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Effect of Honey on some Biochemical Parameters in the Brain Tissues of Wistar Rats Exposed to Cadmium

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Abstract

Cadmium (Cd) toxicity has led to the search for possible ameliorators, which is an interesting area of research currently being explored worldwide. This research investigated the effect of honey on some biochemical parameters in the brain tissues of rats following acute and sub-chronic Cd exposures. Thirty adult Wistar rats were divided into 6 groups (A-F): control, sub-chronic Cd exposure, sub-chronic Cd exposure plus honey, acute Cd exposure, acute Cd exposure plus honey and honey only, respectively. Cadmium chloride ($CdCl_2$) was administered at a dosage of 2 mg/kg body weight by intraperitoneal injection (IP), every two days interval, for a period of 4 weeks (for the sub-chronic study) and a dosage of 4 mg/kg body weight by IP, 12 hours before sacrifice (for the acute study). Honey was administered at a dose of 1 ml/kg body weight orally, once daily for 4 weeks. The study revealed that groups B and D showed significantly higher lipid peroxidation and acid phosphatase (ACP) activity in the brain tissues than that of group A; as well as significantly lower catalase (CAT), superoxide dismutase (SOD), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities. However, administration of honey to Cd-exposed rats ameliorated the Cd-induced changes by causing a reduction in lipid peroxidation and maintaining the activities of these enzymes in the brain tissues within levels significantly similar to that of the control group. This suggests that honey produces an ameliorative effect on Cd-induced injuries in the brain tissues at acute and sub-chronic levels.

Keywords: *Cadmium, Honey, Toxicity, Brain, Acute exposure, Chronic exposure*

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1. Introduction

Cadmium, a naturally occurring heavy metal, can be found in the earth's crust in the form of cadmium oxide, cadmium chloride, or cadmium sulfate/sulfide (Peana *et al*., 2023; ATSDR, 2014). It is a soft, malleable and ductile metal having a silver-white colour/appearance (Bashir *et al.*, 2014), and occurs in the environment as a by-product of zinc, lead and copper extraction, which is released into rivers, air and soil (Souza-Arroyo *et al*., 2022; ATSDR, 2014; Sarkar *et al.*, 2013).

According to Wang *et al*. (2023), Zou *et al*. (2021), Andujar *et al.* (2010), Yu *et al.* (2010) and Buxbaum and Pfaff (2005), cadmium has many common industrial applications including being a key component in battery and plastic production, and its use in electroplating and nuclear fission. In spite of its many useful industrial applications, cadmium, in its various forms, has detrimental effects on humans and animals, as they have been found to be carcinogenic (Souza-Arroyo *et al*., 2022; Ankit *et al*., 2021; Adikwu *et al.*, 2013; Godt *et al.*, 2006). According to Liu *et al*. (2022), Naksen *et al*. (2022), Zou *et al*. (2020) and ATSDR (2014), cadmium has also been found to be a contributor of many cardiovascular, neurological, gastrointestinal, renal, reproductive, respiratory and developmental disorders.

Cadmium-induced toxicity is mediated through different routes in cells and tissues such as oxidative stress and interaction between cadmium and essential metals (Peana *et al*.,2023; Cuypers *et al.*, 2010). Oxidative stress caused by cadmium occurs via increase in reactive oxygen species, which alter tissue antioxidant defense systems and contribute to increased peroxidation of membrane lipids, mutations in DNA, apoptosis and alterations in gene expression (Gasmi *et al*., 2021; Branca *et al*.,2020; Atagana and Asagba, 2015; Ognjanovic *et al.*,

2010). Given the rapid increase in industrialization, oil exploration, burning of fossil fuels and electronic waste, human contact with cadmium is inevitable. Thus, the search for potential ameliorators of cadmium is an important area of research. The deleterious adverse effect on most of the organs/tissues of humans and animals arising from cadmium exposure has been extensively studied (Satarug *et al*., 2022; Lv *et al*., 2021; Asagba 2010; Eriyamremu *et al*., 2005; Asagba and Obi, 2004).

