Global Journals LaTeX JournalKaleidoscope™
Artificial Intelligence formulated this projection for compatibility purposes from the original article published at Global Journals. However, this technology is currently in beta. *Therefore, kindly ignore odd layouts, missed formulae, text, tables, or figures.*

# Cardiac Effects of (?)-Epigallocatechin on Isolated Rat Hearts

Loipa Galan Martinez

*Received: 6 December 2017 Accepted: 31 December 2017 Published: 15 January 2018*

## Abstract

(?)- Epigallocatechin is a flavonoid found in many plants, especially in tea. The consumption of flavonoid- rich foods tends to reduce the risk of cardiovascular diseases and this has been attributed to nonspecific activities such as antioxidant, anti- atherosclerotic and anti-inflammatory properties. However, little is known about direct actions of (?)-epigallocatechin on cardiac muscle. The aim of the present investigation was to evaluate the effects of (?)- epigallocatechin on electrical and contractile activities of isolated rat hearts. Surface electrogram and force of contraction were recorded in isolated rat hearts in control and in increasing concentrations of (?)- epigallocatechin from 0.001 to 3 ?M. (?)-Epigallocatechin tended to prolong the QRS interval, but this effect is significant only at the highest concentration studied (3 ?M). QTc was not significantly affected by the flavonoid. The effects of this flavonoid on RR interval were mild and statistically significant since 0.03 ?M. (?)- Epigallocatechin produced a negative inotropic effect in isolated rat hearts with an IC50 of 0.03 ?M. This flavonoid has direct actions on rat cardiac muscle.

***Index terms—***

## 1 Introduction

atechins are one group of natural polyphenols found in many plants, especially in green tea (leaves of Camellia sinensis) (1)(2)(3). The four main catechin derivatives mainly find in green tea include the isomers epicatechin, (-)-epicatechingallate (ECG), (-)epigallocatechin (EGC), and (-)-epigallocatechin gallate (EGCG) (3). EGC is a flavan-3-ol containing a benzopyran-3,5,7-triol linked to a 3,4,5-hydroxyphenyl moiety. Thus, EGC is considered to be a flavonoid lipid molecule (4) (Figure 1).

The health benefits associated with the consumption of green tea are due to the activity of EGCG and EGC which are both present at higher amounts (5). EGC has many beneficial cardiovascular properties. However, most of these effects are nonspecific, such as antioxidant (1-2, 6-7), antiinflammatory (1,5,7), and antiatherogenic activities (8).

Another remarkable property attributed to tea catechins is the cholesterol-lowering action, involving the upregulation of the LDL receptor, the reduction of cholesterol absorption, and the modulation of both synthetic and metabolic pathways (see for review 9).

## 2 Further

investigations of the cellular mechanisms are needed to investigate the cardiovascular effects of this flavonoid. Other flavonoids such as naringenin, quercetin, and genistein have direct actions on rat cardiac and vascular smooth muscles (10). The present work evaluated the possible direct effects of EGC on electrical and contractile activities of rat isolated rat hearts.

# 3 II.

# 4 Materials and Methods

# 5 a) Animals

Male adult (7-8 weeks) Wistar rats were brought from the National Center for Laboratory Animal Reproduction (CENPALAB; La Habana). Before the experiments, animals were for seven days adapted to laboratory conditions (controlled temperature 25 ± 2°C, relative humidity 60 ± 10%, and 12 h light/dark cycles). Tap water and standard diet for rodents supplied by CENPALAB were freely provided. All procedures fulfilled with the European Commission for the use and care of laboratory animals. The Committee for Animal Care in Research of the Center (No. 08-2012, folio 73, book 01, 2012) approved the present study.

# 6 b) Isolated hearts

As previously reported (11), under pentobarbital anesthesia rat hearts were removed and placed in cold Tyrode (see below). Hearts were carefully dissected, mounted on a Langendorff column and perfused at constant flow (10 mL/min) with a Tyrode solution of the following composition (mmol/L): 140 NaCl, 2.5 KCl, 0.5 MgCl2, 2 CaCl2, 10 Tris-hydroxymethyl amino methane, 10 Glucose (pH =7.4, gassed with O2; T = 35°C). On the ventricular epicardium was placed a bipolar platinum recording electrode to record the surface electrocardiogram. Another bipolar platinum electrode was placed near the atrioventricular ring and was connected to an electronic stimulator. To record the force of contraction (FC), the cardiac apex was fixed to a force-displacement transducer with a surgical 6-0 silk thread. Surface electrocardiogram and FC values were recorded at the heart rate and a fixed stimulus rate (500ms RR interval).

