Research Article

# Effectiveness of *Cinnamomum cassia* against Liver and Kidney Biochemical Assay and Hematology in Bisphenol-A Induced Rats

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**Abstract** | Bisphenol-A (BPA) exhibits toxic, endocrine, mutagenic and carcinogenic effects in living organisms. However, some dietary elements, such as cinnamon is gaining attention as it has antioxidant effects both in vivo and in vitro. The present research study was designed to see the effect of cinnamon against BPA induced Sprague Dawley rats. In the study Sprague Dawley rats of an average 300 gram body weigt were used. The rats were divided into control and treated groups. The control group was comprised of normal control (C; untreated), vehicle control (P; treated with 1ml olive oil), and positive control (BG1; only treated with BPA). Treated groups were included the pretreated group (CG2; pretreated with *C. cassia* at 225 mg/kg/BW 24 hours before BPA) and the post-treated group (CG3; post-treated with *C. cassia* at 225 mg/kg/BW 24 hours before BPA). In the experiment Sprague Dawley rats were fed by BPA that was followed by the intake of *C. cassia* at 225 mg/kg/BW of the rat. Liver (Total bilirubin, alkaline phosphate test, Lactate dehydrogenase, and alanine amino transferase) and kidney (Blood Urea Nitrogen, Creatinine, and Uric acid) biomarkers were assessed. The highest levels of ALT and ALP were linked to liver injury and a higher weight in the liver were observed in BPA treated rats as compared to the control group. Similarly, an increase in blood parameters were recorded in BPA treated rats followed by post -treated rats and pre- treated group. It was concluded by the study that BPA have pronounced adverse effects in the exposed animals particularly in BPA and cinnamon post- treated rats as compared to pre- treated rats.

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## Introduction

BisphenolA (BPA) is an organic chemical commonly used in the manufacturing of polycarbonates, epoxy resins, and other polymer products as a monomer or additive. Its most important applications are the formation of polyacrylate resins, polyester resins, flame retardants, polysulfone resins, and polyethylene resin (Huang *et al.*, 2011; Almeida *et al.*, 2018).

Although, it is a well-studied endocrine disruptor

whose toxicologic and multidirectional behavior is extensively studied (Huang *et al*., 2012; Björnsdotter *et al*., 2017). According to latest study it is a foreign xenoestrogen, that not formed naturally in living organisms but identical to normal 17 β estradiol (Kapustka *et al*.,2020). It was also categorized as a poor environmental estrogen that showed multidirectional toxic behavior (Liliana *et al*., 2019).

The studies indicated that exposure to BPA increases prostatic weight and brain activity, changes the growth, testosterone synthesis, disruption of sperm excretion, and reproductive organ development disturbance in mice (Michałowicz, 2014; Yilmaz *et al*., 2020). Developmental toxicity studies have also shown negative outcomes in rats at the levels or below the current acceptable daily intake levels for this compound (Rubin, 2011). The adverse effects of BPA included changes in puberty time, estrous cycles, the prostate, mammary glands growth, uterus and ovaries, brain sexual dimorphism, brain steroid receptor, sociosexualbehaviour, body weight, and glucose homeostasis (Michałowicz, 2014). Other health risks in human due to this compound are also well known such as cardiovascular illness, diabetes, increased numbers of premature births, the decrease in semen production, and sperm DNA damage (Rubin, 2011; Wu *et al*., 2013).

Natural plant-driven antioxidants are highly demanded than synthetic antioxidants because of their capacity for enhancing fitness, preventing diseases, protecting, and consumer acceptability (Skerget *et al*., 2005; Gulcin, 2006a, b; Gulcin *et al*., 2006c; Majhenic *et al*., 2007). In the present decade, the usage of herbs and spices as antioxidants and anticancer agents are being popular to overcome a numer of diseases (Embuscado, 2015). Cinnamon (Cinnamomum, Lauraceae family) is one of those spices that rich in antioxidants and phytochemical compounds (Udayaprakash *et al*., 2015). It is one of the most commonly used plants with diverse bioactive effects in herbal medicines (Błaszczyk *et al*., 2021). The *Cinnamomum cassia* (*C. cassia*) or Chinese cinnamon plant is an evergreen tall tree with dense leathery leaves and yellow flowers (Suriyagoda *et al*., 2021).

