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Original Article

Effect of Epigallocatechin Gallate on Cadmium Chloride-induced Oxidative Stress in Female Sprague Dawley Rats

Subramani Parasuraman*, James Yu Kar Beng, Lam Chew Hui, Brenda Ngu Yen Qin

ABSTRACT

Background: Epigallocatechin gallate (EGCG) is the ester of epigallocatechin and gallic acid. EGCG is abundant in dry tea leaves and its effect on heavy metal-induced oxidative stress is not clear. Hence, the present study is planned to study the effect of EGCG on cadmium chloride ($CdCl_2$) induced oxidative stress in female Sprague Dawley rats. **Methods:** The rats were divided into six groups with each of six animals *viz.*, control, $CdCl_2$, vitamin C, EGCG, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCG. $CdCl_2$ (5 mg/kg) was suspended in carboxymethyl cellulose and administered orally to induce oxidative stress. Vitamin C and EGCG were dissolved in sterile water for injection and administered intraperitoneally within 15 min after $CdCl_2$ administration. All the animals were administered with respective assigned treatment once daily for 28 consecutive days. At the end of the study, blood samples were collected from all the animals and serum was separated. The serum sample was used for biochemical analysis. Later, the rats were sacrificed and liver samples were collected and used for antioxidant assay. **Results:** EGCG and vitamin C prevented the $CdCl_2$-induced oxidative stress. $CdCl_2$ administered group showed significant increases in the levels of glucose, AST, ALT and urea when compared with control group, whereas vitamin C and EGCG prevented the $CdCl_2$-induced biochemical changes. Vitamin C and EGCG also prevented the $CdCl_2$-induced reduction in levels of reduced glutathione and catalase. **Conclusion:** EGCG had significant ameliorative effect on $CdCl_2$ -induced oxidative stress in experimental animals.

Key words: Cadmium, Catalase, Catechin, Glutathione, Vitamin C.

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INTRODUCTION

Cadmium (Cd) is a toxic environmental heavy metal. Cadmium could badly affect the environment occupationally and environmentally by undergoing mining, metallurgy industries and manufactures of pigments, plastic stabilizers and nickel-cadmium batteries.[1] Cadmium could also affect proliferation, differentiation and cause apoptosis at the cellular level. International Agency for Research on Cancer (IARC) has classified cadmium as a Class-1carcinogen but it is weakly genotoxic and not directly mutagenic itself.[2] Cadmium exposure causes deoxyribonucleic acid (DNA) lesions which are not due to direct effect. Cadmium may interfere with proteins that contain a zinc finger motif, which are involved in the maintenance of genome stability or in DNA repair and DNA damage signaling. Proteins involved in repair are inhibited or diminished activity after cadmium intoxication.[3] Metal mediated formation of free radical causes various modifications to DNA bases, altered calcium and sulfhydryl homeostasis and enhanced lipid peroxidation.[4] Cadmium does not induce the production of reactive oxygen species through a Fenton-like redox cycling mechanism as is characteristic of copper, chromium, iron and vanadium. However, cadmium does cause depletion of reduced glutathione (GSH) and protein-bound sulfhydryls, resulting in the production of an oxidative stress with subsequent oxidative tissue damage.[5] Green Tea is now-a-days a commonly used beverage worldwide as it has many benefits on human's health. Tea is also known as an infusion of the leaves of the *Camellia sinensis* (Theaceae) plant. It has health benefits including chemo-preventive effect and this effect may be because of its polyphenols which is the catechins. Epigallocatechin gallate (EGCG), (-)- epicatechin-3-gallate, (-)-epicgallocatechin and (-)-epicatechin are the most common catechin that usually present in green tea. EGCG, also provides some other beneficial effect in the prevention of diabetes, Parkinson's diseases, Alzheimer's diseases, stroke and obesity.[6] EGCG is abundant in dry tea leaves and its effect on heavy metal-induced oxidative stress is not clear. Hence, the present study is planed to study the effect of EGCG on cadmium chloride ($CdCl_2$)-induced oxidative stress in female *Sprague Dawley* (SD) rats.

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MATERIALS AND METHODS

Chemicals

Vitamin C was purchased from R&M Marketing, Essex, UK and EGCg green tea extract - 400 mg capsules were purchased from Now Foods, USA. Each capsule of EGGg contains 200 mg of EGCG.