# 7 c) ECG and chemicals

Stock solutions of ECG were prepared in ethanol, and diluted in the bathing solution on the day of the experiment. All chemicals were from Sigma Aldrich. Means and standard errors of means expressed the results. Student's t-test evaluated the statistical significance for paired samples, previously checked that the data complied with the premise of normality. Differences were considered statistically significant for $p < 0.05$. The graphics and the statistical processing were done using the software OriginPro 8 SRO v8.0724 (MA, USA).

# 8 Results and Discussion

The corrected QT (QTc) interval of the surface electrocardiogram (QTc = QT/?RR) was not significantly affected by EGC at concentrations from 0.001 to 3 µM (Table 1).

These results should be possible because this flavonoid could exert multiple actions on different ionic channels, resulting in an apparent absence of effects on QT interval of the cardiac surface electrogram. As a fat, catechins modulate several ionic channels (12)(13)(14)(15).

EGC showed a tendency to increase QRS interval of the surface electrocardiogram, but only at the highest concentration studied (3 µM) this increase was statistically significant ($p < 0.05$) (Table 1). EGCG, catechin structurally related to EGC, at 30 µM prolonged QRS interval in isolated spontaneously beating guinea pig hearts (15). The QRS wave is dependent on sodium channel activity, Kang et al., 2010 showed that EGCG inhibited the cloned human cardiac sodium channel Nav1.5 in a dose-dependent manner with 45.7 ± 6.9 % inhibition at 100 µM (15). EGCG reduced the amplitude of voltage-gated sodium channel current in a concentration-depend manner in the range of 0.1 -400 µM in rat hippocampal CA1 neurons (13).

On the other hand, EGC prolonged the RR interval of surface electrocardiogram and this increase was statistically significant ($p < 0.05$) since 0.03 µM (Table 1).

EGCG at 30 µM did not affect heart rate of guinea pig hearts (15). Green tea extract used with dietary supplements did not alter heart rate (16). Other study concluded that Camellia sinensis has effect on heart rate, it decreases the heart rate in normotensive female individuals and increases the heart rate in the normotensive male individuals (17). In the present study in the concentration range from 0.001 to 3 µM, EGC significantly decreased the force of contraction (FC) in isolated rat hearts (Figure 2); concentrations as low as 0.001 µM of EGC decreased FC by 28.4 ± 8.7 %. Since EGC slightly changed RR interval, hearts were paced at 500-ms stimulus interval (over the spontaneous RR interval under control condition; 531.05 ± 18.9 ms) to avoid any frequencydependent change in FC. Experimental data were fitted to a Hill function (Figure 2), and the estimated IC50 for inhibition of contraction was 0.03 ± 7.8 µM for EGC. The action of EGC on FC was not reversible upon washout with the normal Tyrode solution. Although further studies are needed to see if EGC has any direct effect on calcium channels, the decrease of force of cardiac contraction by EGC should be at least partly due to an inhibition of calcium channels.

The L-type calcium channel was inhibited by 20.8% at 30 µM by EGCG, reached a maximum of 37.1 ± 4.2% at a concentration of 100 µM (15). Tadano et al., 2010 reported that EGC had no significant effects on cardiac myofilament Ca2+-sensitivity. However ECG and EGCG were found to decrease Ca2+ sensitivity, they were Ca2+ desensitizers acting through binding to cardiac troponin C (18).

At concentrations within the same range at which similar flavonoid EGCG have vasorelaxant effects related to the inhibition of Ca2+ influx in smooth muscle cells (19), in the present results, EGC concentrationdependently relaxed with almost equal effectiveness the contraction of rat hearts.

