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Original Article

Hepatoprotective effect of sandfish "*Scincus scincus*" extract on cadmium-induced hepatotoxicity in rats

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Abstract

Hepatotoxicity is defined as injury to the liver or impairment of the liver function after exposure to various risk factors. This study was planned to investigate hypothesis of hepatoprotective effect of sandfish (*Scincus scincus*) consumed for its health virtuous by local Saharan peoples from Algeria. For this purpose, sandfish extract benefits against cadmium chloride ($CdCl_2$)-induced liver toxicity in rats was evaluated. The rats (n=23) were divided into 4 groups; the control group (n= 5) received a vehicle, the extract group (n= 5) received via gavage sandfish extract (100mg/kg), Cadmium group (n= 6) received $CdCl_2$ (1 mg/kg, intraperitoneal injection), cadmium +extract group(n= 7) received after the single injection of $CdCl_2$(1mg/kg) the sandfish extract (100 mg/kg, orally).The experimentation was performed over 56 days. Body weight, relative liver weight (LW) and biochemical parameters namely glucose, triglycerides, cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and direct bilirubin (DB) were measured. Glutathione (GSH) and Malondialdehyde (MDA) activities were measured to evaluate the changes in antioxidative system and lipid peroxidation activity in liver tissues. Relative LW, MDA, ALT and TB were significantly increased by $CdCl_2$ treatment. The treatment with sandfish extract after $CdCl_2$ injection reduced significantly ALT, AST and TB. The GSH level was significantly altered (0.19±0.05 mg/g) by Cd treatment, which was recovered (0.43±0.08 mg/g) after that by sandfish extract gavages. In conclusion, inclusion of sandfish in rat diet showed significant evidences of hepatoprotective effect in response to acute Cd hepatotoxicity.

Keywords: Biochemical parameters, Cadmium, GSH, Hepatoprotective effect, *Scincus scincus*

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Introduction

The skink family (Scincidae), which is part of the reptile class (Reptilia), was used in ancient medicine to treat a variety of conditions. The sandfish (*Scincus scincus*) is one of the most well-known members of this family. The name "pharmacist's skink" (*Scincus officinalis*) was given to sandfish because of their medicinal value. A prominent medical usage of sandfish in ancient times was for problems related to the sexual system for female fertility and to enhance male potency (Shemesh, 2011).Because of their high nutritional value (high in tocopherol and zinc, sandfish has been used as a food for male infertility (mixed with honey after drying and milling) (Toumi et al., 2017).

Cadmium (Cd) is known as major toxic and non-biodegradable environmental and industrial contaminant (Rabiya and Basharat, 2018; Khasanah and Rachmawati, 2020). Based on its specific chemical and physical properties, its industrial applications have been established. Cd is a ubiquitous toxic heavy metal inducing wide health problems and diverse clinical manifestation (cardiovascular, pulmonary, skeletal, renal, hepatic and reproductive) by affecting many organs and death in some cases. It is also classified as a group I high potential carcinogen metal (IARC, 2004).Many reports of Cd-induced toxicity showed that its most important target organ is liver because of its long biological half-life leading to metal accumulation in this organ and inducing high oxidative stress, hepatotoxicity and liver necrosis (Swiergosz-Kowalewska, 2001; Krichah et al., 2003;Gong et al., 2014). Various pathological mechanisms of Cd have been demonstrated. It affects cell proliferation, differentiation following a chromosomal aberration and gene mutations, enhancing production of reactive oxygen species (ROS) and inhibiting the activity of antioxidant enzymes (Joseph, 2009; Rani et al., 2014). It also induces cytotoxicity and cells apoptosis by affecting the cellular level of Ca^{2+} as well as the caspases activities and nitrogen-activated protein kinases (MRPKs) (Brama et al., 2012).

Free radicals are formed naturally in the body during metabolic processes, but excessive production of these free radicals can cause oxidative stress, which can lead to a variety of diseases**.** Antioxidants are compounds that prevent oxidative stress by inhibiting free radicals (Patel et al., 2012). Vitamins like ascorbic acid, retinol, and alpha-tocopherol, as well as essential minerals like calcium, selenium, zinc, and magnesium, have been shown to protect against Cd toxicity in some studies (Bolkent et al., 2007; Flora et al., 2008; Zhai et al., 2015). Chelating agents, phytochemicals (Anthocyanin, Naringenin, Quercetin,Catechin), probiotics and application of nanoparticle for Cd poisoning were also experimented (Babaknejad et al., 2015; Zhai et al., 2015). Some edible plants such as soybean, ginger, green tea, curry leaf and tomato showed protective effect against Cd toxicity (Zhai et al., 2015).

