World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

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Effect of red ginger extract (*Zingiber officinale var. Rubrum*) of SGOT and SGPT levels in white rats (*Rattus norvegicus*) induced by Gentamicine

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World Journal of Advanced Research and Reviews, 2024, 21(01), 2609–2613

Publication history: Received on 14 December 2023; revised on 25 January 2024; accepted on 27 January 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.21.1.0355

Abstract

Introduction: The aim of the research was to prove that red ginger extract (*Zingiber officinale var. Rubrum*) could inhibit the increase in SGOT and SGPT levels in Gentamicin-induced rats.

Objective: Twenty-five male rats aged 8-12 weeks with 150-200 gram BW divided into five groups research with C- was given CMC-Na 1% and aqua pro-injection, C+ was given 1% CMC-Na and induction of Gentamicin 80 mg/kg BW, and groups T1, T2, and T3 given induction of Gentamicin 80 mg/kg BW and red ginger extract at individual doses each of 100, 200, and 400 mg/kg BW. All treatments were carried out for 15 days. On the 16th day, all rats were euthanized and their blood was drawn intracardiacly, then SGOT and SGPT levels were examined. The results of the research used the Analysis of Variance (ANOVA) and Games-Howell statistical analysis.

Results: The results showed that the C+ group experienced the highest increase ($p<0.05$) while the C-group experienced the lowest increase ($p<0.05$) compared to the other treatment groups. The T1, T2, T3 groups were able to inhibit the increase in SGOT and SGPT levels.

Conclusion: The effective dose to inhibit the increase in SGOT levels is 400 mg/kg BW and the effective dose to inhibit the increase in SGPT levels is 200 mg/kg BW.

Keywords: Red ginger extract; Gentamicin; SGOT; SGPT; White rats

1. Introduction

Antibiotics are the most widely used type of drug to treat several infectious diseases [1]. One of the antibiotics in the aminoglycoside class is gentamicin which has a broad spectrum [2]. Gentamicin is used in the treatment of infections of the abdomen, urinary tract, soft tissue, bone, lung and heart [3]. Giving gentamicin to animals, especially mammals, is reported to have ototoxic side effects, whereas in experimental clinical use in experimental animals it is reported to have side effects causing liver damage [4, 5].

Gentamicin at a dose of 80 mg/kg BW/day intraperitoneally for 8 days can cause toxic effects [6]. The use of antibiotics in toxic doses can increase oxidative stress and free radicals which can suppress enzymatic and non-enzymatic antioxidant defense systems. This causes the formation of damage to the membrane lipids, proteins, and nucleic acids which can lead to toxicity, dysfunction, and injury to the liver [7, 8, 9]. Damage to the cell membrane affects the osmotic balance and triggers the release of important metabolites such as the enzymes SGOT and SGPT a result of this release, cells cannot regulate the balance of enzymes that are released that SGOT and SGPT levels in serum increase [10].

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The body cannot neutralize excess free radicals, so exogenous antioxidants are needed [11]. Antioxidants work by donating electrons to free radical molecules by binding to oxygen and releasing hydrogen [12]. One source of exogenous antioxidants is red ginger. Ginger contains antioxidant compounds that can inhibit superoxide and hydroxyl radicals. Red ginger rhizome extract contains flavonoids, tannins, saponins, alkaloids and terpenoids which have very strong antioxidant activity with a 1C50 value of 10.35 µg/mL [13].

Flavonoids are inhibiting the cytochrome P-450 enzyme system, which will prevent the formation of free radicals. Flavonoids are antioxidants because they have phenolic hydroxy groups in their molecular structure which have the ability to scavenge free radicals. Flavonoids release hydrogen radicals and produce new radicals which are relatively more stable and unreactive due to the effect of aromatic core resonance [14].

2. Material and methods

This study used 25 male white rats aged 2-3 months weighing 150-200 grams. This research uses true experimental research with a research design the post test-only control group design. Male white rats were divided into five study groups, each with five repetitions. Group C- was given 1% CMC-Na and aqua pro-injection, group C+ 1% CMC-Na and 80 mg/kg BW induction of Gentamicin, and groups T1, T2, and T3 were given 80 mg/kg BW of Gentamicin and Red Ginger extract dose of each treatment 100, 200, and 400 mg/kg BW. White rats were adapted for seven days and then treated for 15 days. Termination was carried out on the 16th day and intracardiac blood samples were taken as much as 3 ml.