Although, according to Bernard (2008), no known compound has been approved for the treatment of cadmium toxicity, many plant extracts and animals products have been evaluated in the treatment of cadmium, one of which is honey, as several studies (Eze and Asomugha, 2022; Quddus *et al*., 2021; Atagana and Asagba, 2015; Abdelaziz *et al*., 2013; Abdel-Moneim and Ghafeer, 2007) on the protective effect of honey on different organs and tissues such as the blood, liver, kidney, lungs, testes of rats exposed to cadmium toxicity have been conducted. The protective effect of other therapeutic agents on cadmium-induced toxicity in different organs and tissues such as the liver, kidney, lungs, testes, as well as the heart and brain of rats have also been extensively studied (Amr *et al*., 2023; Orororo *et al*., 2018; Brzoska *et al*., 2016; Alpsoy *et al*., 2014; Adikwu *et al*., 2013; Obioha *et al*., 2009). However, there is paucity of information on the effect of honey on cadmium-induced brain injury.

Honey has been suggested and shown to play an essential role in ameliorating the adverse effects of cadmium exposure in many organs/tissues (Ahmed *et al*., 2018; Atagana and Asagba, 2015; Abdelaziz *et al*., 2013; Abdel-Moneim and Ghafeer, 2007). According to Ahmed *et al*. (2018) and USDA (2018), honey contains amongst others, zinc, magnesium, vitamins B_6 and C, which independently or along with antioxidant enzymes, protect cells against oxidative damage arising from cadmium-induced oxidative stress. According to Quddus *et al*. (2021), Abdel-Moneim and Ghafeer (2007), Gheldof *et al*. (2002) and Martos *et al*. (2000), honey, in addition to its nutrients, contain minute quantities of catalase, flavonoids and phenolic compounds, which are suggested to have anti-oxidative potentials. The presence of these compounds in honey, may be the reason why it plays a protective role on organ and tissue damage caused by cadmium-induced oxidative stress, as reported in several studies (Eze and Asomugha, 2022; Ahmed *et al*., 2018; Atagana and Asagba, 2015; Abdelaziz *et al*., 2013; Abdel-Moneim and Ghafeer, 2007).

The use of honey in ameliorating the effect of cadmium-induced toxicity in brain tissues is however not well documented and has therefore not been properly addressed. This study would thus provide scientific evidence on the effect of honey on some biochemical parameters in the brain tissues of cadmium-exposed rats at sub-chronic and acute levels.

2. Materials and methods

2.1 Chemicals

All materials (including chemicals and reagents) used for this study were of analytical grade.

2.2 Honey

Natural honey was procured from Black Ebony Resources Technology Incubation Centre (TIC), National Board for Technology Incubation (NBTI), Federal Ministry of Science and Technology, Warri, Delta State.

2.3 Albino Wistar Rats

Thirty (30) adult albino Wistar rats, with mean body weight of 180 ± 5.5 g, which were used for this study, were procured from the animal house of College of Health Sciences, Delta State University, Abraka, Nigeria. The animals were for the duration of the research, cared for, maintained and housed in standard animal cages under controlled environmental condition of 12-hour dark-light cycle, in line with the NIH (1985) guide on the use and care for laboratory animals. They were allowed to acclimatize for a period of one week and were fed with growers mash and water *ad libitum.*

2.4 Experimental design

The experimental design was modified from Atagana and Asagba (2015). The rats were divided into six groups designated A-F, with each group containing five rats each. Animals in group A (control) were fed with growers mash and water daily for a period of four (4) weeks. This served as the normal control group. Group B animals (sub-chronic cadmium only) were administered 2mg/kg cadmium ($CdCl_2$) by intraperitoneal injection (IP), three (3) times per week, for a period of four (4) weeks. Group C animals (sub-chronic cadmium + honey) were for a period of four weeks concurrently administered 2 mg/kg cadmium by intraperitoneal injection (IP), thrice weekly, and 1 ml/kg honey mixed with water (in a ratio 1:2) orally, once daily. Animals in Group D (acute cadmium only) were treated with 4 mg/kg body weight cadmium (in the

form of cadmium chloride [$CdCl_2$]) by intraperitoneal injection (IP), twelve (12) hours before sacrifice. Animals in group E (acute cadmium + honey) were administered cadmium (in the form of cadmium chloride [$CdCl_2$]) at a dosage of 4 mg/kg body weight by intraperitoneal injection (IP), twelve (12) hours before sacrifice; and 1 ml/kg body weight of honey mixed with water (in a ratio 1:2) orally. Group F (honey only) comprised of animals administered 1 ml/kg of honey mixed with water (in a ratio 1:2) orally, once daily for four weeks. Animals in all the groups were also fed with growers mash and water *ad libitum* for the duration of the treatment.