The use of saharian animal remedies is very widespread (opotherapy) in the southern Algeria, especially by the famous sandfish (*Scincus scincus*) (Toumi et al., 2019). It is consumed to fight against iron deficiency (contains 27mg / 100g of iron) (Toumi et al., 2017) and given to anemic people and pregnant women for preventive purposes (Toumi et al., 2019).The use of sandfish as a remedy for certain diseases has been very well known in this region for several years, in particular against male's lack of vitality (natural aphrodisiac), infertility, arthritis, hormonal imbalance and poisoning(Toumi et al., 2016).The sandfish consumption is anchored in the food habits of the natives. This reptile was always omnipresent in their homes. However, there are no studies on its hepatoprotective effect. The objective of this study is to evaluate the efficacy of sandfish (*Scincus scincus*) in Cd-induced liver toxicity of rats.

Material and Methods

Animals and experimental design

The experiment was performed on 23 male Albino Wistar rats weighing approximately 250 g. During the experiment, these rats were permitted unrestricted access to regular rat chow and drinking water after being acclimatized for 15 days under standard controlled circumstances (temperature 25 ± 2 °C, relative humidity 35% to 60%, 12-hour light-dark cycle). All animals were weighed at the beginning of the experiment and at the last day of the experiment before their sacrifice. The rats were randomly divided into four groups (Table 1): Control group (C-group, n=5), extract group (Ext-group, n=5), cadmium group (Cd-group, n=6, Cadmium + extract group (Cd-extract group, n=7). Parenteral administration of NaCl 0.9% was performed for C-goup and Ext-group followed next day by a period of 56 days of oral gavage using Gum Arabic solution 1% and *Scincus scincus* extract

(100 mg/kg), respectively. Animals of theCd-group and Cd-extract group were injected parenterally by cadmium (1 mg/kg) one day before a period of 56 days of oral gavage using Gum Arabic solution 1% and *Scincus scincus* extract (100 mg/kg), respectively.

Table-1. Experimental protocol, administration form and experimental duration for the studied groups

Groups	One day before oral gavage	56 days of oral gavage
C-group (n= 5)	Injection of NaCl 0.9%	Gum Arabic solution 1%
Ext-group (n=5)	Injection of NaCl 0.9%	*Scincus scincus* extract 100mg/kg
Cd-group (n=6)	Injection of cadmium 1 mg/kg	Gum Arabic solution 1%
Cd-extract group (n=7)	Injection of cadmium 1 mg/kg	*Scincus scincus* extract 100mg/kg
C-group: Control group; Ext-group: Extract group; Cd: Cadmium.		

Scincus scincus extraction

Forty-eight dry *Scincus scincus* were purchased from Oued Souf (south east of Algeria) and they were used for the extraction (Figure 1). The extraction was done with maceration technique according to Minaiyan et al. (2014). Dry *Scincus scincus* were finely powdered and the obtained powder (347 g) was macerated in 104ml of ethanol (96%) during 72 h under continuous agitation. After cooling, the mixture is filtered through gauze and then through Whatman paper (3mm).The filtrate was evaporated using a rotary evaporator which removes the solvent under vacuum; the obtained aliquots were placed in Petri dishes and then dried in laboratory oven at 40°C until the dry extract was obtained with a yield production of 6.98 %. The obtained dry residue was scraped off and then stored at 4°C in a tightly closed bottle. A quantity of 1g of obtained dry residue was dissolved in 100ml of Gum arabic solution to obtain a homogenized solution for gavage.

Blood samples collection

On the final day of experimental period (56 days), blood samples were collected by retro-orbital bleeding, after anesthetic administration. Hematological parameters were measured using a blood tube containing the heparin as an anticoagulant. Plasma was separated and frozen (−80 °C) for biochemical assays. The liver was removed and weighed on an electric balance in grams, and relative liver weight (liver to body weight ratio) was calculated. For the investigation on antioxidant status, the hepatic tissue sample was immediately frozen and stored at 80 °C.

Figure-1. Freshly collected sandfish (A) which were dried (B) ready to be used for preparing *Scincus scincus* extract.

Biochemical Assays

Fresh plasma from rats starved by 12 h was used for determinations of some metabolites like glucose, triglyceride, cholesterol and some hepatic enzymes such as direct bilirubin, total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). All biochemical assays were performed by using standard kits (ERBA) in automated random access clinical chemistry analyzer (Erba Mannheim XL 200, India).