Due to the possible toxicity risks of BPA in different biological systems, it is important to implement less costly and non-synthetic products against BPA for the safer use of organisms. This is why bioactive compounds from different plants are exponentially used to track their viability in studies compared to synthetic ones. This study is novel as it explore valuable effects of natural products, *C. cassia* extracts to assess their effect against liver and kidney toxicity caused by BPA. The present research study was designed to evaluate Bisphenol-A induced toxicity in the liver of Sprague Dawley rats and its treatment with *C. cassia* through various bioassays like hematology, biomarkers of liver and kidney function tests.

## Materials and Methods

*Experimental plan*

Twenty-five post-weaning male Sprague Dawley rats of similar weight were divided into five groups (control + treated). The Sprague Dawley rats were kept in steel cages according to standard conditions (temperature, 25˚C; humidity, 45–65%; light/dark cycle, 12 h/12 h). The rats were provided with open access to water and food. The experimental study was designed for 30 days and included Bisphenol A (BPA) induced subacute toxicity in Sprague Dawley rats and its amelioration by *Cinnamomum cassia* (*C. cassia*) effective dose (225 mg/kg) from the previously reported study of Iqbal *et al*. (2020). BPA dose was based on previously reported LD50 of BPA (3250 mg/kg body weight) Furuya *et al*. (2006).

*Grouping of rats*

The study was allocated into two major groups (control and treated). A control group was further divided into a negative control group (C) that was remained untreated and only administrated with commercial feed and water. A vehicle control group (P) was fed olive oil (1m) for equivalency of shock (to see any toxic effect of olive oil as Bisphenol-A was dissolved in olive oil to prepare the dose for the treatment groups ). A BG1 (positive) group that was treated with only Bisphenol-A.

A treated group was divided into two groups that were fed on selected doses of *C. cassia* for 3 days per week. One was the CG2 group that was pretreated with *C. cassia* (225 mg/kg per BW of rat) 24 hours before the administration of Bisphenol-A and CG3 that were post-treated with *C. cassia* after 24 hours of the administration of Bisphenol-A.

After 30 days, the rats were sacrificed and selected

samples were collected for the biochemical assay (liver and kidney function tests) and hematology.

*Source of bisphenol A and C. cassia*

BPA was purchased from sigma Aldrich (CAS80-05-7) and *C. cassia* bark was purchased from local market of Faisalabad an further be confirmed by Department of botany from Goveronment College University Faisalabad.

*Preparation of C. cassia extract*

*C. cassia* was prepared with slight modifications in the methodology of Dahal *et al.* (2017). For this 500 grams of dried and crushed *C. cassia* bark were mixed with methanol and kept for 15 days at room temperature. After 15 days solution was filtered by Whatman No.1 filter paper and dried at room temperature. The extracts were stored in dark at room temperature (Dahal *et al.*, 2017).

*Liver function tests*

To study the potential toxicities of the BPA, the biochemical parameters such as Total bilirubin (TB), alkaline phosphate test (ALP), Lactate dehydrogenase (LDH), and alanine aminotransferase (ALT) of blood samples were determined by using commercially available assay kit and following the instruction of the manufacturer.

*Kidney function test*

For kidney function biomarkers such as creatinine(CRT), blood urea nitrogen (BUN) and uric acid (UA) tests were performed.

*Hematological analysis of blood*

For CBC analysis blood samples were collected through caudal puncture of animals in the tubes that contained calcium EDTA. By using a hematology auto-analyzer blood parameters such as hemoglobin (HB), red blood cells (RBCs), hematocrit (HCT), mean corpuscles volume (MCV), mean corpuscles hemoglobin (MCH), mean corpuscles hemoglobin concentration (MCHC), white blood cells (WBCs), and platelets (PLT) were determined for each control and treated groups.

## Results and Discussion

*Impact of BPA on relative weight and histoarchitecture of liver*

The relative weight of the liver were weighed after BPA administration. A significant increase was noticed in the liver weight in experimental groups as compared to control (Figue 1).

