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Article

Attenuation of Rutin on Butachlor-Induced Hepatotoxicity in Rats

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Abstract

Butachlor, a chloroacetanilide herbicide, is used globally as pre-emergence control of unwanted weeds and concerns about its potential adverse effects and toxicity have risen. Rutin is a natural flavonoid with hepatoprotective potentials. The current study aims to investigate the hepatoprotective effect of Rutin on Butachlor-induced hepatotoxicity in rats. Twenty-four male wistar rats weighing between 260 g – 280g were randomized into four (4) groups of six animals each. Group A (control) received only distilled water, group B (Butachlor) received 100 mg/kg body weight (B.W.) Butachlor, and group C (Butachlor + Rutin) received 100 mg/kg B.W. Butachlor and 100 mg/kg Rutin while group D (Rutin) received 100 mg/kg B.W. Rutin. Administration lasted for 14 days and the rats were sacrificed, the liver excised and further processed for biochemical analysis. Administration of Butachlor resulted in hepatotoxicity that was characterized by a significant increase in plasma ALT, AST and ALP levels relative to the control group ($p<0.05$). Also, a significant increase ($p<0.05$) in the level of MDA and NO of Butachlor-treated rats were observed when compared with the control group. Furthermore, altered antioxidant status was observed as activities of enzymatic antioxidants (SOD, CAT, and GST) and concentration of non-enzymatic antioxidants (GSH and AA) were down-regulated. However, co-administration of Rutin with Butachlor significantly attenuated all the alterations in the markers of liver injury and oxidative stress relative to the Butachlor-treated group. Data obtained from this study showed that Rutin offered a protective effect against Butachlor-induced hepatotoxicity in rats.

Keywords: Butachlor; Rutin; Herbicide; Hepatotoxicity; Anti-oxidants; Oxidative stress

1. Introduction

Exposure to several pollutants can cause liver damage, being the principal detoxification organ and site for biotransformation of xenobiotics [1]. Exposure to environmental pollutants such as herbicides induces hepatic damage through different pathways that involve lipids, proteins, carbohydrates, and nucleic acids which then resultin harmful effects [2]. Herbicides such as glyphosate have been shown to cause liver damage in rats [3].

Butachlor (2-chloro-2', 6''-diethyl-N-(butoxymethyl) acetanilide) (figure 1) is a member of chloroacetanilide herbicides used as a pre-emergence control for the undesirable grasses and broadleaf weeds [4]. There have been several reported toxicities of butachlor such as genotoxic effect on amphibians, induction of apoptosis in mammalian cells [5], jaundice, increase in the liver enzyme [6], and pathological changes in the testes and liver of rats [7].

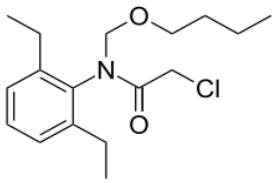

Figure 1: Structure of Butachlor

Butachlor's mechanism of action is through the inhibition of non-sphingolipid very-long-chain fatty acids (VLCFAs) biosynthesis, resulting in a lack of lipids, proteins, and lignin for the plant [8]. Exposure to butachlor symptoms includes eye contact, nose(nasal), and skin (dermal) [9]. Investigations into the metabolism and pharmacokinetics of butachlor have revealed species differences in the way that this molecule is biotransformed and eliminated from the body [10, 11, 12]. Rutin (Figure 2) also called rutoside, is a natural flavonoid from citrus fruit with significant roles in combating cellular oxidative stress and possesses hepatoprotective activity [13,14]. Therefore, this study was designed to investigate the protective effect of rutin against Butachlor - induced hepatoxicity and oxidative stress in rats.

