INTRODUCTION

Ginger belongs to the Zingiberaceae family with a long history of use as a flavor and a food. Ginger has also been used medicinally for indigestion, vomiting, arthritis, fever, pains, cramps, etc (Ali, Blunden, Tanira, & Nemmar, 2008). It is used as a traditional medicine in South Asia for cardiopathy and hypertension (Ghareib et al., 2015). It has active ingredients that mediate its effects, and ginger extracts are used extensively in beverages, liquors, pickles, and so on (Wohlmuth, Leach, Smith, & Myers, 2005). Gingerols are one of the most common active components (Koo, Ammit, Tran, Duke, & Roufogalis, 2001). Gingerols are thermally sensitive and dehydrated to 6-, 8-, and 10-shogaol at high temperature (Ezzat, Ezzat, Okba, Menze, & Abdel-Naim, 2018; Kou et al., 2018). The major bioactive constituent of ginger is 6-gingerol (6-Gin) (Shukla & Singh, 2007), 8-gingerol, and 10-gingerol account for only a fraction. 6-Gin is the most abundant and pungent gingerol in ginger, and its structural formula was shown in Figure 1. It has diverse and interesting pharmacological effects including antipyretic, anti-inflammatory, anti-angiogenic, anti-cancer, cardio-tonic, and anti-aging effects. It inhibits spontaneous motor activity and prostaglandin biosynthesis (Ajayi, Adedara, ...
External Ca\(^{2+}\) enters the cell by passing through calcium channels. Ca\(^{2+}\) can also be released from internal Ca\(^{2+}\) stores including the endoplasmic reticulum (ER) or sarcoplasmic reticulum (SR) (Berridge, 1993; Clapham, 1995). This area houses protein synthesis and transport to membranous networks. The Ca\(^{2+}\) mainly enters through L-type Ca\(^{2+}\) channels (LTCCs), which are essential to cardiac excitability and excitation–contraction coupling (Ferrier & Howlett, 2001).

In cardiac myocyte, Ca\(^{2+}\) activates the ryanodine receptor (RYR2) to create the “spark” triggering contraction. Contractility is related to intracellular Ca\(^{2+}\) ([Ca\(^{2+}\)\(_{i}\)]) and the sensitivity of myofilaments to Ca\(^{2+}\). There is ample evidence that excess Ca\(^{2+}\) can produce pathological changes in cardiac tissue (Grinwald, 1982; Harding & Poole-Wilson, 1980; Sharma, Saffitz, Lee, Sobel, & Corr, 1983; Shen & Jennings, 1972) such as increased contractility, hypertrophy (Frey & Olson, 2003), and apoptosis (Chen et al., 2005). In addition, the increased contractility of cardiomyocyte can lead to ischemic myocardial diseases (Gao et al., 2014).

L-type Ca\(^{2+}\) channels are related to Ca\(^{2+}\) influx (Liu et al., 2016). Therefore, LTCCs blockers generally protect against myocardial ischemic injury via the inhibition of calcium channels. Previous studies have emphasized the inhibitory effect of verapamil (VER) on myocardial contraction and the protective effect on excess calcium overload (Song et al., 2017). Hence, drugs that can weaken ICa-L are promising for myocardial protection (Song et al., 2016).

Recent reports have detailed the cardio-protective effect of 6-Gin against ischemia-reperfusion injury in rats (Lv et al., 2018); however, the precise mechanism underlying the cellular Ca\(^{2+}\) homeostasis remains poorly understood. The pathogenesis of ischemic disease is related to Ca\(^{2+}\) signaling and cardiac function; thus, it is important to explain the direct action of 6-Gin on Ca\(^{2+}\) homeostasis and contractility in cardiomyocytes as well as the potential character of 6-Gin on treatment of Ca\(^{2+}\)-related cardiac disease. This work systematically characterized the regulatory effects of 6-Gin on L-type Ca\(^{2+}\) current (ICa-L), contractility, and Ca\(^{2+}\) transients in isolated rat ventricular myocytes via the patch-clamp technique and the Ion Optix system. It further explored the possible cellular mechanism of 6-Gin for the management of ischemic cardiac diseases.