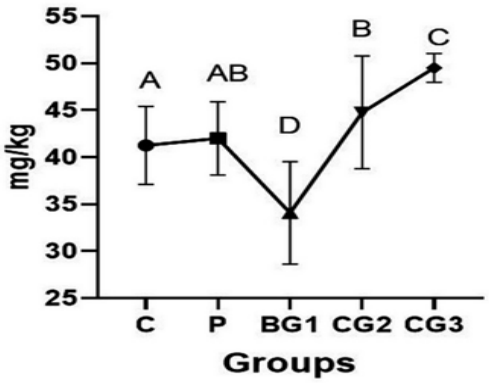


**Figure 1:** *Relative weight of liver.*

*Biomarkers of liver function*

The biomarkers of liver test total bilirubin (TB), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and alanine transaminase (ALT) were recorded after 30 days. A statistically significant ($p< 0.05$) differences were noticed in the TB, ALP, LDH, and ALT of the control and experimental groups (Figure 2). An overall increase in liver biomarkers such as TB, ALP, LDH, and ALT were recorded only in BPA treated rats rather than C and P control groups. The biomarkers of liver function were highly improved in *C. cassia* treated groups although the maximum improvement were recorded in pretreated rats as compared to post treated rats.

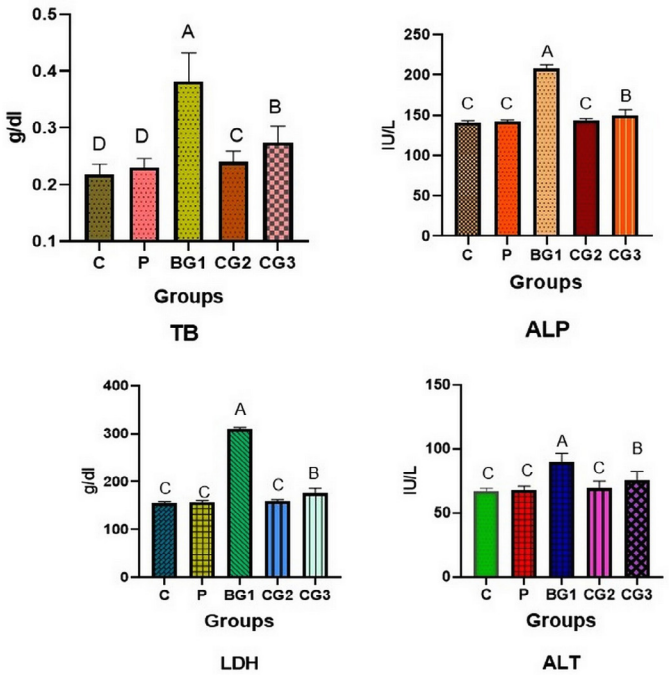


**Figure 2:** *Biomarkers of Liver in BPA, C. cassia treated and control groups.*

*Biomarkers of Kidney function*

The biomarkers of renal function such as blood urea nitrogen (BUN), creatinine (CRT), and uric acid (UA) were found significantly higher ($p < 0.05$) in BPA-treated rats than the control rats (C and P) (Table 1). The levels of biomarkers of kidney function were restored in *C. cassia*-treated groups (CG2 and CG3) although the maximum improvement was observed in pre-treated rats as compared to post-treated rats.

**Table 1:** *Biomarkers of kidney function test in control and treated groups.*

| Groups | BUN (IU/L) | CRT (g/dl) | UA (g/dl) |
|---|---|---|---|
| C | 67.34±0.03$^{C}$ | 0.504±0.05$^{C}$ | 2.91±0.06$^{C}$ |
| P | 67.80±0.266$^{C}$ | 0.506±0.05$^{C}$ | 3.10±0.023$^{C}$ |
| BG1 | 89.41±0.19$^{A}$ | 0.851±0.03$^{A}$ | 5.53±0.03$^{A}$ |
| CG2 | 69.01±0.38$^{BC}$ | 0.526±0.03$^{BC}$ | 3.58±0.03$^{BC}$ |
| CG3 | 71.22±0.23$^{B}$ | 0.576±0.05$^{B}$ | 4.01±0.05$^{B}$ |

*The results were expressed as Mean ± SD; means with different letters in the column are significantly different at p<0.05.*

*Hematological analysis*

The hematological analysis of Sprague Dawley rats that recorded after 30 days and shown in Table 2. The hemoglobin (HB) and red blood cells (RBCs) were decreased significantly ($p < 0.05$) in only BPA treated group (BG1) than the control groups (C and P). The RBCs and HB indices such as mean corpuscles hemoglobin (MCH), hematocrit (HCT), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular volume (MCV) were also reduced significantly ($p < 0.05$) in the BG1 group. White blood cells (WBCs) and Platelets (PLTs) were elevated significantly ($p<0.05$) in the BG1 (only BPA treated rats) group. The RBCs, HB, along with their indices were improved in both groups (CG2, and CG3) *C. cassia* pre-treated and post-treated rats than only BPA treated groups. The levels of WBCs and PLTs were also restored after *C. cassia* supplementation in pre-treated and co-treated groups. However, maximum improvements were observed in *C.cassia* pre-treated group (CG2).