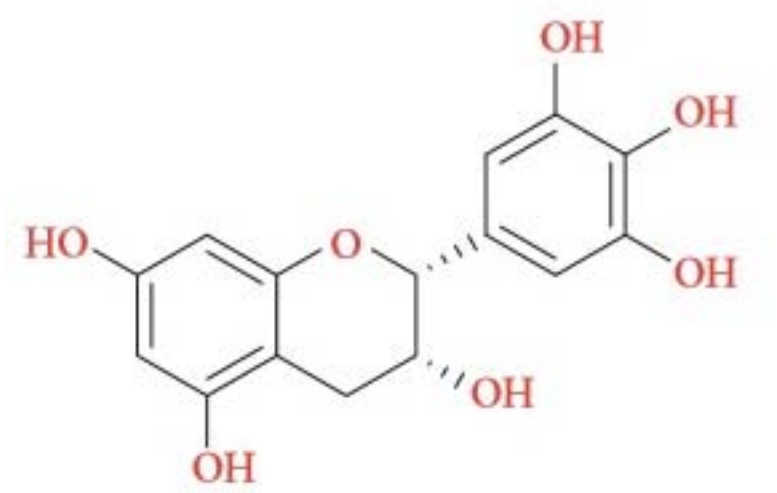
On the strength of these results, the physiological relevance of the decrease of force of cardiac contraction by EGC can be asserted by considering the data available on the in vivo level of the related catechin EGCG ([EGCG] = 0.3-7.5 µM in the blood of green tea consumers (20).

Three-month supplementation with green tea capsules decreased systolic (SBP) and diastolic blood pressure (DBP) by four mmHg in obese hypertensive (21) but not obese subjects (22). A recent metaanalysis which included eleven trials concluded that short-term consumption (>6 months) of black tea could decrease SBP and DBP by 1-2 mmHg and green tea by three mmHg (23).

IV.

# 9 Conclusions

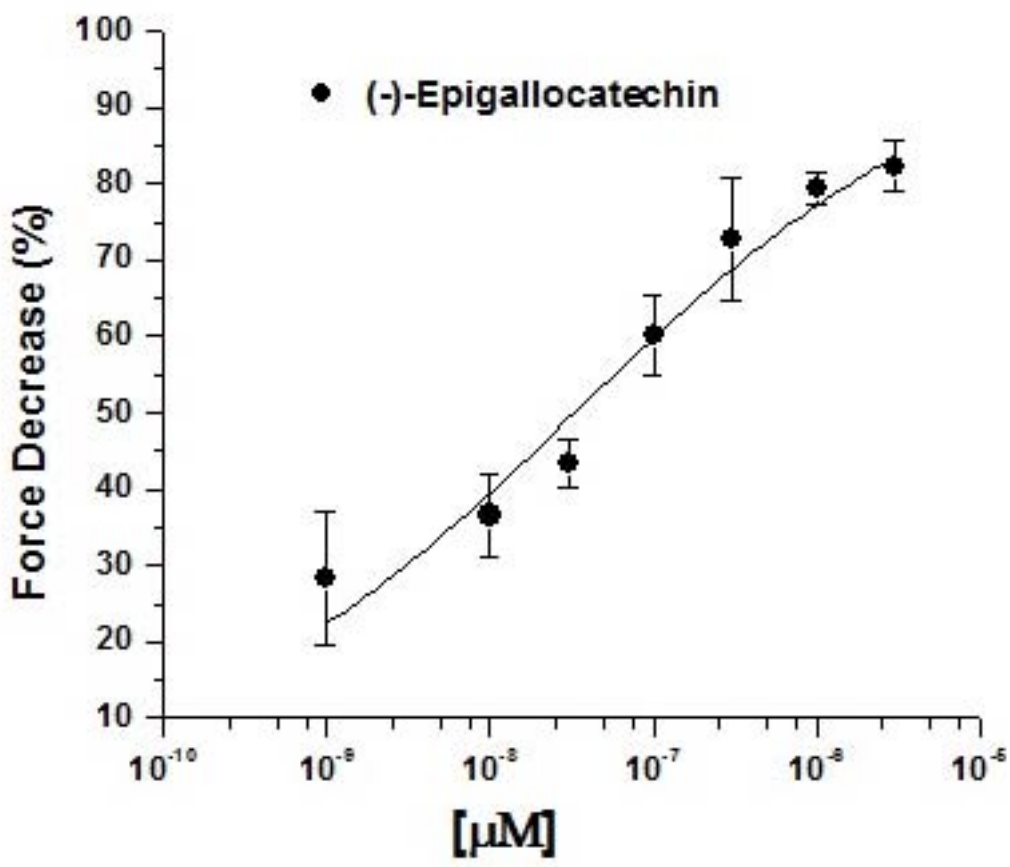
The present study revealed that EGC has direct cardiac effects. The results presented here con firm the role of tea catechin EGC, as a precursor for the development of novel drugs for the treatment of cardiovascular disorders.