At the end of the treatment period, the animals from all the groups were sacrificed under chloroform anesthesia. The animals were then dissected and their brains and hearts harvested, washed in normal saline, blotted individually on ash free filter paper, patted dry and weighed. The weighed organs were homogenized under cold conditions in 0.9% normal saline (sodium chloride) using mortar and pestle. The homogenates were centrifuged at 5000 g for 10 minutes and the supernatants obtained were collected in universal bottles and stored in a refrigerator, awaiting biochemical assays.

2.5 Lipid peroxidation analysis

Lipid peroxidation was analysed by measuring the formation of malondialdehyde (MDA), following the method described by Varshney and Kale (1990).

2.6 Determination of alanine aminotransferase (ALT) activity

Alanine aminotransferase (ALT) activity was determined using an assay kit (Randox) as described by Reitman and Frankel (1957).

2.7 Determination of aspartate aminotransferase (AST) activity

The assay for aspartate aminotransferase (AST) activity was carried out using an assay kit (Randox) as described by Reitman and Frankel (1957).

2.8 Determination of alkaline phosphatase (ALP) activity

The assay for alkaline phosphatase (ALP) activity was carried out using an assay kit (Teco diagnostics) as described by Roy (1970).

2.9 Determination of acid phosphatase (ACP) activity

The assay for acid phosphatase (ACP) activity was carried out using an assay kit (Teco diagnostics) as described by Hillman (1971).

2.10 Determination of superoxide dismutase (SOD) activity

Superoxide dismutase (SOD) activity was determined using a method described by Misra and Fridovich (1972).

2.11 Determination of catalase (CAT) activity

Catalase (CAT) activity was carried out using a method described by Kaplan *et al*. (1972).

2.12 Statistical analysis

Mean ± standard deviation was used to show data obtained from the study. One-way analysis of variance (ANOVA) was implored to analyze data of test samples and Fisher's LSD test was implored for significance testing ($P < 0.05$) using SPSS version 21 Statistical software.

3. Results

Table 1 showed the effect of honey on MDA levels, SOD and CAT activities in the brain tissues of Wistar rats exposed to cadmium. The rate of lipid peroxidation (MDA levels) in the brain tissues of the rats exposed to cadmium only were significantly higher ($P<0.05$) when compared with the control at the end of the treatment period. This was observed for both the sub-chronic and acute treatments. Rats treated with honey alone had MDA levels significantly lower ($P<0.05$) than the control while cadmium-exposed rats treated with honey (at acute and sub-chronic levels) had MDA levels lower than the groups treated with cadmium only, but higher than the control group and the group treated with honey only. This indicates the protective effect of honey against lipid peroxidation in the brain tissues. These findings showed that cadmium toxicity in the brain tissues was manifested by elevation of lipid peroxidation for both the acute and sub-chronic exposures. However, treatment of cadmium-exposed rats with honey reduced the effect of cadmium on lipid peroxidation in the brain tissues. The activity of SOD and CAT were significantly lower in rats exposed to cadmium alone (Group B and D) compared to control (Group A). Conversely, the activity of SOD and CAT were not significantly affected in rats maintained on honey alone (Group F) relative to control at the end of the exposure periods. The treatment of cadmium-exposed rats with honey (Groups C and E) resulted in significantly higher ($P<0.05$) SOD and CAT

activities when compared with rats exposed to cadmium alone (Group B and D) after the treatment periods. The results indicate that exposure to cadmium lowered the activity of SOD and CAT for both treatments (acute and sub-chronic), but the treatment of cadmium-exposed rats with honey resulted in a significantly higher SOD and CAT activities in the brain tissues.