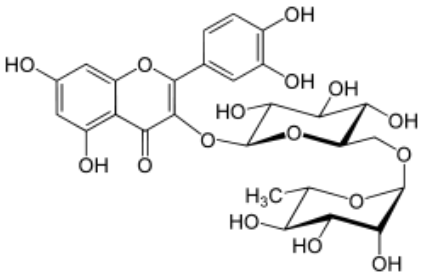

Figure 2: Structure of Rutin

2. Materials and Methods

2.1 Chemicals and Reagents

Sinochem Ningbo Ltd, China, produces butachlor (Striker®). AK Scientific U.S.A. produces Rutin. Sigma Chemical Company (London, UK) provided glutathione (GSH), 1-chloro-2, 4-dinitrobenzene (CDNB), 5', 5'-dintrobenzoic acid (DTNB), para-nitrophenyl phosphate (PNPP), thiobarbituric acid (TBA), and epinephrine. All other chemicals and reagents were purchased from British Drug House in Poole, London, and were of analytical grade.

2.2 Experimental Animals

In this investigation, 24 male rats weighing between 260-280 grams were employed. The animals were obtained from the University of Ibadan's veterinary medicine department's animal breeding section. Prior to the start of the investigation, the animals were acclimatized to laboratory settings for two weeks at the animal breeding facility, Department of Chemical Sciences, Ajayi Crowther University, Oyo, Nigeria. The rats were kept in wire-mesh cages and given free access to food and water.

They were housed under normal conditions of temperature and humidity and fed with a commercial rat diet from Ladokun® Feeds, Nigeria Ltd., Ibadan, Nigeria. Handling of the experimental animals is consistent with international principles on the care and use of experimental animals [15].

2.3 Experimental Design

The animals were compartmentalized into four experimental groups of six animals each. The groupings of the rats is depicted in table 1. 1ml each of the prepared treatments, Butachlor and Rutin were administered. Oral gavage with an oral intubator was used to administer the doses, which were given once a day for 14 days. 24 hours following the last dose, the animals were sacrificed.

Table 1: Animal grouping and drug administration

Experimental Groups	Treatments
Control	Distilled Water
Butachlor	Butachlor (100 mg/kg body weight)
Rutin	Rutin (100 mg/kg body weight)
Butachlor + Rutin	Butachlor (100mg/kg body weight) + Rutin (100 mg/kg body weight)

2.4 Collection of blood samples for plasma preparation

Blood samples were collected by ocular punctures into heparinized tubes. Plasma was prepared by centrifugation for 10 minutes at 4000g in a ThermoFisher Scientific benchtop centrifuge. The clear supernatant was used for the estimation of biomarkers of liver injury.

2.5 Collection of tissue samples

The liver was removed, rinsed in ice-cold 1.15% KCl, blotted, weighed, and homogenized in 4 volumes of ice-cold 0.1M phosphate buffer (pH 7.4). The homogenates were centrifuged at 12000g for 10mins using Eppendorf (UK) refrigerated centrifuge. The supernatant, termed post mitochondria fraction was obtained and stored frozen for subsequent analysis.

2.6 Assay of Biomarkers of Liver Injury

2.6.1 Determination of alkaline phosphatase (ALP) activity in plasma

Alkaline phosphatase activity was determined according to the method described by Wright et al. [16].

2.6.2 Determination of aspartate aminotransferase (AST) activity in plasma

RANDOX® assay kit was used for the determination of AST activity in the plasma, according to the manufacturer's protocol.

2.6.3 Determination of alanine aminotransferase (ALT) in plasma

RANDOX® assay kit was used for the determination of ALT activity in the plasma, according to the manufacturer's protocol.

2.7 Assay of Biomarkers of Oxidative Stress

2.7.1 Determination of hepatic ascorbic acid level

The ascorbic acid concentration was determined according to the method of Jagota and Dani,[17].

2.7.2 Determination of hepatic catalase (CAT) activity

The activity of catalase was determined according to the procedure described by Claiborne [18].

2.7.3 Determination of hepatic superoxide dismutase (SOD) activity

SOD activity was determined by the method of Sun and Zigman [19].

2.7.4 Determination of hepatic reduced glutathione (GSH) concentration

The level of reduced glutathione (GSH) in the samples was determined by the method described by Jollow *et al.* [20].

2.7.5 Determination of hepatic glutathione-S-transferase (GST) activity

Glutathione-S-transferase (GST) activity was determined by the method according to Habig *et al*. [21].

2.7.6 Determination of hepatic malondialdehyde level (MDA)

Lipid peroxidation was assayed by measuring the thiobarbituric acid reactive (TBAR) products present in the test sample using the procedure of Vashney and Kale [22].