Animals

Healthy, adult, female SD rats (180 ± 20 g) were used. The animals were obtained from Central animal house, AIMST University, Malaysia. The SD rats were housed and maintained in the large, spacious poly acrylic cages at an ambient room temperature with 12-h light/12 h dark cycle. The animals were fed with water and normal rats pellet diet *ad libitum*. The study was approved by AIMST University Human and Animal Ethics Committee (AUAEC/FOP/2019/10) and the study was conducted according to the Animal Research Review Panel guidelines.

Effect of EGCG on $CdCl_2$-induced oxidative stress

Healthy, adult, female SD rats were used for the study. The animals were divided into six groups each of 6 animals as follows

Group I: Control

Group II: $CdCl_2$ (5 mg/kg)

Group III: Vitamin C (200 mg/kg)

Group IV: EGCG (50 mg/kg)

Group V: $CdCl_2$ (5 mg/kg) + Vitamin C (200 mg/kg)

Group VI: $CdCl_2$ (5 mg/kg) + EGCG (50 mg/kg)

Dose of vitamin C and EGCG were selected based on available literature.[7,8] $CdCl_2$ (5 mg/kg) was used to induce oxidative stress.[9] $CdCl_2$ was suspended in carboxymethyl cellulose and administered orally. Vitamin C and EGCG were dissolved in sterile water for injection and administered intraperitoneally within 15 min after $CdCl_2$ administration. All the animals were administered with respective assigned treatment once daily for 28 days. The animals in Group I to VI were administered with drug vehicle, $CdCl_2$, vitamin C, EGCG, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCG, respectively. At the end of the study, blood samples were collected from all the animals and serum was separated. The serum sample was used for biochemical analysis. Later, the rats were sacrificed and liver samples were collected and used for antioxidant assay.[10]

Body Weight Analysis

Changes in Body Weight (BW) of each rat in each group were recorded at regular intervals.

Biochemical Analysis

At the end of the study, 1 ml of the blood sample was collected from the experimental animals in plain glass tube through retro-orbital plexus and the serum was separated by centrifuging at 3000 RPM for 20 min. The serum sample was used for estimation of biochemical markers such as glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, creatinine, total cholesterol (TC), triglyceride (TG) and high-density cholesterol (HDL-C) by using Reflotron® Plus biochemical analyzer (Roche Diagnostics, Germany) with the help of commercially available Reflotron strips. The low-density cholesterol (LDL-C) [LDL-C = TC – HDL-C – (TG/5)], very low-density cholesterol (VLDL-C) [VLDL-C = TG/5] and cholesterol radio [cholesterol radio = TC/HDL-C] were calculated mathematically.

Organ Weight Analysis

At the end of the study, all the experimental animals were sacrificed under mild ether anesthesia followed by cervical dislocation. The animal was dissected and the gross pathology was observed. The organs such as brain, lung, heart, liver and kidney were harvested and absolute organ weights were measure and relative organ weight was calculated. Part of the liver sample was collected from all the experimental animals and used for antioxidant assay.

Antioxidant Assay

a) Reduced Glutathione (GSH) estimation: Liver homogenate (in 0.1 M phosphate buffer pH 7.4) was added with equal volume of 20% trichloroacetic acid contacting 1 mM ethylenediaminetetraacetic acid (EDTA) to precipitate the tissue proteins and allowed to stand for 5 min. The reaction mixture was centrifuged at 2000 RPM for 10 min. A 200 µL supernatant transferred to test tube contacting 1.8 mL of Ellman's reagent. Later absorbance was measured spectrophotometrically (Model UV 1800, Shimadzu, Japan) at 412 nm against blank. Absorbance values were compared with a standard curve generated from known GSH.[11]

b) Catalase (CAT): Fifty microliter of the lysate was added to a cuvette containing 2 mL of phosphate buffer (pH 7.0) and 1 mL of 30 mM H_2O_2. CAT activity was measured at 240 nm for 1 min using spectrophotometer. The CAT activity was determined using molar extinction coefficient of H_2O_2, 43.6 M cm^{-1} at 240 nm. One unit of CAT activity is equal to 1mmol of H_2O_2 degraded per minute. Activity of catalase was expressed as unit/mg protein.[11,12]

Statistical Analysis

Data were represented as Mean ± Standard Error of the Mean (SEM). Statistical analysis was carried out using One-way ANOVA followed by Turkey's *post-hoc* test. A value of $p<0.05$ shall be considered to be significant.