**1**

Figure 1: Figure 1 :

[1]




**2**

Figure 2: Figure 2 :

**1**

| | QTc (mseg) | p | QRS (mseg) | p | RR (mseg) | p |
|---|---|---|---|---|---|---|
| Control | 88.55 ± 7.2 | | 11.80 ± 0.7 | | 531.05 ± 18.9 | |
| EGC 0.001 ?M | 84.20 ± 4.7 | 0.71 | 12.50 ± 0.1 | 0.36 | 541.48 ± 20.2 | 0.72 |
| EGC 0.003 ?M | 98.01 ± 7.1 | 0.46 | 12.65 ± 0.2 | 0.28 | 552.20 ± 20.1 | 0.47 |
| EGC 0.01 ?M | 84.20 ± 11.2 | 0.74 | 12.85 ± 0.3 | 0.22 | 605.63 ± 41.4 | 0.15 |
| EGC 0.03 ?M | 98.70 ± 0.3 | 0.39 | 13.20 ± 0.3 | 0.12 | 639.13 ± 37.5 * | 0.04 |
| EGC 0.1 ?M | 90.02 ± 10.0 | 0.91 | 13.30 ± 0.2 | 0.09 | 669.50 ± 30.1 * | 0.008 |
| EGC 0.3 ?M | 86.50 ± 5.5 | 0.86 | 13.40 ± 0.3 | 0.08 | 676.50 ± 33.4 * | 0.009 |
| EGC 1 ?M | 87.40 ± 6.7 | 0.91 | 13.60 ± 0.3 | 0.05 | 682.78 ± 33.4 * | 0.008 |
| EGC 3 ?M | 95.10 ± 13.1 | 0.65 | 13.78 ± 0.3 * | 0.04 | 678.05 ± 34.8 * | 0.009 |
| $p < 0.05$ vs. Control | | | | | | |

Figure 3: Table 1 :

[Ullmann et al. ()] 'A single ascending dose study of epigallocatechin gallate in healthy volunteers'. U Ullmann , J Haller , J P Decourt , N Girault , J Girault , A S Richard-Caudron , B Pineau , P Weber . *J. Int. Med. Res* 2003. 31 p. .

[Hertog and Feskens ()] 'Antioxidant flavonols and coronary heart disease risk'. M G Hertog , E J Feskens , KromhoutD . *Lancet* 1997. 349 p. 699.

[Chacko et al. ()] *Beneficial effects of green tea: A literature review*, S M Chacko , P T Thambi , R Kuttan , I Nishigaki . 2010. p. 13.

[Tadano et al. ()] 'Biological actions of green tea catechins on cardiac troponin C'. N Tadano , C K Du , F Yumoto , S Morimoto , M Ohta , M F Xie , K Nagata , D Y Zhan , Q W Lu , Y Miwa , F Takahashi-Yanaga , M Tanokura , I Ohtsuk , T Sasaguri . *Br. J. Pharmacol* 2010. 161 p. .

[Galán et al. ()] 'Characteristics of Ca2+ channel blockade by oxodipine and elgodipine in rat cardiomyocytes'. L Galán , K Talavera , G Vassort , J L Alvarez . *Eur. J. Pharmacol* 1998. 357 p. .

[Chyu et al. ()] 'Differential effects of green tea-derived catechin on developing versus established atherosclerosis in apolipoprotein E-null mice'. K Y Chyu , S M Babbidge , X Zhao , R Dandillaya , A G Rietveld , J Yano , P Dimayuga , B Cercek , P K Shah . *Circulation* 2004. 109 p. .

[Galán-Martínez et al. ()] 'Direct actions of the flavonoids naringenin, quercetin and genistein on rat cardiac and vascular muscles'. L Galán-Martínez , I Herrera-Estrada , A Fleites-Vázquez . *J. Pharm. Pharmacogn. Res* 2018. 6 (3) p. .

[Seifert et al. ()] 'Effect of acute administration of an herbal preparation on blood pressure and heart rate in humans'. J G Seifert , A Nelson , J Devonish , E R Burke , S J Stohs . *Int. J. Med. Sci* 2011. 8 p. .

[Ullah et al. ()] 'Effect of Green tea on Heart Rate of Male and Female'. N Ullah , M A Khan , A H Asif , A A Shah , S Anwar , H Wahid , A Nazir . *Asian J. Med Sci* 2011. 3 (4) p. .

[Kim et al. ()] 'Effects of (-)-epigallocatechin-3-gallate on Na(+) currents in dorsal root ganglion neurons'. T H Kim , J M Lim , S S Kim , J Kim , M Park , J H Song . *Eur. J. Pharmacol* 2009. 604 p. .