2.7.7 Determination of hepatic nitric oxide (NO) level

The level of NO was determined by the method of Green et al. [23].

2.8 Statistical Analysis.

The data were expressed as Mean ± SD. The data were analyzed using one-way ANOVA using GraphPad Prism® (v 6.01) for comparison between control and treated rats in all groups. *P* values less than 0.05 ($p<0.05$) were considered statistically significant.

3. Results

3.1 Rutin attenuates Butachlor-induced alterations in markers of hepatic injury

The protective effects of Rutin on Butachlor-induced changes in ALT, AST, and ALP activities in the plasma of rats are shown in table 2. Plasma ALT, AST, and ALP activities were significantly increased in the Butachlor group by 17.8%, 16.95%, and 29.4% respectively when compared with the control ($P<0.05$). Co-administration of Butachlor and Rutin significantly attenuated the increase in ALT, AST, and ALP activities relative to the Butachlor group ($P<0.05$).

Table 2: Protective Effects of Rutin on Butachlor Induced Changes on Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) And Alkaline Phosphatase (ALP) activities in the Plasma of rats.

Treatment	ALT (U/L)	AST (U/L)	ALP(nM/min/mL/mg Protein)
Control	59.6 ± 1.14	73.02 ± 0.77	57.70 ± 1.53
BUTA	72.5 ± 0.5 (17.8%)*	87.88±0.72 (16.95%)*	81.67 ± 1.37 (29.4%)*
RUT	61.3 ± 1.20*	74.60 ± 0.90*	60.33 ± 2.10
BUTA + RUT	63.8 ± 0.91*,a	76.74 ± 0.68*,a	66.4 ± 1.14*,a

The results are expressed as Mean ± SD for six rats in each group.Values in parenthesis represent percentage (%) decrease.

* Significantly different from the control (<0.05). a- significantly different from the butachlor group.

BUTA= Butachlor (100 mg/kg BW); RUT= Rutin (100 mg/kg BW)

3.2 Rutin attenuates Butachlor-induced alterations in markers of oxidative stress, lipid peroxidation, and inflammation

Table 3 presents the protective effects of Rutin on Butachlor-induced changes on SOD, CAT, and GST activities in the liver of rats. SOD, CAT, and GST activities were significantly decreased in the Butachlor group by 48.6%, 37.9%, and 32.4% respectively when compared with the control ($P<0.05$). The co-administration of Butachlor and Rutin significantly protected the decrease inSOD, CAT, and GST activities relative to the Butachlor group ($P<0.05$).

Table 3: Protective Effects of Rutin on Butachlor-Induced Changes in Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione-S-Transferase (GST) Activities in the Liver of Rats.

TREATMENT	SOD (Unit)	CAT (μmol H_2O_2 consumed/min)	GST (nmol/min/mg protein)
CONTROL	3.8 ± 0.10	28.0 ± 1.0	68.5 ± 0.71
BUT	1.95 ± 0.13 (48.6%)*	17.4 ± 0.58(37.9%)*	46.5 ± 0.84(32.4%)*
RUT	2.85 ± 0.1*	25.8 ± 0.60*	64 ± 0.82*
BUT + RUT	3.4 ± 0. 08*,a	22.2 ± 0.60*,a	58.25 ± 0.96*,a

The results are expressed as Mean ± SD for six rats in each group. Values in parenthesis represent percentage (%) decrease. * Significantly different from the control (<0.05). a- significantly different from the butachlor group. BUTA= Butachlor (100 mg/kg BW); RUT= Rutin (100 mg/kg BW)

3.3 Protective effect of Rutin on Butachlor-induced alterations in AA and GSH.

The protective effect of rutin on butachlor-induced alterations in levels of AA and GSH in the liver of rats was shown in figure 3. Levels of AA and GSH were significantly down-regulated in the liver of butachlor-treated rats relative to the control. However, co-administration of rutin and butachlor significantly ameliorated the alteration observed relative to the butachlor-treated group.