Table 1: Effect of honey on MDA levels, SOD and CAT activities in the brain tissues

Groups	MDA level and Antioxidant Enzyme Activity in Brain Tissues		
	MDA (µmole/mg)	SOD (U/g)	CAT (U/g)
Group A: Control	2.74 ± 1.12^{a}	21.75 ± 1.50^{a}	2.32 ± 0.03^{a}
Group B: Sub-chronic Cadmium Only	8.54 ± 1.86^{b}	15.75 ± 0.96^{b}	1.36 ± 0.09^{b}
Group C: Sub-chronic Cadmium + Honey	3.58 ± 1.20^{c}	22.50 ± 1.92^{a}	2.33 ± 0.01^{a}
Group D: Acute Cadmium Only	6.03 ± 2.11^{b}	16.25 ± 1.96^{b}	1.25 ± 0.16^{b}
Group E: Acute Cadmium + Honey	3.23 ± 1.67^{c}	22.20 ± 2.00^{a}	2.49 ± 0.25^{a}
Group F: Honey Only	1.46 ± 1.50^{d}	23.26 ± 1.54^{a}	2.32 ± 0.02^{a}

Values are expressed in Mean ± Standard Deviation (SD). n = 5.
Values on the same column with different superscript are significantly different at ($P<0.05$).

The effect of honey on ALT, AST, ALP and ACP activities in the brain tissues of rats exposed to cadmium are presented in Table 2. ALT, AST and ALP activities in the brain tissues of rats exposed to cadmium at sub-chronic levels (Group B) and acute levels (Group D) were significantly lower ($P<0.05$) when compared to the control (Group A). However, no significant difference was observed in their activities in the brain tissues of cadmium-exposed rats treated with honey (Groups C and D), those maintained on honey alone (Group F) and the control group. Thus, the result shows that cadmium lowered ALT, AST and ALP activities in the brain tissues of cadmium-exposed rats, whereas treatment with honey led to increase in their activities. The activities of ACP in the brain tissues of rats exposed to cadmium (Groups B and D) were significantly higher ($P<0.05$) compared to the control (Group A) indicating that cadmium caused a significant increase in the activity of the enzyme in the brain tissues after acute and sub-chronic exposure. Conversely, cadmium-exposed rats treated with honey revealed significantly lower ACP activity which was comparable with the control rats and to rats exposed to honey alone (Group F). The result indicates that exposure to cadmium increased the activity of ACP in the brain tissues of rats whereas treatment with honey lowered its activity to level similar to that of the control.

Table 2: Effect of honey on ALT, AST, ALP and ACP activities in the brain tissues of rats exposed to cadmium.

Groups	Enzyme Activity in Brain Tissues (U/L)			
	ALT	AST	ALP	ACP
Group A: Control	21.75 ± 1.50^{a}	41.20 ± 1.25^{a}	148.81 ± 23.69^{a}	13.15 ± 1.10^{a}
Group B: Sub-chronic Cd Only	15.75 ± 0.96^{b}	18.32 ± 0.98^{b}	57.08 ± 11.31^{b}	21.61 ± 0.53^{b}
Group C: Sub-chronic Cd + Honey	22.50 ± 1.92^{a}	38.50 ± 1.50^{a}	138.50 ± 26.42^{a}	13.75 ± 0.55^{a}
Group D: Acute Cd Only	16.25 ± 1.96^{b}	15.40 ± 3.20^{b}	57.02 ± 8.68^{b}	22.00 ± 1.30^{b}
Group E: Acute Cd + Honey	22.20 ± 2.00^{a}	38.32 ± 1.53^{a}	128.34 ± 7.30^{a}	14.99 ± 1.59^{a}
Group F: Honey Only	23.26 ± 1.54^{a}	39.40 ± 1.50^{a}	156.40 ± 22.85^{a}	13.77 ± 1.48^{a}

Values are expressed in Mean ± Standard Deviation (SD). n = 5.
Values on the same column with different superscript are significantly different at ($P<0.05$).