### MATERIAL AND METHOD

#### 2.1 Chemicals

6-Gin was purchased from Yuanye Biotechnology Co., Ltd (China). Type II collagenase was bought from Worthington Biochemical Corporation (USA). VER was from Hefeng Pharmaceutical Co., Ltd. (China). Other chemicals and reagents were acquired from Sigma (USA) and were of analytical grade.

#### 2.2 Animals

Male Sprague-Dawley rats (180–220 g) were from the National Experimental Animal Center of Hebei, National Science Council. They were housed in cages at a constant temperature of 25 ± 1°C and supplied with food and water (approval number: 1803064; approval date: March 7, 2018).

#### 2.3 Isolation of ventricular myocytes

Rat ventricular myocytes were isolated via Mitra and Morad (Mitra & Morad, 1985). Briefly, rats were injected with heparin (1,500 IU/kg, i.p.) and anesthetized with sodium urethane (40 mg/kg, i.p.). The hearts were then quickly excised and perfused at 6 ml/min with Ca\(^{2+}\)-free Tyrode solution for 4 min and Ca\(^{2+}\)-free Tyrode’s solution containing CaCl\(_2\) (34 μmol/L) and collagenase (500 mg/L) for 15–20 min via Langendorff equipment. The hearts were then washed with Tyrode’s solution after the digestion. The freshly dissociated cells were stored in Kreb’s buffer solution.

Rats were injected with vasopressin via tail vein (1.5 IU/kg, i.v.) to induce cardiac ischemia (Li et al., 2014). After 10 min of ischemia, the heart was removed as above to isolate normal rat ventricular myocytes.

#### 2.4 Measurement of ICa-L

The Ca\(^{2+}\)-current was recorded via the whole cell patch-clamp10.0 software using an Axon patch 200B amplifier (Axon Instrument, CA). The data were expressed as mean ± SEM (n = 5 cells). **p < 0.01 versus control.

![FIGURE 1](image1.png)

**FIGURE 1** Chemical structure of 6-Gin

![FIGURE 2](image2.png)

**FIGURE 2** Confirmation of ICa-L in cardiomyocytes. (a) Exemplary traces and (b) pooled data showed the representative ICa-L recordings with application of VER (10 μmol/L). Data are expressed as mean ± SEM (n = 5 cells). **p < 0.01 versus control.
USA). The patch electrodes were pulled with a pipette puller (Sutter Instruments, USA). By recording the $I_{\text{Ca-L}}$, the external solution contained (in mmol/L) TEACl 140, MgCl$_2$ 2, CaCl$_2$ 1.8, glucose 10, and HEPES 10, and the pH was adjusted to 7.4 with CsOH. The intracellular pipette solution contained (in mmol/L) CsCl 120, tetra-ethylammonium chloride (TEACl) 20, HEPES 10, Mg-ATP 5, and EGTA 10, and the pH was adjusted to 7.2 with CsOH. Drugs were dissolved in Tyrode’s solution.

**FIGURE 3** Reversible effects of 6-Gin on $I_{\text{Ca-L}}$ in normal ventricular myocytes and ischemic ventricular myocytes. Exemplary traces (a, d), pooled data (b, e), and time course (c, f) of $I_{\text{Ca-L}}$ were measured under the treatment of 6-Gin (300 μmol/L) and during washout. (g) Exemplary traces and (h) time course of $I_{\text{Ca-L}}$ in exposure to 3, 10, 30, 100, 300 μmol/L 6-Gin or 10 μmol/L VER. (i) Concentration-response curves of 6-Gin. Data are expressed as mean ± SEM ($n=6–8$ cells). **p < 0.01, versus control.
2.5 | Measurement of contractility

The contractions of ventricular myocytes were recorded with a video-based edge-detection system (Ion Optix, USA). Cells were placed on the stage of inverted microscope, and contractility was induced at a frequency of 0.5 Hz. Clear myocytes were selected to measure contractions.