RESULTS

The animal administered with $CdCl_2$ showed significant decreases in BW form day 14 onwards when compared with control. The animals administered with vitamin C, EGCC, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCC did not showed any significant body weight changes when compared with control group (Figure 1). In absolute organ, no significant changes in the organ weights of brain, lung, heart, liver and kidney in any of the treatment groups. There were no significant changes in relative organ weights of brain, lungs, heart, liver and kidney in

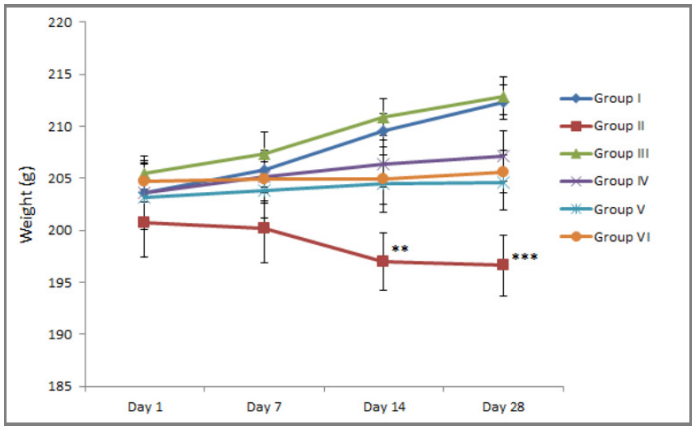

Figure 1: Effect of EGCG on body weight of of SD rats.
Values are expressed as mean ± SEM (n = 6). **P<0.01 and ***P<0.001 compare with control (One-way ANOVA followed by Tukey's *post-hoc* test)

vitamin C, EGCC, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCC administered group when compared with control group. Whereas, the animals administered with $CdCl_2$ showed significant increases in the relative organ weights of lungs and liver when compared with control group (Table 1).

The effect of vitamin C, EGCC, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCC on biochemical parameter on experimental animals was summarized in Table 2. The animals administered with $CdCl_2$ showed significant increases in the levels of glucose, AST, ALT and urea when compared with control group whereas the animals administered with vitamin C/ EGCC/ $CdCl_2$ + EGCC did not showed any significant changes in biochemical parameters. The animals administered with $CdCl_2$ + vitamin C showed significant increases in the levels of ALP when compared with control animals. The effect vitamin C, EGCC, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCC on lipid profile of experimental rats was summarized in Table 3. The animals administered with vitamin C, EGCC, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCC did not showed significant changes in total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C and cholesterol ratio when compared with control.

In antioxidant assay, the $CdCl_2$, $CdCl_2$ + vitamin C and $CdCl_2$ + EGCG administered animals showed significant decreases in the levels of GSH and catalase when compare with control. The animals administered with vitamin C/ EGCG didn't showed alterations in the levels of GSH and catalase when compared with control. The animals administered with $CdCl_2$ + vitamin C / $CdCl_2$ + EGCG restored level of GSH and catalase and the results were significant when compared with $CdCl_2$ administered group (Table 4).

DISCUSSION

Cadmium is an important environmental pollutant present in air, soil, water and food. Anthropogenic sources add 3–10 times more cadmium to the atmosphere than natural sources.[13] Acute intoxication of cadmium may result in lung, liver, kidney and testes damage and chronic intoxication may lead to obstruction of pulmonary disease, disturbance of metabolism and immune system, disregulation of blood pressure and obstruction of kidney function.[14] Cadmium also alters antioxidant defense mechanisms and increases generation of reactive oxygen species (ROS) and its interference with cellular antioxidant system.[15] In this study, antioxidant effect of EGCG against $CdCl_2$-induced oxidative stress was studied.

The polyphenolic compound EGCG is the major catechin found in green tea and this catechin is believed to be responsible for the health benefits associated with the consumption of green tea.[16] EGCG has antioxidant, autoxidation, anti-inflammatory, anticoagulant, antifibrotic and anticancer effect.[17] The animal administered with $CdCl_2$ showed significant decreases in the body weight, which may due to toxicity

Table 1: Effect of EGCG on relative organ weight (in grams) of SD rats.