4. Discussion

This study investigated the effect of honey on some biochemical parameters in the brain tissues of Wistar rats following sub-chronic and acute exposures. The study revealed that upon exposure to cadmium, there was a significant increase in MDA levels brought about by lipid peroxidation in the brain tissues of the rats. This increase in MDA levels was due to increased lipid peroxidation as a result of the toxic effect of cadmium, which is supported by studies (Morsy *et al*., 2021; Waheeb and Ali, 2020; Kheradmand *et al.*, 2015; Alpsoy *et al*., 2014; Kini *et al.*, 2011; Shagirtha *et al*., 2011)

in which cadmium has been fingered as a toxicant capable of inducing oxidative stress which results in increased lipid peroxidation. In the presence of honey however, it was observed that MDA levels were significantly reduced in the brain tissue, compared to the control group. This indicates that honey plays a protective role against cadmium-induced lipid peroxidation in the brain of rats. Honey contains sugars as well as flavonoids, phenolic compound and carotenoid which function as antioxidants to scavenge free radicals (Quddus *et al*., 2021). This decrease in lipid peroxidation in the presence of honey has also been previously reported by Atagana and Asagba (2015), Shalaby and Saleh (2011) and Abdel-Moneim and Ghafeer (2007).

There was decrease in the activity of CAT and SOD in the brain tissue of rat exposed to cadmium only. This could be due to oxidative stress caused by cadmium toxicity. CAT and SOD are responsible for the cytoprotection of the brain. This agrees with the work of Oladele *et al*. (2020), that reported a decrease in CAT and SOD of rat exposed to cadmium only. The oxidative stress biomarkers were ameliorated by honey resulting in the increase of CAT and SOD activities. The protective activity of honey is because it possesses antioxidants, bioactive compounds and the ability to mop up free radicals (Quddus *et al*., 2021; Oladele *et al*., 2020)

Cadmium exposure caused a significant increase in the activity of ACP in the brain tissues but induced a decrease in the activities of ALT, AST and ALP. This is an indication that cadmium exposure resulted in injuries in the brain tissues which is in conformity with the observed increase in lipid peroxidation in the tissues following chronic cadmium exposure. It has been demonstrated that bioaccumulation of cadmium in the tissues cause cellular damage due to oxidative stress, which then initiates oxidative tissue cell damage through membrane lipid peroxidation (Oladele *et al*., 2020; Waisberg *et al*., 2003).

Alkaline phosphatase (ALP) is found predominantly in the plasma membrane and endoplasmic recticulum (Shahjahan *et al*., 2004), and is generally used alongside aminotransferases (AST and ALT) to assess plasma membrane integrity. Thus, the decreased activity of these enzymes was as a result of their leakage into blood stream due to the cadmium-induced compromise of the brain membrane integrity. The decrease in ALP, AST and ALT activity in the brain tissues due to cadmium toxicity is supported by Asagba *et al*. (2007), where similar data on liver, testis and prostate was reported. On the other hand, there was a significant increase in the activities of these enzymes (ALP, AST and ALT) in the groups treated with honey compared to the test (cadmium only) groups, indicating a reduction in damage to the cells and tissues of the brain. This observation is in tandem with previous studies (Abdel-Monein and Ghafeer, 2007; Atagana and Asagba, 2015). Thus, honey induced normalization in the activities of ALP, AST and ALT observed in the brain tissues of Cd-exposed rats. The decrease in the incidence of brain tissue injury is brought about by the protective properties of honey and it is also in synergy with the observed ameliorative effect of honey against membrane lipid peroxidation brought about by cadmium exposure.

Increased ACP activity was as a result of the increase in acidity of the tissues brought about by oxidative stress. Reduction in intracellular pH has been linked to the onset of lipid peroxidation brought about by oxidative stress (Ciriolo *et al*., 1997). Increase in ACP activity due to cadmium-induced oxidative stress has also been previously reported by Oladele *et al*. (2020), Onwuka *et al*. (2010), Obianime and Roberts (2009) and Asagba *et al*. (2007).

5. Conclusion

This study has demonstrated that cadmium-induced oxidative stress altered the activity of some important enzyme systems in the brain tissues. However, treatment of cadmium-exposed rats with honey exhibited significant ameliorative and protective actions against cadmium-induced toxicity in the brain brought about by oxidative stress. The ameliorative and protective actions are carried out by the inhibition of lipid peroxidation, as well as the normalization of the activities of antioxidant enzymes (SOD and CAT) and other important enzymes (ALP, AST, ALP and ACP) in the brain tissues. The protective role of honey is due to the presence of flavonoids, catalase, ascorbic acid and phenolic compounds, which confer anti-oxidative properties on it. It may therefore be suggested that honey can serve as a potential therapeutic and ameliorative candidate in the treatment of cellular and tissue damage associated with cadmium-induced oxidative stress in the brain tissues.

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