Article

Scintica:

SAFETY PHARMACOLOGICAL EVALUATION OF THE COFFEE COMPONENT, CAFFEOYLQUINIC ACID, AND ITS METABOLITES, USING EX VIVO AND IN VITRO PROFILING ASSAYS

Yuto Amano 1, Hiroshi Honda 2, Yuko Nukada 3, Naohiro Ikeda 3, Masayuki Yamane 3, Koji Nakano 4, Akiyo Kameyama 3, Osamu Morita 3

Scintica:

Safety Pharmacological Evaluation of the Coffee Component, Caffeoylquinic Acid, and Its Metabolites, Using Ex Vivo and In Vitro Profiling Assays

Yuto Amano [1], Hiroshi Honda [2], Yuko Nukada [3], Naohiro Ikeda [3], Masayuki Yamane [3], Koji Nakano [4], Akiyo Kameyama [3], Osamu Morita [3]

Affiliations + expand

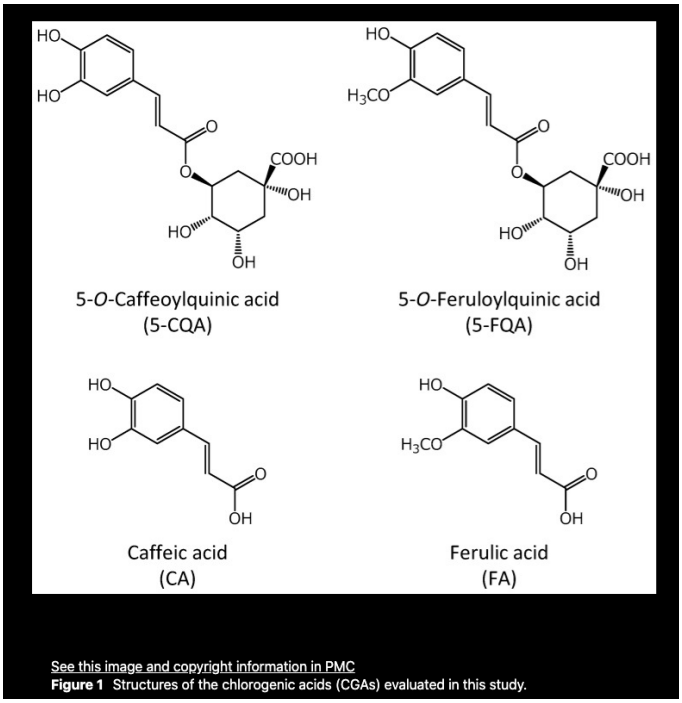
PMID: 31319524 PMCID: PMC6789782 DOI: 10.3390/ph12030110

Free PMC article

Abstract

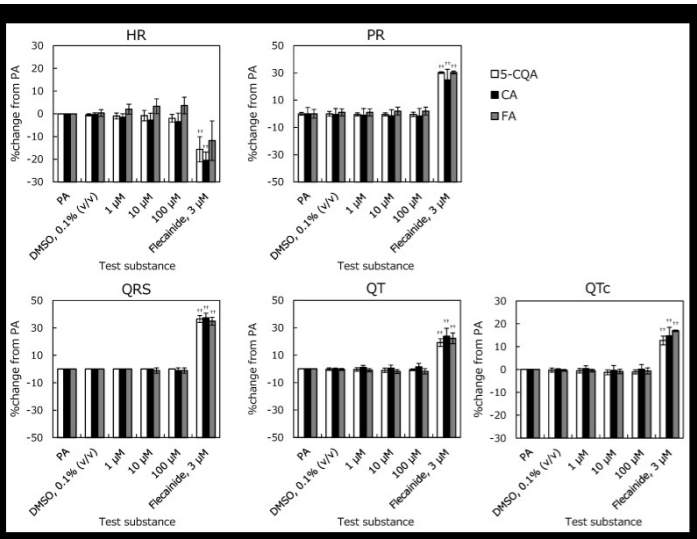
Although coffee components have gained interest for use as pharmaceuticals, little is known about their safety pharmacological effects. Hence, we aimed to evaluate the safety pharmacological effects of a chlorogenic acid (CGA)-related compound contained in coffee, 5-*O*-caffeoylquinic acid (5-CQA), and its metabolites, 5-*O*-feruloylquinic acid (5-FQA), caffeic acid (CA), and ferulic acid (FA). Langendorff perfused heart assay, electrophysiological assay of acute rat hippocampal slices, and in vitro Magnus assay of gastrointestinal tracts were conducted at 1-100 µM. Moreover, in vitro profiling assays against 38 major targets were conducted. In the Langendorff assay, no significant adverse effects were observed. In the electrophysiological assay, although epileptiform discharge rates were increased at 10 µM CA with 4-aminopyridine, and area under the curve (AUC) and number of population spike were increased at 10 µM FA with bicuculline, dose dependency was not confirmed, and no significant changes were observed at 1 µM and by CGAs alone. In the Magnus assay, a slight increase in contraction activity was observed at >1 µM FA in the stomach fundi and 100 µM 5-CQA in the ileum, suggesting enterokinesis promotion. No significant interactions were observed in the in vitro profiling assays. Therefore, CGAs could have a fundamental function as safe pharmaceuticals.