Group	Brain	Heart	Lungs	Liver	Kidney (R)	Kidney (L)
Control	0.87 ± 0.02	0.31 ± 0.01	0.89 ± 0.03	3.17 ± 0.09	0.32 ± 0.01	0.33 ± 0.01
$CdCl_2$	0.95 ± 0.02	0.31 ± 0.01	1.06 ± 0.03**	3.45 ± 0.05*	0.34 ± 0.01	0.35 ± 0.01
Vitamin C	0.86 ± 0.03	0.30 ± 0.01	0.87 ± 0.02	3.21 ± 0.06	0.32 ± 0.01	0.33 ± 0.01
EGCG	0.89 ± 0.03	0.31 ± 0.01	0.89 ± 0.01	3.20 ± 0.04	0.33 ± 0.01	0.33 ± 0.01
$CdCl_2$ + Vitamin C	0.91 ± 0.03	0.30 ± 0.01	0.91 ± 0.04	3.19 ± 0.07	0.34 ± 0.01	0.34 ± 0.01
$CdCl_2$ + EGCG	0.89 ± 0.02	0.31 ± 0.01	0.91 ± 0.02	3.22 ± 0.04	0.32 ± 0.01	0.32 ± 0.01

Values are expressed as mean ± SEM (n = 6). *$P<0.05$ and **$P<0.01$ compare with control (One-way ANOVA followed by Tukey's *post hoc* test)

Table 2: Effect of EGCG on Biochemical Analysis of SD rats.

Group	Glucose (mmol/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	Urea (mg/dl)	Creatinine (mg/dl)
Control	6.15 ± 0.20	73.83 ± 02.54	50.17 ± 4.57	86.67 ± 5.17	27.33 ± 3.24	0.21 ± 0.03
$CdCl_2$	7.78 ± 0.42**	118.17 ± 8.36**	87.33 ± 7.28***	79.83 ± 3.25	44.83 ± 5.38**	0.34 ± 0.06
Vitamin C	6.03 ± 0.16	86.33 ± 2.50	46.33 ± 4.88	82.67 ± 2.09	22.83 ± 2.04	0.25 ± 0.02
EGCG	6.12 ± 0.27	77.17 ± 5.20	50.83 ± 2.40	83.8 ± -4.19	26.67 ± 3.19	0.24 ± 0.02
$CdCl_2$ + Vitamin C	6.15 ± 0.21	79.67 ± 5.67	47.50 ± 4.01	107.17 ± 6.17*	21.17 ± 1.22	0.28 ± 0.01
$CdCl_2$ + EGCG	6.32 ± 0.20	92.17 ± 6.07	59.67 ± 7.44	84.83 ± 3.05	29.33 ± 3.21	0.32 ± 0.04

Values are expressed as mean ± SEM (n = 6). *$P<0.05$; **$P<0.01$ and ***$P<0.001$ compare with control (One-way ANOVA followed by Tukey's *post-hoc* test)

Table 3: Effect of EGCG on Lipid Profile of SD rats.

Treatment	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	Cholesterol Ratio
Control	82.17 ± 3.43	77.50 ± 3.39	18.67 ± 1.26	48.00 ± 4.63	15.50 ± 0.68	4.54 ± 0.46
$CdCl_2$	81.67 ± 3.89	74.67 ± 6.33	16.17 ± 1.25	50.57 ± 4.07	14.93 ± 1.27	5.14 ± 0.31
Vitamin C	84.67 ± 5.58	77.00 ± 3.69	21.17 ± 1.85	48.10 ± 6.91	15.40 ± 0.74	4.22 ± 0.54
EGCG	81.83 ± 5.59	78.50 ± 3.70	17.50 ± 1.23	56.20 ± 14.00	15.70 ± 0.74	4.79 ± 0.44
$CdCl_2$ + Vitamin C	89.19 ± 5.75	86.33 ± 2.80	18.50 ± 1.12	53.40 ± 14.32	17.27 ± 0.56	5.65 ± 0.51
$CdCl_2$ + EGCG	88.17 ± 3.98	87.67 ± 3.09	17.83 ± 1.30	52.80 ± 3.86	17.53 ± 0.62	5.08 ± 0.44

Values are expressed as mean ± SEM ($n = 6$).

Table 4: Effect of EGCG on antioxidant parameters.