[Deng et al. ()] 'Effects of EGCG on voltage-gated sodium channels in primary cultures of rat hippocampal CA1 neurons'. H M Deng , S T Yin , D Yan , M L Tang , C C Li , J T Chen , M Wang , D Y Ruan . *Toxicology* 2008. 252 p. .

[Suliburska et al. ()] 'Effects of green tea supplementation on elements, total antioxidants, lipids, and glucose values in the serum of obese patients'. J Suliburska , P Bogdanski , M Szulinska , M Stepien , D Pupek-Musialik , A Jablecka . *Biol. Trace elem Res* 2012. 149 p. .

[Xuan ()] 'Epigallocatechin gallate exerts protective effects against myocardial ischemia/reperfusion injury through the PI3K/Akt pathway-mediated inhibition of apoptosis and the restoration of the autophagic flux'. F Xuan , Jian , J . *Int. J. Mol. Med* 2016. 38 p. .

[Aneja et al. ()] 'Epigallocatechin, a green tea polyphenol, attenuates myocardial ischemia reperfusion injury in rats'. R Aneja , P W Hake , T J Burroughs , A G Denenberg , H R Wong , A B Zingarelli . *Molecular Medicine* 2004. 10 (1-6) p. .

[Mozzicafreddo et al. ()] 'Epigallocatechin-3-gallate potently inhibits the in vitro activity of hydroxy-3-methyl-glutaryl-CoA reductase'. M Mozzicafreddo , M Spina , M Tran , C N Falconi , M Eleuteri , AM , Angeletti , M . *J. Lipid. Res* 2010. 52 p. .

[Hartley et al. ()] 'Green and black tea for the primary prevention of cardiovascular disease'. L Hartley , N Flowers , J Holmes , A Clarke , S Stranges , L Hooper , Rees , K . *Cochrane Database Syst. Rev* 2013. 6 p. D009934.

[Graham ()] 'Green tea composition, consumption, and polyphenol chemistry'. H N Graham . *Preventive Medicine* 1992. 21 (3) p. .

[Bogdanski et al. ()] 'Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients'. P Bogdanski , J Suliburska , M Szulinska , M Stepien , D Pupek-Musialik , A Jablecka . *Nutr. Res* 2012. 32 p. .

[Kelemen et al. ()] 'Green tea flavonoid epigallocatechin-3-gallate (EGCG) inhibits cardiac hERG potassium channels'. K Kelemen , C Kiesecker , E Zitron , A Bauer , E Scholz , R Bloehs , D Thomas , J Greten , A Remppis , W Schoels , H A Katus , C A Karle . *Biochem. Biophys. Res. Commun* 2007. 364 p. .

[Tipoe et al. ()] 'Green tea polyphenols as an antioxidant and anti-inflammatory agent for cardiovascular protection'. G L Tipoe , T M Leung , M W Hung , M L Fung . *Cardiovascular and Hematological Disorders-Drug Targets*, 2007. 7 p. .

[Kang et al. ()] 'In vitro electrocardiographic and cardiac ion cannel effects of (-)-epigallocatechin-3-gallate, the main catechin of green tea'. J Kang , H Cheng , J Ji , J Incardona , D Rampe . *J. Pharmacol. Exp. Ther* 2010. 334 p. .

166 [Fechtner et al. ()] 'Molecular insights into the differences in anti-inflammatory activities of green tea catechins
167 on IL-1? signaling in rheumatoid arthritis synovial fibroblasts'. S Fechtner , A Singh , M Chourasia , Ahmed
168 , S . *Toxicol. Appl. Pharmacol* 2017. 329 p. .

169 [Record Name: (-)-Epigallocatechin (2018)] *Record Name: (-)-Epigallocatechin*, `http://www.hmdb.ca/`
170 `metabolites/HMDB0038361.Consulted` february 27. 2018. (Human Metabolome Database (HMDB))

171 [Leung et al. ()] 'Theaflavins in black tea and catechins in green tea are equally effective antioxidants'. L Leung
172 , Y Su , R Chen , Z Zhang , Y Huang , Z Y Chen . *J. Nutr* 2001. 131 p. .

173 [Huang et al. ()] 'Vasorelaxant effects of purified green tea epicatechin derivatives in rat mesenteric artery'. Y
174 Huang , A Zhang , C W Lau , Z Y Chen . *Life Sci* 1998. 63 p. .