Assay of oxidative stress

For this study, glutathione (GSH) and Malondialdehyde (MDA) levels were measured by following methods of Weckbecker and Cory (1988) and Esterbauer et al. (1992), respectively.

Statistical analysis

Descriptive statistics were applied for each parameter studied using SPSS 25 (SPSS Inc. Chicago, IL, USA) software. The significance level of the independent variables (treatments) on the averages of the quantitative continues parameters (body weight and blood biochemical) was investigated using One-way ANOVA and Kruskal-Wallis nonparametric tests according to normality distribution of each parameter.

For pairwise comparison, LSD was carried out for normally distributed parameters and Mann-Whitney U test was used for non-normally distributed parameters. P-values less than 0.05 were considered significant.

Results

The gain in body weight was compared with that of control group (Table 2). Non-significant ($p \geq 0.05$) changes were observed in the body weight. Cd treatment increased ($p<0.01$) the relative liver weight (L.W) in Cd-group (3.08±0.13) compared to C-group (2.48±0.02). However, the administration of sandfish extract in Cd-extract group did not change significantly the relative L.W when compared with Cd-group (3.08±0.13 vs.2.99±0.10 g, $p \geq 0.05$, Table 2).

Table-2. Mean ± SE of body weight gain and relative liver weight.

	C-group	Ext-group	Cd-group	Cd-extract group
Gain of B.W(g)	12.4±5.15	3.28±1.66	15.8±5.90	26.5±5.94
Relative L.W	2.48 ± 0.02^{b}	2.54 ± 0.08^{b}	$3.08\pm0.13^{a**}$	$2.99\pm0.10^{a**}$

B.W: body weight; L.W: liver weight; Cd: Cadmium; C-group: Control group; Ext-group: Extract group; *a, b: The same letters in the same line marks statistically no significant differences between the groups (p >0.05);* * $p < 0.05$; ** $p < 0.01$.

Cadmium treatment in Cd-group did not alter significantly triglyceridemia (42.3±1.94 mg/dl) and glycaemia (130±3.11 mg/dl) when compared with C-group (50.4±4.98 and132.75±3.30 mg/dl, respectively). The Cd-extract group showed significantly ($p<0.05$) high level of plasma triglycerides (59.1±6.89 mg/dl) but not that of plasma glucose (134±7.73mg/dl) compared with Cd-group (42.3±1.94 and 130±3.11 mg/dl, respectively, Table 3).

Alanine aminotransferase (ALT) and total bilirubin were increased ($p<0.05$) by Cd treatment compared with control group. Aspartate aminotransferase (AST) was increased ($p>0.05$) in Cd treated group as compared to control group. Administration of sandfish extract decreased the level of ALT, AST and total bilirubin in Cd-extract treated rats as compared to Cd treated rats. For the rest of the parameters there was no significant difference between groups (Table 3).

Figure 2 illustrates the levels of GSH in the liver tissue of the control and experimental rats. Results showed a significant ($p<0.05$) decrease of GSH activity in Cd-treated rats (0.19±0.05 mg/g) in comparing with C-group (0.29± 0.02 mg/g). Treatment with sandfish extract (100 mg/kg) in Cd-extract treated rats significantly increased GSH activities in liver tissue (0.43±0.08 mg/g)as compared to Cd group (0.19±0.05 mg/g).Sandfish extract alone significantly ($p<0.05$) increased the level of GSH (0.51± 0.07 mg/g)compared with control group (0.29± 0.02 mg/g).

Table 3. Mean± SE of plasmabiochemical parameters of different groups.

	C-group	Ext-group	Cd-group	Cd-extract group
Glucose (mg/dl)	$132\pm3.30^{a*}$	113 ± 4.27^{b}	$130\pm3.11^{a*}$	$134\pm7.73^{a**}$
Triglyceride (mg/dl)	$50.4\pm4.98^{b*}$	$50.2\pm4.06^{b*}$	$42.3\pm1.94^{b*}$	59.1 ± 6.89^{a}
Cholesterol (mg/dl)	58±4.76	49.7±5.37	57.3±3.10	52±2.97
AST (IU)	131 ± 15.9^{ab}	$108\pm6.75^{b**}$	153 ± 5.08^{a}	$125\pm3.20^{b*}$
ALT (IU)	$57.2\pm2.88^{b*}$	$48\pm6.48^{b**}$	98.6 ± 26.10^{a}	$61.6\pm6.27^{b*}$
Direct bilirubin(mg/dl)	0.034±0.005	0.044±0.004	0.043±0.002	0.04±0.002
Total bilirubin(mg/dl)	$0.17\pm0.005^{b*}$	$0.14\pm0.05^{b**}$	0.49 ± 0.03^{a}	$0.16\pm0.05^{b**}$

Cd: Cadmium; AST: Aspartate transaminase; ALT: Alanine transaminase; a, b: Means with the same letter are not significantly different between the groups (p>0.05); * $p< 0.05$; ** $p< 0.01$.