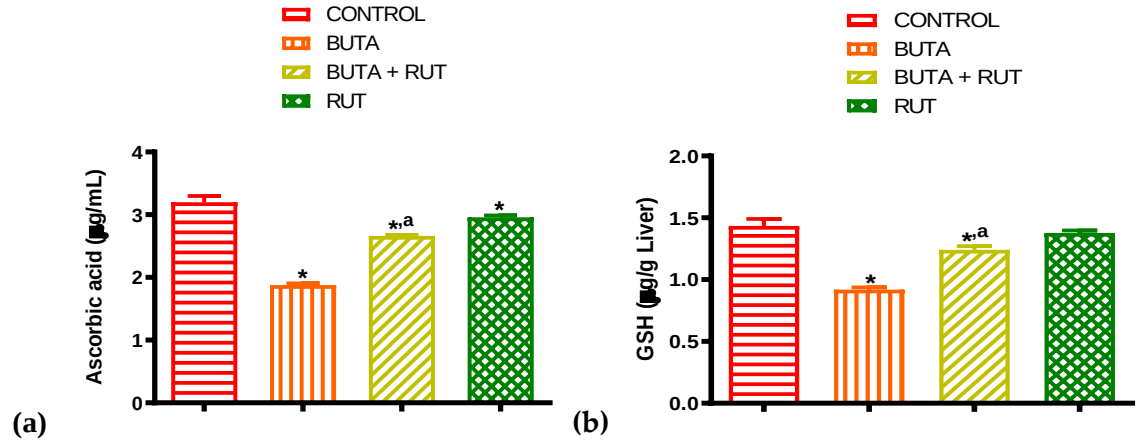

Figure 3: Protective effect of Rutin on butachlor-induced alterations in levels of (a) ascorbic acid (AA) and (b) reduced glutathione (GSH) in the liver of rats. RUT= Rutin, BUTA= Butachlor.

*Each bar represents the mean ± SD (n=6). * - significantly different compared with control (P < 0.05). a- significantly different compared with butachlor (P<0.05).*

3.4 Protective effect of Rutin on Butachlor-induced alterations in MDA and NO

The protective effect of rutin on butachlor-induced alterations in levels of malondialdehyde (MDA) and nitric oxide (NO) in the liver of rats was presented in figure 4. There were significant increase in the level of MDA and NO in the liver of butachlor-treated rats when compared with control. However, co-administration of Rutin and Butachlor significantly attenuated the alteration relative to the Butachlor-treated group.

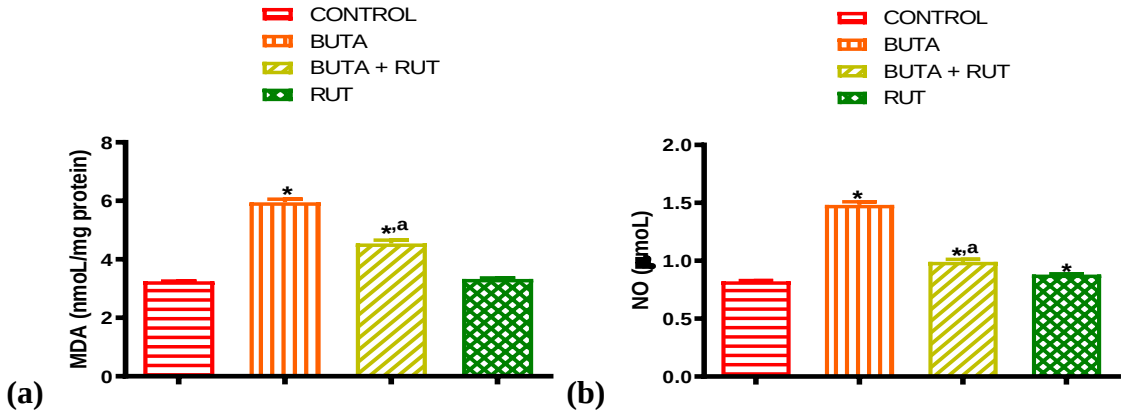

Figure 4: Protective effect of Rutin on butachlor-induced alterations in levels of (a) malondialdehyde (MDA) and (b) nitric oxide (NO) in the liver of rats.