2.6 | Measurement of Ca$^{2+}$ transients

Fura-2/AM (1 mmol/L) was fitted with a 340 or 380 nm optical filter and used to study ventricular myocyte [Ca$^{2+}$]$_i$ dynamics and associated myocyte contractile function. Ventricular myocyte was loaded with the fluorescent dye in the dark and measured with a fluorescence system (Ion Optix). The contractility of the myocytes was stimulated with a 0.5 Hz field.

2.7 | Data analysis

The results were presented as mean ± SEM. Comparisons were analyzed via one-way analysis of variance (ANOVA) followed by the Student’s t test using Origin Pro version 9.1 software. $p < 0.05$ was considered to be statistically significant.

3 | RESULTS

3.1 | Confirmation of I$_{Ca-L}$

Verapamil (10 μmol/L) is a specific I$_{Ca-L}$ blocker and nearly completely stopped current flow ($p < 0.01$) (Figure 2), indicating that the L-type channels are functional in cardiomyocytes.

---

**FIGURE 4** Effects of 6-Gin on I-V relationship of I$_{Ca-L}$. Representative I$_{Ca-L}$ (a) and pooled data (b) are shown under the treatment of control (□), 6-Gin at 3 μmol/L (○), 30 μmol/L (△), 30 μmol/L TG (▽) or VER at 10 μmol/L (◇). Data are expressed as means ± SEM ($n = 8$ cells).
3.2 | Effects of 6-Gin on I_{Ca-L} of normal and ischemic ventricular myocytes

Figure 3 shows that 6-Gin (300 μmol/L) significantly reduced the I_{Ca-L} of normal (Figure 3a–c) and ischemic ventricular myocytes (Figure 3d–f) by 58.17 ± 1.04% and 55.22 ± 1.34%, respectively (p < 0.01). Nevertheless, the I_{Ca-L} partially recovered after washing with an external solution, suggesting reversible effects of 6-Gin on the I_{Ca-L} of normal and ischemic ventricular myocytes. The time course of I_{Ca-L} was progressively decreased by increasing doses of 6-Gin (3, 10, 30, 100, and 300 μmol/L) or VER (Figure 3g). The time dependency of the 6-Gin on I_{Ca-L} is shown in Figure 3h. The half-maximal inhibitory concentration (IC_{50}) of 6-Gin was 31.25 μmol/L. The inhibition rates of 6-Gin at 3, 10, 30, 100, and 300 μmol/L were 8.71 ± 0.60%, 16.2 ± 0.8%, 32.67 ± 0.76%, 54.33 ± 1.89%, and 58.17 ± 1.04%, respectively (Figure 3i).

**FIGURE 5** Effects of 6-Gin on steady-state activation and inactivation of I_{Ca-L}. Steady-state activation curves (a) and inactivation curves (b) of I_{Ca-L} are shown under the treatment of control (□), 6-Gin at 3 μmol/L (○), 30 μmol/L (△), 300 μmol/L TG (▽). Data are expressed as means ± SEM (n = 8 cells).

**FIGURE 6** Effects of 6-Gin on contractility in ventricular myocytes. (a) Recordings of contractility on time course in the absence and presence of 6-Gin (300 μmol/L). (b) Exemplary traces recordings of contractility under control conditions and 6-Gin (300 μmol/L). (c) Summary data of contractility before and after treatment of 300 μmol/L 6-Gin. Data are expressed as means ± SEM (n = 6–8 cells). **p < 0.01, versus control.
3.3  Effects of 6-Gin on I-V relationship of \( I_{\text{Ca-L}} \)

Figure 4a shows the current–voltage relationship curves for different concentrations of 6-Gin (3, 30, and 300 \( \mu \text{mol/L} \)) and VER (10 \( \mu \text{mol/L} \)). Figure 5b shows the current generated from −60 to 60 mV. Nevertheless, the I-V relationship and reversal potential of \( I_{\text{Ca-L}} \) did not change significantly.