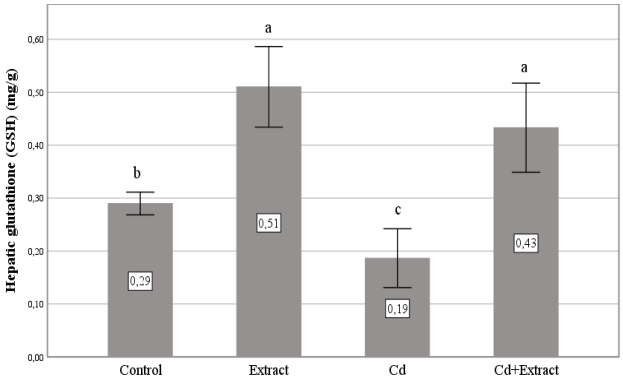

Figure-2. Hepatic glutathione (GSH) levels in different groups.

a, b, c: The same letters marks statistically no significant differences between the groups (p>0.05).Cd: Cadmium.

The changes in the levels of hepatic Malondialdehyde (MDA) in control and experimental rats are shown in Figure 3. Cd induced a significant (P< 0.05) increase of hepatic MDA level (10±0.94 nmoles/g) compared with C-group (7.59±0.49nmoles/g). Treatment with

sandfish extract non-significantly decreased the hepatic levels of MDA (8.72±0.39 nmoles/g, $p>0.05$) compared with Cd-group (10±0.94 nmoles/g).

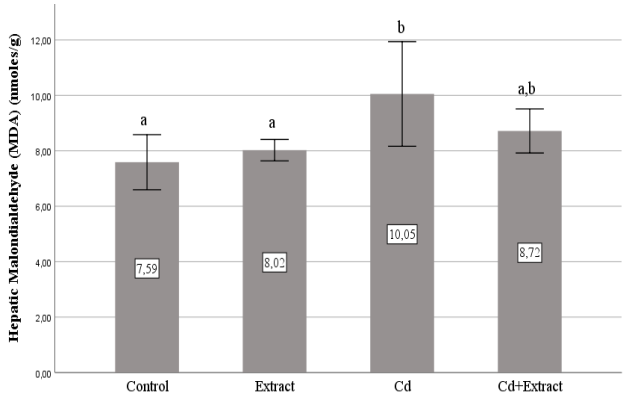

Figure-3. Hepatic Malondialdehyde (MDA) levels in different groups.

Cd: Cadmium; a, b: The same letters marks statistically no significant differences between the groups (p>0.05).

Discussion

The obtained results revealed no significant change in body weight gain (Table 1) in the four experimental groups, which is in disagreement with findings reported by Toumi et al. (2018). These authors found that the rats given *Scincus scincus* head and body showed a significant increase in body weight gain during the experiment period (6 weeks) when compared to the control group. According to Toumi et al. (2017) the increase in body weight of rats is due to the very rich composition of protein, lipid, sugar and mineral salts of *Scincus scincus*.

The acute Cd-administration in our study resulted in a significant increase in liver relative weight. This finding is similar to that of Krichah et al. (2003) and Habeebu et al. (2000), who found granulomatous inflammation and proliferating nodules in the liver parenchyma of treated mice.

The plasma levels of ALT and total bilirubin were found to be higher in Cd-intoxicated rats in this study, which agrees with the findings of Prabu et al. (2008) and Renugadevi and Prabu (2010). In this way, El Maraghy et al. (2001) found that a single Cd dose (0.5 mg/kg and 2 mg/kg) resulted in a significant increase in ALT. However, Andjelkovic et al. (2019) found no significant change in AST and ALT levels after a single oral dose of Cd (15mg/kg). According to Hoffmann and Solter (2008), serum ALT activity increased in the liver than in other organs after inducing hepatocellular injury. This finding led to the early conclusion that changes in serum ALT activity are unique to hepatocellular injury. In the current study, the administration of sandfish extract (100 mg/kg) after a single intraperitoneal dose of Cd (1 mg/kg) could attenuate Cd-induced hepatotoxicity as demonstrated by a marked reduction in levels of ALT, AST and total bilirubin in Cd-extract group, thus providing protection against Cd toxicity in rats. Similarly, Naringenin (50 mg/kg) reduced Cd-induced hepatotoxicity in rats, as attested by decreased levels of AST, ALT, ALP, LDH, GGT, and serum bilirubin, providing protection against Cd toxicity (Renugadevi and Prabu, 2010). This suggests that naringenin can stabilize the cell membrane and give protection against Cd-induced hepatic damage.