Keywords: adverse effects; bioactive compounds; caffeoylquinic acid; cardiovascular system; central nervous system; chlorogenic acid; coffee; gastrointestinal system; safety pharmacology.



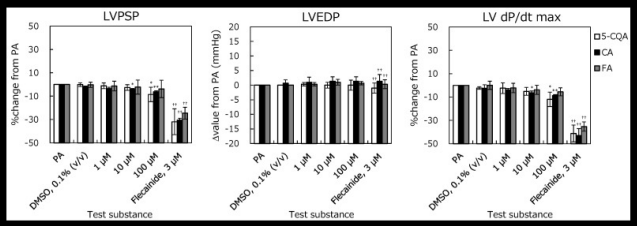
See this image and copyright information in PMC

Figure 1 Structures of the chlorogenic acids (CGAs) evaluated in this study.



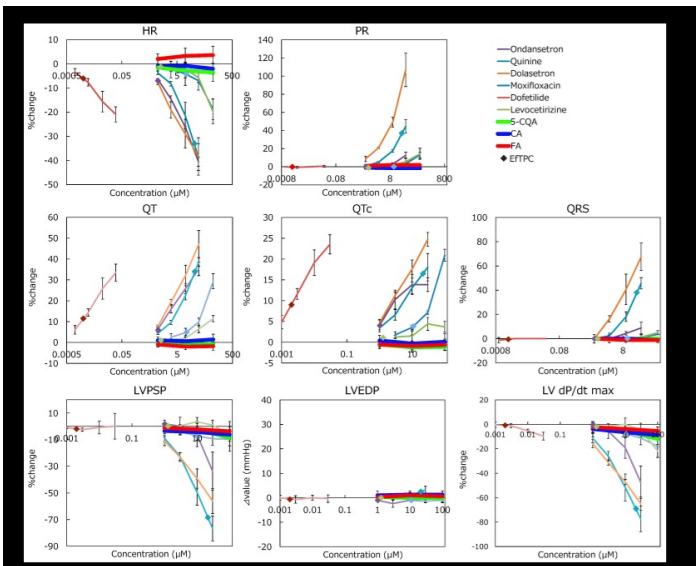
See this image and copyright information in PMC

Figure 2 Relationships between electrocardiogram parameters and accumulation of each perfusate. The isolated perfused guinea pig heart was respectively conditioned with 0.1% dimethyl sulfoxide (DMSO), 1–10–100 μM of 5-*O*-caffeoylquinic acid (5-CQA), caffeic acid (CA), and ferulic acid (FA), and 3 μM of flecainide. Heart rate (HR), PR, QRS, QT, and QTc



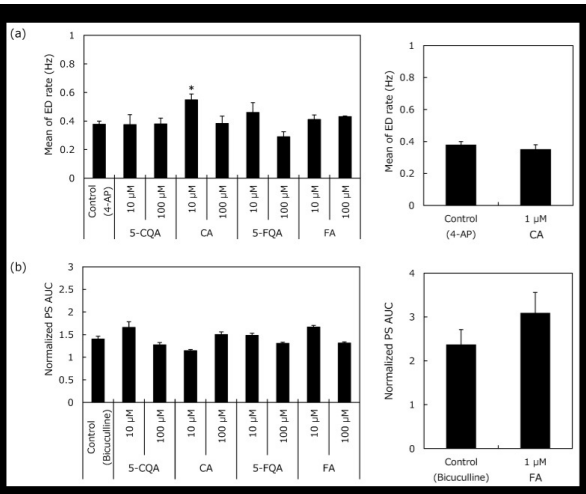
See this image and copyright information in PMC

Figure 3 Relationships between left ventricular pressure (LVP) parameters and concentrations of 5-CQA, CA, and FA in the isolated perfused guinea pig heart system. Left-ventricular Peak Systolic Pressure (LVPSP), Left-ventricular End Diastolic Pressure (LVEDP), and left-ventricular-pressure rise (LV dP/dt max) are represented as % change from PA. Each error bar represents mean ± SD (n = 3). *: $p < 0.025$, **: $p < 0.005$; Significantly different from DMSO (Williams test). †: $p < 0.01$; Significantly different from DMSO (Student's t-test).