3.4  Effects of 6-Gin on steady-state activation and inactivation of \( I_{\text{Ca-L}} \)

Figure 5 shows the effects of 6-Gin concentrations (3, 30 and 300 \( \mu \text{mol/L} \)) on steady-state activation and inactivation of \( I_{\text{Ca-L}} \). The \( V_{1/2} \) value for activation of 3, 30, and 300 \( \mu \text{mol/L} \) 6-Gin was \(-6.54 \pm 0.28 \text{ mV}/-6.70 \pm 0.24\), \(-6.66 \pm 0.28 \text{ mV}/-6.78 \pm 0.25\), \(-6.14 \pm 0.29 \text{ mV}/-6.96 \pm 0.26\), and \(-6.44 \pm 0.28 \text{ mV}/-6.71 \pm 0.25\), respectively. The \( V_{1/2} \) value for inactivation of 0, 3, 30, and 300 \( \mu \text{mol/L} \) 6-Gin was \(-17.78 \pm 1.17 \text{ mV}/7.44 \pm 0.98\), \(-18.80 \pm 1.22 \text{ mV}/8.01 \pm 1.06\), and \(-17.81 \pm 1.06 \text{ mV}/7.08 \pm 0.99\), respectively.

3.5  Effects of 6-Gin on \( \text{Ca}^{2+} \) contractility

Changes in the 6-Gin on myocyte shortening are shown in Figure 6. 6-Gin (300 \( \mu \text{mol/L} \)) significantly inhibited myocyte shortening by 48.87 \( \pm \) 5.44\%. The contractility recovered partially after washing out.

3.6  Effects of 6-Gin on transients

The changes of the 6-Gin on \( \text{Ca}^{2+} \) transients are shown in Figure 7. The 6-Gin (300 \( \mu \text{mol/L} \)) significantly inhibited the \( \text{Ca}^{2+} \) transients by 42.5 \( \pm \) 9.79\%. The transients partially recovered partially after washing.
### 3.7 Effects of 6-Gin on contractile and relaxation function

The time to 50% of the peak (Tp) describes the speed of myocyte shortening or Ca$^{2+}$ elevation, the time to 50% of the baseline (Tr) is a parameter of cellular relaxation or Ca$^{2+}$ reuptake. 6-Gin at 300 μmol/L decreased the Tp and Tr (p < 0.05) (Figure 8). Also, 6-Gin at 300 μmol/L decreased the maximum velocity of contraction-relaxation (∆dL/dt) (p < 0.05 or p < 0.01) (Figure 8).

### 4 DISCUSSION

Ginger is a food and traditional medicine used for centuries. 6-Gin is a major active ingredient in ginger and possesses a variety of interesting pharmacological effects. However, the molecular mechanisms of 6-Gin on cardiac protection have yet to been reported to the best of our knowledge. This work reports intracellular $I_{\text{Ca-L}}$, contractility, and Ca$^{2+}$ transients in isolated rat ventricular myocytes to detail the molecular mechanisms of 6-Gin underlying its cardio-protective effects.

The isolated myocyte model provides a specific opportunity to observe physiological adaptations of cardiac function. Calcium is a ubiquitous signal that is responsible for a broad range of cell activities (Berridge, Bootman, & Roderick, 2003; Clapham, 2007). Ca$^{2+}$ is rapidly removed from the cytoplasm via pumps (Pozzan, Rizzuto, Volpe, & Meldolesi, 1994) and exchangers (Blaustein & Lederer, 1999), for example, the Ca$^{2+}$-ATPase pumps and Na$^+$/Ca$^{2+}$ exchangers. This is then reported via signals. Internal calcium stores are held in the ER or SR membrane systems of muscle cells (Berridge, Lipp, & Bootman, 2000). Calcium ion release is then controlled by various channels including the inositol-1, 4, 5-trisphosphate receptor (InsP3R) and ryanodine receptor (RYR) families (Berridge, 1993; Clapham, 1995). Ca$^{2+}$ passing through the calcium channel is important for cardiac electrical activity and the excitation-contraction coupling of cardiac muscle. The principal activator of these channels is Ca$^{2+}$ itself.