RUT= Rutin, BUTA= Butachlor. *Each bar represents the mean ± SD (n=6).*

** - significantly different compared with control (P < 0.05). a- significantly different compared with butachlor (P<0.05).*

4. Discussion

The liver is known for its detoxifying activity and is also the site for the formation of reactive oxygen species (ROS); superoxide anions, hydrogen peroxides, and hydroxyl radicals [1, 24]. Also, present in the system are the enzymic and non-enzymic antioxidants activated to neutralize reactive oxygen species. Deficiency in this defense mechanism results in oxidative destruction which may damage the tissue affected [24].

Previous reports indicated that the toxic effects of butachlor, an herbicide used as pre-emergence control of unwanted weeds, are mainly related to the induction of oxidative stress [25], while rutin is a natural flavonoid with significant roles in combating cellular oxidative stress and possess hepatoprotective activity [13,14]. The current study investigated the hepatoprotective effect of Rutin on Butachlor-induced hepatotoxicity in rats.

In this study, plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were significantly increased in butachlor-treated rats when compared to control. ALT, AST, and ALP are marker enzymes for assessing liver integrity [26]. However, ALT is more specific for the liver tissue because other enzymes and metabolites could be released as impairment brought about by the elevated plasma ALP, ALT, and AST [26]. Rutin has been shown to possess hepatoprotective activity [13] which is evident from the result generated from this study as co-administration of rutin and butachlor ameliorated the alterations in markers of hepatic injury.

The formation of reactive oxygen species (ROS), superoxide anions, hydrogen peroxides, and hydroxyl radicals by the liver exposes it to oxidative damage and subsequently membrane lipid peroxidation when there is a deficiency in the antioxidant defence mechanism of the liver [27]. Malondialdehyde (MDA) is a by-product of membrane lipid peroxidation, its level was significantly high in butachlor-treated rats relative to control indicating the susceptibility of the liver membrane to oxidative damage. However, rutin was able to significantly ameliorate the lipid peroxidation occasioned by butachlor administration.

Present in the living systems is the enzymic and non-enzymic antioxidants defense activated to neutralize reactive oxygen species. Deficiency in this defense mechanism results in oxidative destruction which may damage the tissue affected [28]. Superoxide dismutase (SOD), catalase, and glutathione-s-transferase (GST) are enzymatic antioxidants involved in scavenging free radicals or reactive oxygen species. SOD catalyzes the reaction that converts superoxide anion (O_2-) to hydrogen peroxide (H_2O_2), preventing the O_2- from producing highly harmful hydroxyl radicals. The H_2O_2 produced in this way is a powerful membrane-permeant oxidant in and of itself, and it must be quickly removed from the cell to avoid oxidative damage to lipids, proteins, and DNA. [29].

Glutathione-S-Transferase (GST) is an enzyme involved in the detoxification of ingested xenobiotics and catalyzes the reduction of peroxide-containing compounds in the cell. This peroxidase activity exhibited by GST is however dependent on the availability of GSH [30]. On the other hand, ascorbic acid (AA) scavenges free radicals and functions in the regeneration of a membrane-bound antioxidant, vitamin E [31].

Alterations in enzymic and non-enzymic antioxidants superoxide dismutase (SOD), catalase, glutathione-s-transferase (GST), ascorbic acid (AA), and reduced glutathione (GSH) involved in scavenging reactive oxygen species were observed upon administration of butachlor which is an indication of susceptibility of the liver to reactive oxygen species leading to oxidative stress, however, co-administration of rutin and butachlor was able to significantly protects against the oxidative injury.

5. Conclusions

Butachlor impaired hepatic antioxidant systems, thereby, leading to oxidative stress and ultimately, disruption of liver functions. However, Rutin, a potent antioxidant positively attenuates the effects of Butachlor, and this may be due to its antioxidant properties.

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Institutional Review Board Statement: The Ethical Review Committee of Ajayi Crowther University's Faculty of Natural Sciences provided approval and permission to use the animals with the ethical number FNS/ERC/2021/071A.

Conflicts of Interest: The authors declare no conflict of interest.

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