{2+} cycling defects (Kapur et al., 2010; Rosca and Hoppel, 2010). Inotropic therapy is still widely used in the management of acute and chronic HF to alleviate the symptoms and improve myocardial contractility, particularly for patients who cannot benefit from hemodynamic therapy. The therapeutic value of currently available cardiotonics for chronic inotropic therapy is hampered by their adverse effects, thereby leading to cardiotoxicity and increased mortality via various mechanisms. At the cellular level, the direct inotropic action of TA_{AqE} appears to share the advantageous properties of newly-developed cardiotonics and show no adverse effect observed with current cardiotonics. Thus, to make TA_{AqE} more effective *in vivo* would improve inotropic therapy for HF, as previously indicated in clinic trials. Although organic extracts of *TA* bark have adverse effects on AVM with no direct inotropic value, their variety of bioactivities (such as antioxidant properties) might still play significant roles in treatments of other disorders described above. The lack of standardized usage and the recent dramatic increase in availability of the crude powder of *TA* bark as an over-the-counter supplement (a nutraceutical) marketed for maintaining a healthy heart raises safety concerns. The selective separation of active constituents of *TA* bark powder and/or the

method of administration could be crucial to the efficacy and safety of *TA* bark used as a naturoceutical and a nutraceutical.

CONFLICT OF INTERESTS

The authors have no conflicting financial interests.

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