BPA is absorbed rapidly upon its exposure to the biological system and imposes significant impacts on animals. Its bioavailability is poorer after oral administration than subcutaneous exposure (Almeida *et al.*, 2018). It is absorbed in the gastrointestinal tract and transferred to the liver, where it is metabolized by glucuronidation and sulfation to produce inactive forms of BPA. In human fluids and tissues, its unconjugated or free forms with estrogenic activity are comparatively low (ng/mL) due to its natural similarity to natural estrogen hormone (Soriano *et al.*, 2016). Antioxidants slow or prevent lipid or other molecule oxidation by preventing the initiation or proliferation of oxidizing chain reactions (Velioglu *et al.*, 1998). Free radicals are absorbed and neutralized, singlet and triplet oxygen (Osawa, 1994).

In the present research study Sprague Dawley rats were used to measure the toxic impact of BPA and its amelioration was done by *C. cassia* at an effective natural product. An increase in liver weight was noticed in BPA exposed rats in previous study and similar findings were noticed in the present study (Yıldız and Barlas, 2013). The relative weight of the liver BPA- treated rats was observed higher as compared to the control, which marks the liver injuries. Furthermore, this significant increase in serum concentration might be due to liver enzymatic and non-enzymatic biomarkers that leads to changes in the liver structure like infiltration of inflammatory cells, change in mitochondrial ATPase activity and congestion in liver cells which are chief factors that brought about a decrease in the relative liver weight (Hassan *et al.*, 2012; Iqbal *et al.*, 2021). While *C. cassia* supplementations either pretreated (only *C. cassia*) or post-treated (BPA+ *C.cassia*) improved the relativeiver weight in rats. These findings were corroborated with results of Morgan *et al.* (2014) who reported

**Table 2:** *Blood biochemistry in treated and control groups.*

| Groups | HB | RBCs ($10^6$/mm$^3$) | HCT (%) | MCV (fl) | MCH (pg) | MCHC (g/dl) | WBCs ($10^3$/mm$^3$) | PLT ($10^3$/mm$^3$) |
|---|---|---|---|---|---|---|---|---|
| C | 16.076±0.16$^{A}$ | 8.128±0.15$^{A}$ | 46.508±0.6$^{A}$ | 56.9±0.2$^{A}$ | 18.058±0.09$^{A}$ | 38.106±0.68$^{A}$ | 16.058±0.15$^{D}$ | 923.8±2.7$^{D}$ |
| V | 15.998±0.10$^{A}$ | 8.086±0.10$^{A}$ | 46.402±0.59$^{A}$ | 56.78±0.44$^{A}$ | 18.054±0.09$^{A}$ | 38.082±0.72$^{A}$ | 16.016±0.4$^{D}$ | 923.6±2.4D |
| BG1 | 13.156±0.12$^{C}$ | 6.404±0.2$^{C}$ | 39.88±0.43$^{D}$ | 47.992±0.81$^{D}$ | 14.352±0.2$^{D}$ | 31.848±0.49$^{D}$ | 20.156±0.14$^{A}$ | 1100±1.5A |
| CG2 | 15.912±0.14$^{B}$ | 8.024±0.1$^{B}$ | 46.062±0.97$^{B}$ | 56.184±0.34$^{B}$ | 17.832±0.4$^{B}$ | 37.822±0.79$^{B}$ | 17.97±0.11$^{C}$ | 924.43±2.73C |
| CG3 | 15.126±0.11$^{C}$ | 7.862±0.2$^{BC}$ | 45.644±1.3$^{C}$ | 55.244±0.82$^{C}$ | 16.926±0.2$^{8C}$ | 36.886±0.78$^{C}$ | 18.32±0.24$^{B}$ | 925.83±1.64B |

*Values are presented as mean ± S.D. (n = 5 animals/group).Means that do not share the same letter are significantly different in column at p<0.05*

*C. cassia* supplementations before and after octylphenol treatments helped to restore relative organ weight and body weight due to the improvement of various biochemical alterations in rats.