There is a depolarizing current when calcium ions flow into cells and calcium current flow after the calcium channels open. Other mechanisms for influx of Ca$^{2+}$, for example, Na$^+$/Ca$^{2+}$ exchange, can also lead to depolarization and increase cytosolic calcium. A trace of calcium entry from the calcium channel causes more release of Ca$^{2+}$ from the SR, that is, Ca$^{2+}$-induced Ca$^{2+}$ release (CICR). The CIRC hypothesis (Fabiato, 1983) states that the release of calcium from the SR is not only promoted by a rapid elevation of the Ca$^{2+}$ activity [Ca$^{2+}$]$/\text{dt}$ but also inactivated by a moderate or prolonged elevation of [Ca$^{2+}$].

Myocardial contractility was triggered mainly by cytosolic calcium ions entry through calcium channels (Blaustein & Lederer, 1999), which can mediate excitation-contraction coupling. Cardiac muscle is activated by the depolarization-dependent Ca$^{2+}$ current and the release of calcium from SR that elevates myoplasmic calcium and allows the myofilaments to contract (Atwater, Rojas, & Vergara, 1974).

Alternatively, Ca$^{2+}$ stores can help generate Ca$^{2+}$ transients. This sequence of biochemical events is triggered by a Ca$^{2+}$ transient, beginning with Ca$^{2+}$ binding to troponin C. Cell shortening resulting from a rise in [Ca$^{2+}$], is also activated following repolarization from positive potentials. Measurements of cell shortening, especially of [Ca$^{2+}$], show that the activation process closely mirrors both the time course and the voltage dependence of the Ca$^{2+}$ current. The Ca$^{2+}$ current in cardiac cells does not act primarily as a direct activator of the contractile filaments but that it acts indirectly by releasing Ca$^{2+}$ from the SR. A wave of depolarization opens the T-type channels first followed by LTCCs. Calcium antagonists (CCAs) act by changing the mode of channel opening from long-duration to shorts. Thus, CCAs lower the rate at which Ca$^{2+}$ enters via the LTCCs. VER is a CCA and interfered with the calcium-dependent processes.

Our data suggest that 6-Gin reduces the $I_{\text{Ca-L}}$ (Figure 3) in a concentration-dependent manner with an IC$_{50}$ of 31.25 μmol/L in cardiomyocytes. Figure 4 shows that the I-V relationship or the reverse potential of $I_{\text{Ca-L}}$ did not change. Furthermore, the contractility and Ca$^{2+}$ transients were inhibited by 6-Gin (Figures 6 and 7). Also, 6-Gin at 300 μmol/L reduced the $I_{\text{Ca-L}}$ in ischemic ventricular myocytes (Figure 3d-f). Ischemia causes membrane depolarization, calcium influx in ischemic cells is increased. Elevated intracellular calcium accelerates the activity of several ATP-consuming enzymes, which further depletes already marginal cellular energy stores, making the heart even more susceptible to ischemic damage (Undrovinas & Matlasev, 1998). Our data suggest that 6-Gin could inhibit the increase in [Ca$^{2+}$], via decreasing the extracellular Ca$^{2+}$ influx. Excitation-contraction coupling in all cardiac cells requires Ca$^{2+}$ influx, therefore the inhibitory effects of 6-Gin on contractility may through the reduction on Ca$^{2+}$ influx. Collectively, these results detail the cardio-protective effects of 6-Gin on rat ventricular myocytes as well as and its cellular mechanism.

### 5 CONCLUSIONS

These results clearly indicate that 6-Gin inhibits the Ca$^{2+}$ transients and contractility of cardiomyocytes. This is mainly via inhibition of the L-type Ca$^{2+}$. This restricts Ca$^{2+}$ flow into the ventricle myocytes and decreases [Ca$^{2+}$]. The findings of the present study provide new perspectives for further research on pharmacology of 6-Gin as a possible candidate for the treatment of cardiovascular diseases.