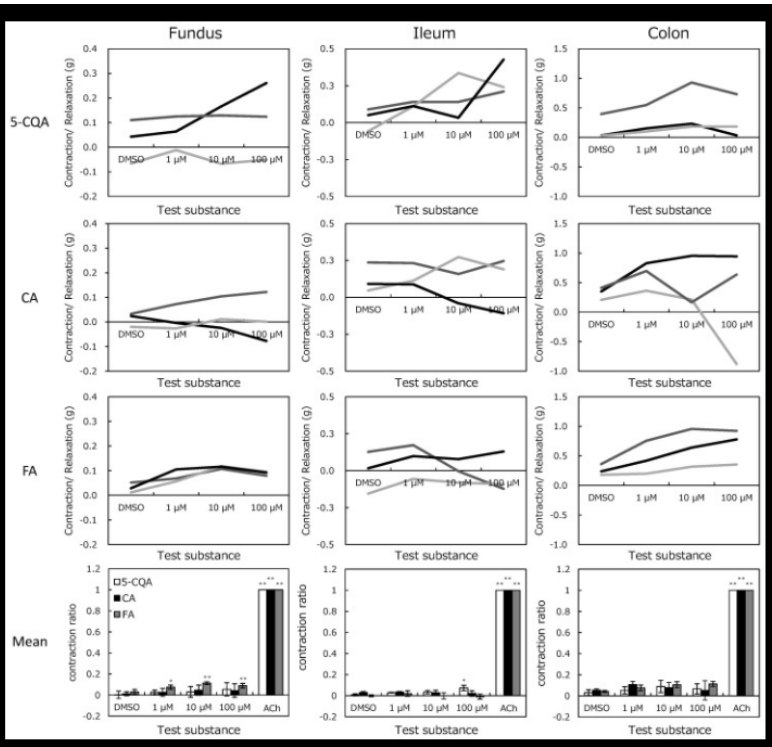
See this image and copyright information in PMC

Figure 4 Comparison between drugs with cardiovascular effects and chlorogenic acid (CGA) in the parameters of the Langendorff perfused heart assay. Each error bar represents mean ± SD (n = 3). ◆: depicts effective free therapeutic plasma concentration (color corresponds to each drug). CGA's effect on each parameter was weaker than that of the drugs.



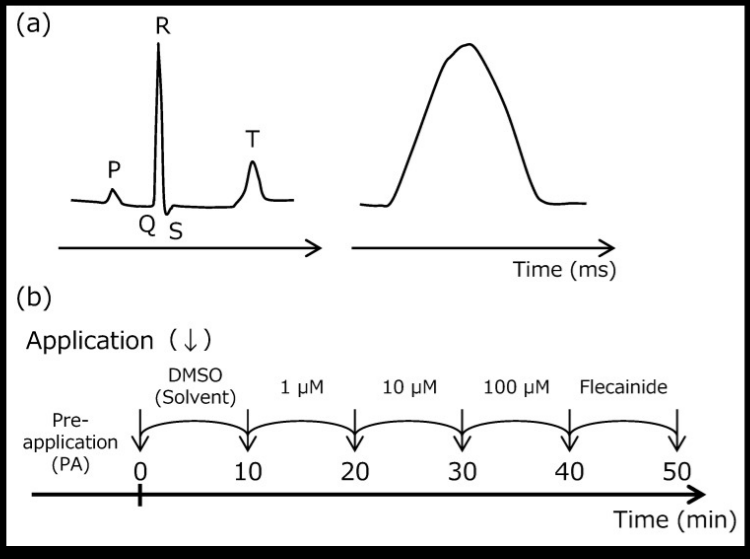
See this image and copyright information in PMC

Figure 5 Effects of the chlorogenic acids on the electrophysiological activity of hippocampal slices with convulsive compounds. (**a**) ED rate with 10 μM 4-aminopyridine and (**b**) Population spikes (PS) area under the curve (AUC) with 1 μM bicuculline. (**a**) Amplitudes higher than 15 μV were counted as ED and frequency was averaged by 30-s time slots. The frequency of ED



See this image and copyright information in PMC

Figure 6 Concentration-response curves of chlorogenic acids from the fundus, ileum, and colon isolated from guinea pig. Test substances were applied to organs after a stabilization period. Values represent the exchange of isolated organ tension compared to before dimethyl sulfoxide (DMSO) application. Mean represents mean ± SEM of the contraction normalized to



See this image and copyright information in PMC

Figure 7 Parameters recorded from the Langendorff perfused heart assay. (**a**) One wave shape of electrocardiogram (ECG) and left ventricular pressure (LVP) recording. The letters represent peak name on the ECG. (**b**) The standard protocol of this assay. 5-*O*-caffeoylquinic acid (5-CQA), caffeic acid (CA), and ferulic acid (FA) were applied at 1, 10, and 100 uM.