Sandfish extract caused hypoglycemia, according to our findings. In contrast to our findings, Toumi et al. (2019) found no significant difference in plasma glucose levels between groups. The normal value of blood glucose can be explained by the low sugar content of sandfish. Statistical analysis showed that sandfish extract administration did not change significantly plasma level of triglycerides and cholesterol. In contradiction to our results, Toumi et al. (2019) found that sandfish body and head significantly induced very highly decrease in cholesterol and triglycerides levels which helps to maintain a reduced level of circulating levels of lipid metabolites and avoids lipid disturbance complications in peoples consuming it when the cytoplasmic membranes as well as circulating lipids undergo oxidative attacks, they generate Malondialdehyde (MDA). Thus, this molecule constitutes a reliable marker of lipid peroxidation (Djukić-Ćosić et al., 2008; Alyasiri et al., 2018).The proposed hypothesis to explain mechanisms by which Cd induced damage is lipid peroxidation as a major result of oxidative stress induced by Cd and was found to be correlated with Cd exposure levels (Valko et al., 2006).Several authors found that MDA levels in liver tissue were significantly increased subsequently to a single administration of Cd (0.5 mg/kg) or (1 mg/kg), which is consistent with our results (El Maraghy et al., 2001; Kara et al.,2005).However, Andjelkovic et al. (2019) found that MDA was not altered in rat liver after single oral dose of Cd (15 and 30 mg/kg body weight). El Maraghy et al. (2001) reported that the reason for Cd intoxication in acute Cd intake was the induction of lipid peroxidation. Lipid peroxidation can

be related not only to antioxidative status disturbances, but also to changes in Fe content in liver (Matović et al., 2015).

Glutathione (GSH) is a tripeptide that carries more than 90% of the human body's non-tissue sulphur and is one of the most essential antioxidant non-enzymatic defense components (Matović et al., 2015; Razali et al., 2019).The tripeptide GSH is the first line of antioxidant defense and is thought to be the most important redox buffer in the cell (Branca et al., 2020).In agreement with our findings; El Maraghy et al. (2001) found thatsingle Cd dose (0.5 mg/kg) and (2 mg/kg) induced the decrease of hepatic GSH level. According to Sunitha et al. (2001), Cd binds exclusively to GSH's sulfhydryl groups, making it inactive. The observed decrease in GSH might be a result of its utilization in the scavenging of free radicals (El Maraghy et al., 2001). Another important mechanism by which Cd causes oxidative stress is depletion of intracellular GSH (Nemmiche, 2017). According to Matović et al. (2013), one of the key mechanisms of Cd intoxication is oxidative stress, with the liver being a critical target organ of acute Cd exposure. Sandfish extract was effective in increasing GSH level and reducing MDA formation non-significantly. Although, there is no precedent studies discussed the effect of sandfish extract on hepatic GSH and MDA. According to Renugadevi and Prabu (2010), naringenin decreased lipid peroxidation and restored antioxidant defenses in the liver. Since the 4-hydroxyl group in the β-ring is a radical target and has electron donating properties, naringenin effectively quenches free radicals. As a result, the membrane is protected from free radical attack and lipid peroxidation is inhibited (Amić et al., 2003).

Conclusion

We evaluated the antioxidant effect of the sandfish extract on the induced experimental hepatotoxicity by Cd in rats. The study provided new insights into therapeutic and hepatoprotective activity that can be resulted by hypoglycemic effect, reduction of MDA, transaminases and total bilirubin levels and increase of GSH level. These findings could be of interest for future research on bioactive molecules, pharmacology and other benefits of sandfish extract.

Ethical Statement: All procedures performed in this study involving experimental animals were in accordance with the ethical standards of the national and international guidelines.

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Conflict of Interest: None
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Contribution of Authors

Lamraoui R & Gherissi DE: Designed the experiment, collected data, performed data analysis and wrote manuscript.
Hachemi M. Laabassi F, Djellal D, Kadrine N, Haddad S, Saoudi SE, Chouit Z, Djellal Z, Fellahi M & Chacha F: Prepared and analyzed the chemicals, prepared the research material, helped in sampling and data collection.