### ACKNOWLEDGMENT

This work was supported by the Foundation of Project of Graduate Students Project of Hebei Province (No. CXZZBS2018152) and the Training Project of Students Innovation and Entrepreneurship of Hebei Province (No. 201714432021).

### CONFLICT OF INTEREST

The authors declare no conflict of interest.
ETHICAL STATEMENT

All animal care and experimental protocols were ethically reviewed and approved by the Ethics Committee of Hebei University of Chinese Medicine.

ORCID

Li Chu https://orcid.org/0000-0003-4555-8721

REFERENCES

Ajayi, B. O., Adedara, I. A., & Farombi, E. O. (2018). Protective mechanisms of 6-gingerol in dextran sulfate sodium-induced chronic ulcerative colitis in mice. Human & Experimental Toxicology, 37(10), 1054–1068. https://doi.org/10.1177/0960327117751235

Ali, B. H., Blunden, G., Tanira, M. O., & Nemmar, A. (2008). Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): A review of recent research. Food and Chemical Toxicology, 46(2), 409–420. https://doi.org/10.1016/j.fct.2007.09.085

Atwater, I., Rojas, E., & Vergara, J. (1974). Calcium influxes and tension development in perfused single barnacle muscle fibres under membrane potential control. The Journal of Physiology, 243(2), 523–551. https://doi.org/10.1113/jphysiol.1974.sp010765

Berridge, M. J. (1993). Inositol trisphosphate and calcium signalling. Nature, 361(6410), 315–325. https://doi.org/10.1038/361315a0

Berridge, M. J., Bootman, M. D., & Roderick, H. L. (2003). Calcium signalling: Dynamics, homeostasis and remodelling. Nature Reviews Molecular Cell Biology, 4(7), 517–529. https://doi.org/10.1038/nrm1155

Berridge, M. J., Lipp, P., & Bootman, M. D. (2000). The versatility and universality of calcium signalling. Nature Reviews Molecular Cell Biology, 1(1), 11–21. https://doi.org/10.1038/35036035

Blaustein, M. P., & Lederer, W. J. (1999). Sodium/calcium exchange: Its physiological implications. Physiological Reviews, 79(3), 763–854. https://doi.org/10.1152/physrev.1999.79.3.763

Chen, X., Zhang, X., Kubo, H., Harris, D. M., Mills, G. D., Moyer, J., & Heuer, S. R. (2005). Ca2+ influx-induced sarcoplasmic reticulum Ca2+ overload causes mitochondrial-dependent apoptosis in ventricular myocytes. Circulation Research, 97(10), 1009–1017. https://doi.org/10.1161/01.RES.0000189270.72915.D1

Clapham, D. E. (1995). Calcium signaling. Cell, 80(2), 259–268. https://doi.org/10.1016/0092-8674(95)90408-5

Clapham, D. E. (2007). Calcium signaling. Cell, 131(6), 1047–1058. https://doi.org/10.1016/j.cell.2007.11.028

Dugasani, S., Pichika, M. R., Nadarajah, V. D., Balijepalli, M. K., Tandra, S., & Korlakunta, J. N. (2010). Comparative antioxidant and anti-inflammatory properties of ginger (Zingiber officinale Roscoe) in Caenorhabditis elegans. Biomolecules & Therapeutics (Seoul), 26, 568–575. https://doi.org/10.4062/biomolther.2017.215

Lee, H. S., Seo, E. Y., Kang, N. E., & Kim, W. K. (2008). [6]-Gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. The Journal of Nutritional Biochemistry, 19(5), 313–319. https://doi.org/10.1016/j.jnutbio.2007.05.008

Li, P., Song, Q., Liu, T., Wu, Z., Chu, X., Zhang, X., & Chu, L. (2014). Inhibitory effect of cinobufagin on L-type Ca2+ currents, contractility, and Ca2+ homeostasis of isolated adult rat ventricular myocytes. Scientific World Journal, 2014, 496705. https://doi.org/10.1101/2014/496705