Treatment	Reduced Glutathione (µmol/g)	Catalase (Units/mg protein)
Control	20.13 ± 0.37	40.56 ± 0.52
$CdCl_2$	6.10 ± 0.53***	19.15 ± 1.25***
Vitamin C	21.46 ± 0.38###	41.70 ± 0.56###
EGCG	20.53 ± 0.37###	39.83 ± 0.43###
$CdCl_2$ + Vitamin C	18.29 ± 0.22*###	37.00 ± 0.47*###
$CdCl_2$ + EGCG	18.23 ± 0.27*###	36.12 ± 0.50**###

Values are expressed as mean ± SEM ($n = 6$). *P<0.05, **P<0.01and ***P<0.001 compare with control group; ###P<0.001 compare with cadmium chloride administered group (One-way ANOVA followed by Tukey's *post-hoc* test)

of $CdCl_2$. Gaurav *et al.* also reported the effect of cadmium on body weight; In this study reduction in body weight was observed in $CdCl_2$ administered animals.[18] The animals administered with $CdCl_2$ showed significant increase in the relative organ weights of lung and liver and the same was reported elsewhere.[19] Gaurav *et al.* reported increases of liver and kidney weight in cadmium exposed rats.[18] In animals, exposure of 5–10 mg Cd/m^3 as cadmium oxide dust, cadmium oxide fume, or $CdCl_2$ for 1–5 hours showed increased lung weight focal interstitial thickening, edema and necrosis of alveolar.[19]

In biochemical analysis, the animals administered with $CdCl_2$, showed a significance increases in the levels of glucose, AST, ALT and urea. The aminotransferases are the sensitive indicators of liver cell injury and helpful in detect the hepatocellular diseases.[20] Alterations in serum levels of ALT may be changes in cell membrane permeability and increased the serum activity of ALT indicates hepatic lesion in liver cells.[21] The increased levels of urea observed when there is kidney damage or kidney is not functioning well. In this study there is an increases of glucose level (hyperglycemia) is observed in $CdCl_2$ exposed group, which is also a one of the major causes of progressive renal damage.[22] CiCiK and ENGiN studied the effect of cadmium on fish and observed that there is an increase in the levels of glucose and reduced levels of glycogen with the fish exposed with cadmium at concentrations of 0.05, 0.1, 0.5 and 1.0 mgl^{-1}. The decreases in the levels of glycogen indicating that the heavy metals like cadmium affecting the enzymes that play a role in the carbohydrate metabolism by stimulating glycolytic enzymes like lactate dehydrogenase, pyruvate dehydrogenase and succinate dehydrogenase.[23] In this present study, no significant changes in the levels of TC, TG, HDL, LDL, VLDL and cholesterol ratio. Samarghandian *et al.* studied the effect of chronic exposure (2.0 mg Cd/L of drinking water for three months) in SD rats and found significant increases in the levels of TC, TG and LDL-C and significant decreases in the levels of HDL compared with control.[24] In this study, the animals administered with only EGCG/vitamin C did not showed any alteration in the levels of normal lipid levels. Raederstorff *et al.* reported a dose-dependent cholesterol lowering effect of EGCG in hypercholesterolemic rats and this effect is may be dye to inhibition of cholesterol absorption.[25]

The animal administered with $CdCl_2$ showed significant decreases (P<0.001) in the levels of GSH and catalase levels compared with control. Whereas the animals administered with $CdCl_2$ + vitamin C or $CdCl_2$ + EGCG showed significant increases (P<0.001) in the levels of GSH and catalase levels ompared with $CdCl_2$ administered group. This indicates that, both vitamin C and EGCG prevented $CdCl_2$-induced free radicals. In both *in vitro* and *in vivo* studies, $CdCl_2$ showed significant increases in the levels of oxidative stress.[14,26] Skipper *et al.* studied the effect of $CdCl_2$-induced toxicity to $HepG_2$ cells and found significant increase of lipid hydroperoxide levels, a major degradation product of unsaturated phospholipids and glycolipids.[27] Oladele *et al.* also found reduced levels of GSH and catalase in the animals administered with $CdCl_2$ at the dose of 5mg/kg for 14 consecutive days.[26] Cadmium also stimulates the formation of metallothioneins and reactive oxygen species, as a results oxidative damage to various tissues resulting in loss of the membrane functions.[14] Both vitamin C and EGCG has significant antioxidant effect. Vitamin C is known antioxidant and the antioxidant effect of EGCG is reported elsewhere.[28,29] The polyphenolic compound EGCG is most abundant catechin in green tea (7380 mg per 100 g) also present in white tea (4245 mg per 100 g), black tea (9.36 mg per 100 g) and dry tea fruit (415 mg per 100 g). Trace amount of EGCG are found in apples, avocados, blackberries, canberries, kiwifruit, peaches, pears, plums,

raspberries, strawberries, sweet onions, hazelnuts nuts, pecans nuts, pistachio nuts and carob flour.[30] The calculated safe intake level of EGCG is 32 mg /person/day for a 70 kg adult and excess intake may results in liver and gastrointestinal toxicities.[31]