The occurrence of liver injury or inflammation was assessed by the liver function tests including ALP, ALT, TB, and LDH. The liver profile revealed biochemical improvements, with a considerable ($p<0.05$) rise in liver biomarkers in the BG1 group (only treated with BPA) compared to those of the control group. The results of our research showed that a high dose of BPA dramatically increased the serum indices of liver function, whereas the lower dosage groups were close to average. In our findings both ALT and ATP were found higher while high levels of ALP are linked to liver injury and ALT not found affected by the study of Tsung *et al.* (2019). Similarly elevated levels of serum indices for liver damage were previously identified in rats exposed to 30 mg BPA/kg/day, with no symptoms at less than 5 mg (Hassan *et al.*, 2012). A similar research found that BPA participants had higher serum ALT levels than the test group (Korkmaz *et al.*, 2010). *C. cassia* pretreatments and co-treatment (225 mg/kg per BW of rat) with BPA restored the liver profile including enzymatic and non-enzymatic biomarkers. Previous studies reported that *C.cassia* exert a protective effect owing to the presence of phytoconstituents such as flavonoid and phenolic contents that assist to scavenge free radicals and reduce oxidative stress which is the primary mechanism of action. The antioxidant level ultimately increases that helped to improve the liver and kidney profiles (Hassan, 2022).

The result of the renal function test indicated a considerable elevation of (BUN, CRT, and UA) in the BG1 group (only BPA treated-rats) than other groups. BPA was reported to induce hyperglycemia, which could cause kidney damage and renal dysfunction, thereby significantly increasing serum urea, creatinine, and uric acid (El-Yamani, 2011). After the treatment of *C. cassia* bark methanolic extract, either pre-treatment or post-treatment with BPA helped to restore the normal renal profile of rats. Although the best results were found in *C. cassia* (225 mg/kg) pre-treated rats. Previous research by Iqbal *et al.* (2020) found consistent with our study who observed that *C. cassia* treatments at various doses (175, 225, and 200 mg/kg B.W) reduced CRT, UA, and BUN levels after Ni nanoparticles induced renal toxicity in rats (Iqbal *et al.*, 2020).

The findings of the hematological analysis showed a considerable ($p<0.05$) reduction of HB and RBCs only in the BPA exposed group which marked anemia. The anemia may be due to the lysis of blood cells or decrease in haemoglobin (Lukose *et al.*, 2019; Hoque *et al.*, 2020). The blood lysis after the treatment with bisphenol A was might be due to oxidative stress-induced cell and membrane damage in erythrocytes of rats (Suthar *et al.*, 2014). The significant ($p<0.05$) production of platelets and WBCs were observed in the BG1 group because of the immunogenic response to deal with infectious conditions after BPA exposure (Srivastava and Reddy, 2020). It was reported in literature that high levels of BPA administration gradually increased the degree of cellular infiltration and the number of Kupffer cells (Verma and Sangai, 2009; Kamel *et al.*, 2018). However, *C. cassia* pretreatments and post-treatments (BPA+ *C. cassia*) improved the RBCs and HB levels as well as their indices (HT, MCV, MCH, and MCHC). WBCs and PLTs were also significantly decreased in *C. cassia* (225 mg/kg per BW of rat) pretreated and post-treated groups. It was also reported that usage of *C. cassia* improved the hematological parameters in various *in vivo* studies and they suggested the surplus polyphenol and flavonoids components assisted to scavenge free radicals that are coherent with blood cell lysis (Iqbal *et al.*, 2020; Shakeel *et al.*, 2018).

## Conclusions and Recommendations

It was concluded that BPA at 225 mg/kg/BW caused adverse effects on the exposed animals after oral administration as evidenced by the change in blood biochemistry, liver and kidney profile. Besides, the relative weight of the liver was decreased after BPA exposure. *C. cassia* treatments improved all the parameters and pretreatments played a prominent defensive function against such side effects as compared to post trreatments.

*Conflict of interest*

The authors have declared no conflict of interest.

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