Liu, T., Chu, X., Wang, H., Zhang, X., Zhang, Y., Guo, H., & Zhang, J. (2016). Crocin, a carotenoid component of Crocus sativus, exerts inhibitory effects on L-type Ca2+ current, Ca2+ transient, and contractility in rat ventricular myocytes. Canadian Journal of Physiology and Pharmacology, 94(3), 302–308. https://doi.org/10.1139/cjpp-2015-0214

Frey, N., & Olson, E. N. (2003). Cardiac hypertrophy: The good, the bad, and the ugly. Annual Review of Physiology, 65, 45–79. https://doi.org/10.1146/annurev.physiol.65.092101.142243

Gao, Y., Zhang, K., Zhu, F., Wu, Z., Chu, X., Zhang, X., & Chu, L. (2014). Salvia miltiorrhiza (Danshen) inhibits L-type calcium current and attenuates calcium transient and contractility in rat ventricular myocytes. Journal of Ethnopharmacology, 158 Pt A, 397–403. https://doi.org/10.1016/j.jep.2014.10.049

Ghareibi, S. A., El-Bassossy, H. M., Elberry, A. A., Azhar, A., Watson, M. L., & Banjar, Z. M. (2015). 6-Gingerol alleviates exaggerated vasoconstriction in diabetic rat aorta through direct vasodilation and nitric oxide generation. Drug Design, Development and Therapy, 9, 6019–6026. https://doi.org/10.2147/DDDT.S94346

Grinwald, P. M. (1982). Calcium uptake during post-ischemic reperfusion in the isolated rat heart: Influence of extracellular sodium. Journal of Molecular and Cellular Cardiology, 14(6), 359–365. https://doi.org/10.1016/0222-2828(82)90251-6

Harding, D. P., & Poole-Wilson, P. A. (1980). Calcium exchange in rabbit myocardium during and after hypoxia: Effect of temperature and substrate. Cardiovascular Research, 14(8), 435–445. https://doi.org/10.1093/cvr/14.8.435

Jolad, S. D., Lantz, R. C., Chen, G. J., Bates, R. B., & Timmermann, B. N. (2005). Commercially processed dry ginger (Zingiber officinale): Composition and effects on LPS-stimulated PGE2 production. Phytochemistry, 66(13), 1614–1635. https://doi.org/10.1016/j.phytochem.2005.07.007

Kim, E. C., Min, J. K., Kim, T. Y., Lee, S. J., Yang, H. O., Han, S., & Kwon, Y. G. (2005). [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. Biochemical and Biophysical Research Communications, 335(2), 300–308. https://doi.org/10.1016/j.bbrc.2005.07.076

Kuoch, F., Iwakami, S., Shibuya, M., Hanaoka, F., & Sankawa, U. (1992). Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chemical & Pharmaceutical Bulletin (Tokyo), 40(2), 387–391. https://doi.org/10.1248/cpb.40.387

Koo, K. L., Ammit, A. J., Tran, V. H., Duke, C. C., & Roufogalis, B. D. (2001). Gingerols and related analogues inhibit arachidonic acid-induced human platelet serotonin release and aggregation. Thrombosis Research, 103(5), 387–397. https://doi.org/10.1016/S0049-3848(01)00338-3

Kou, X., Ke, Y., Wang, X., Rahman, M. R. T., Xie, Y., Chen, S., & Wang, H. (2018). Simultaneous extraction of hydrophobic and hydrophilic bioactive compounds from ginger (Zingiber officinale Roscoe). Food Chemistry, 257, 223–229. https://doi.org/10.1016/j.foodchem.2018.02.125

Lee, E. B., Kim, J. H., An, C. W., Kim, Y. J., Noh, Y. J., Kim, S. J., & Kim, D. K. (2018). Longevity and stress resistant property of 6-Gingerol from Zingiber officinale Roscoe in Caenorhabditis elegans. Biomolecules & Therapeutics (Seoul), 26, 568–575. https://doi.org/10.4062/biomolther.2017.215

Lee, H. S., Park, S., Kang, N. E., & Kim, W. K. (2008). [6]-Gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. The Journal of Nutritional Biochemistry, 19(5), 313–319. https://doi.org/10.1016/j.jnutbio.2007.05.008