CONCLUSION

EGCG had significant ameliorative effect on $CdCl_2$-induced oxidative stress in experimental animals. In animals, $CdCl_2$ decreases in the levels of reduced glutathione and catalase, whereas Vitamin C and ECGC prevented the $CdCl_2$-induced changes in the level of reduced glutathione and catalase.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ALP: Alkaline phosphatase; **ALT:** Alanine aminotransferase; **ANOVA:** Analysis of variance; **AST:** Aspartate aminotransferase; **BW:** Body weight; **Cd:** Cadmium; **$CdCl_2$:** Cadmium chloride; **DNA:** Deoxyribonucleic acid; **EDTA:** Ethylenediaminetetraacetic acid; **EGCG:** Epigallocatechin gallate; **GSH:** Reduced glutathione; **HDL-C:** High-density cholesterol; **IARC:** International Agency for Research on Cancer; **LDL-C:** Low-density cholesterol; **ROS:** Reactive oxygen species; **RPM:** Revolutions Per Minute; **SD:** Sprague Dawley; **SEM:** Standard error of the mean; **TC:** Total cholesterol; **TG:** Triglyceride; **VLDL-C:** Very low-density cholesterol.

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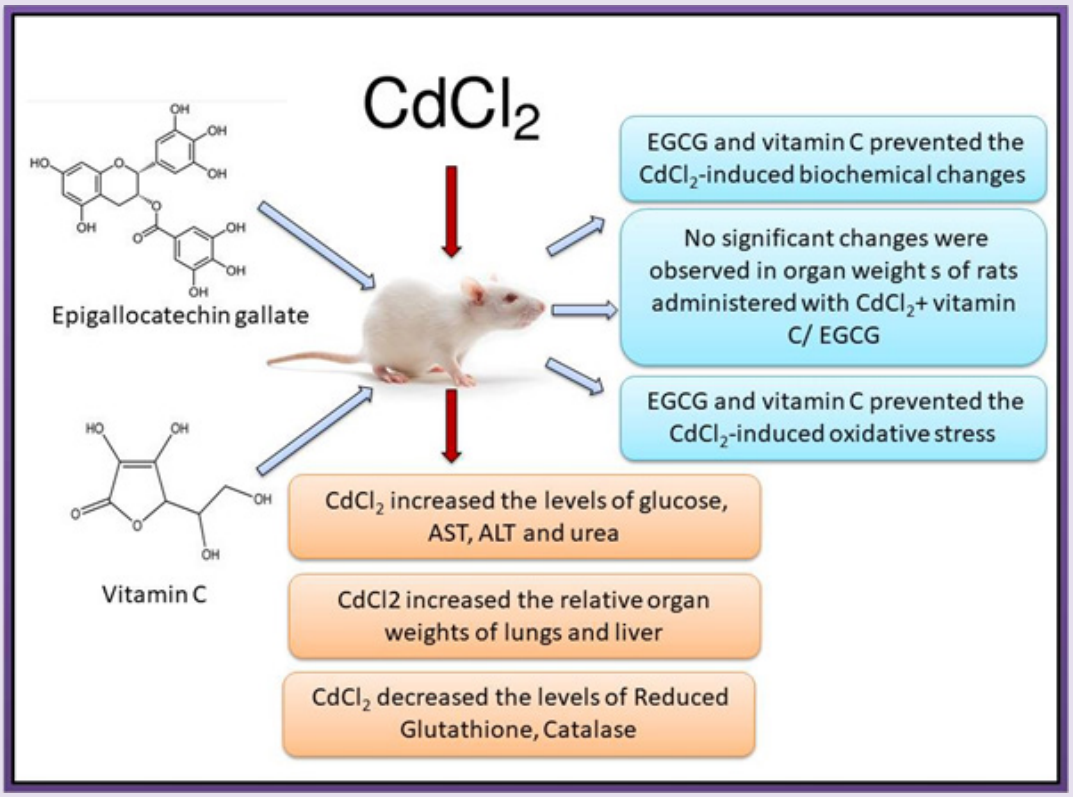
GRAPHICAL ABSTRACT



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SUMMARY

- Epigallocatechin gallate (EGCG) is the most abundant catechin in tea.
- Cadmium chloride induces oxidative stress by decreasing glutathione and catalase.
- EGCG prevents cadmium chloride-induced changes in glutathione and catalase in rodents.

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