Liu, Y. G. (2005). [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. American Journal of Physiology-Cell Physiology, 280(5), H1928–H1944. https://doi.org/10.1152/ajpheart.2001.280.5.H1928
Lv, X., Xu, T., Wu, Q., Zhou, Y., Huang, G., Xu, Y., & Zhong, G. (2018). 6-Gingerol activates PI3K/Akt and inhibits apoptosis to attenuate myocardial ischemia/reperfusion injury. Evidence-Based Complementary and Alternative Medicine, 2018, 9024034. https://doi.org/10.1155/2018/9024034

Mitra, R., & Morad, M. (1985). A uniform enzymatic method for dissociation of myocytes from hearts and stomachs of vertebrates. American Journal of Physiology, 249(5 Pt 2), H1056–H1060. https://doi.org/10.1152/ajphysiol.1985.249.5

Pozzan, T., Rizzuto, R., Volpe, P., & Meldolesi, J. (1994). Molecular and cellular physiology of intracellular calcium stores. Physiological Reviews, 74(3), 595–636. https://doi.org/10.1152/physrev

Sharma, A. D., Saffitz, J. E., Lee, B. I., Sobel, B. E., & Corr, P. B. (1983). Alpha adrenergic-mediated accumulation of calcium in reperfused myocardium. Journal of Clinical Investigation, 72(3), 802–818. https://doi.org/10.1172/JCI111051

Shen, A. C., & Jennings, R. B. (1972). Myocardial calcium and magnesium in acute ischemic injury. The American Journal of Pathology, 67(3), 417–440.

Shukla, Y., & Singh, M. (2007). Cancer preventive properties of ginger: A brief review. Food and Chemical Toxicology, 45(5), 683–690. https://doi.org/10.1016/j.fct.2006.11.002

Song, Q., Chu, X., Zhang, X., Bao, Y., Zhang, Y., Guo, H., & Chu, L. (2016). Mechanisms underlying the cardioprotective effect of Salvianolic acid A against isoproterenol-induced myocardial ischemia injury in rats: Possible involvement of L-type calcium channels and myocardial contractility. Journal of Ethnopharmacology, 189, 157–164. https://doi.org/10.1016/j.ejep.2016.05.038

Song, T., Chu, X., Zhang, X., Song, Q., Zhang, Y., Zhang, Y., & Chu, L. (2017). Bufalin, a bufanolid steroid from the parotoid glands of the Chinese toad, inhibits L-type Ca2+ channels and contractility in rat ventricular myocytes. Fundamental & Clinical Pharmacology, 31(3), 340–346. https://doi.org/10.1111/fcp.12265

Tahir, A. A., Sani, N. F., Murad, N. A., Makpol, S., Ngah, W. Z., & Yusof, Y. A. (2015). Combined ginger extract & Gelam honey modulate Ras/ERK and PI3K/AKT pathway genes in colon cancer HT29 cells. Journal of Nutrition, 14, 31. https://doi.org/10.1186/s12937-015-0015-2

Undrovinas, A. I., & Maltsev, V. A. (1998). Cytochalasin D alters kinetics of Ca2+ transient in rat ventricular cardiomyocytes: An effect of altered actin cytoskeleton? Journal of Molecular and Cellular Cardiology, 30(8), 1665–1670. https://doi.org/10.1006/jmcc.1998.0715

Wohlmuth, H., Leach, D. N., Smith, M. K., & Myers, S. P. (2005). Gingerol content of diploid and tetraploid clones of ginger (Zingiber officinale Roscoe). Journal of Agricultural and Food Chemistry, 53(14), 5772–5778. https://doi.org/10.1021/jf050435b

How to cite this article: Han X, Zhang Y, Liang Y, et al. 6-Gingerol, an active pungent component of ginger, inhibits L-type Ca2+ current, contractility, and Ca2+ transients in isolated rat ventricular myocytes. Food Sci Nutr. 2019;7:1344–1352. https://doi.org/10.1002/fsn3.968