2.1 Materials

The materials used were Red Ginger extract, Gentamicin (Interchemie, Genta-100®), 1% CMC-Na, SGOT reagent, SGPT reagent, cage, food and drink container, syringe, sonde, one cell surgical instrument, plain Venoject tube, Eppendorf tube, clinical chemistry testing kit (ERBA Mannheim GmbH XL 600).

2.2. Data Analysis

Data analysis used the SPSS application for windows version 26. Data and variables from this study were tested using ANOVA statistics. The data was then further tested using Games-Howell with a significance level of $P<0.05$ to see the differences in each treatment.

3. Results and discussion

3.1 The Effect of Red Ginger Extract on SGOT

In this study, the negative control group showed the lowest results and was significantly different ($p<0.05$) evenly from the other groups. These results occurred because the negative control group was not given Gentamicin induction as hepatotoxic. The AST levels in the negative control group can be used to increase or decrease the AST levels shown in the other groups. The positive control group showed the highest results due to the administration of Gentamicin at a dose of 80 mg/kg BW for eight days without giving red ginger extract. Gentamicin causes liver cell damage which begins with the production of free radicals in the liver which cause oxidative stress [15, 16]. Oxidative stress causes Gentamicin to resist phospholipid degradation which disrupts the integrity of lysosomal membranes which ends in enzyme leakage thereby increasing AST levels in the blood [17].

Table 1 Average SGOT and SGPT Levels Induced by Red Ginger Extract (*Zingiber officinale var. Rubrum*) and Gentamicine.

Group	C-	C+	T1	T2	T3
SGOT (U/L) Mean ± SD	119.00^{a} ± 11.33	271.00^{d}± 22.17	232.40^{c} ± 3.84	217.80^{c} ± 9.25	168.40^{b} ± 33.22
SGPT (U/L) Mean ± SD	64.20^{a} ± 6.05	103.00^{c} ± 7.24	91.60^{b} ± 8.98	74.40^{a} ± 6.65	67.20^{a} ± 3.27

Note: Superscripts with the different letter indicate no significant difference ($p<0.05$). C- was given CMC-Na 1% and aqua pro-injection, C+ was given 1% CMC-Na and induction of Gentamicin 80 mg/kg BW, and groups T1, T2, and T3 given induction of Gentamicin 80 mg/kg BW and red ginger extract at individual doses each of 100, 200, and 400 mg/kg BW.

The results of this study indicate that red ginger extract at doses of 100, 200, and 400 mg/kg BW can reduce Gentamicin-induced levels of SGOT in wistar rats. Treatment 3 with a dose of 400 mg/kg BW of red ginger extract could best reduce

SGOT levels, although it was significant (p <0.05) but this decrease was not close to the results of a negative control. The results of reducing SGOT levels in treatment 3 which were not yet close to negative control results could be possible because SGOT can also be found in other organs. Adriani et al. stated that increased AST levels were also found in the muscles and heart organs [18]. Treatments 1 and 2 at doses of 100 and 200 mg/kg BW also significantly reduced AST levels ($p<0.05$) but not better than treatment 3.

Administration of red ginger ethanol extract before Gentamicin induction showed a significant difference ($p<0.05$). This is in accordance with the results of Al-Azhary's research, the ethanol extract of red ginger can increase the total plasma antioxidant capacity and reduce lipid peroxidation [19]. Lipid peroxidation is reduced by changing the enzymatic levels of superoxide dismutase, catalase, and glutathione peroxidase in the blood. In addition, Ahmed et al. stated that the ethanol extract of red ginger contains antioxidant compounds that can reduce the effects of free radicals in the body and reduce histopathological changes in the liver organs, so that red ginger extract has hepatoprotective properties against damage caused by free radicals 20].

Phytochemical tests identified that red ginger contains secondary metabolites such as alkaloids, flavonoids, phenolics, and triterpenoids [21]. Based on the results of research conducted by Herawati and Saptarini, it was reported that red ginger rhizome extract showed strong antioxidant activity. Antioxidants will transfer protons to DPPH radicals by direct abstraction of phenol atoms and through electron transfer processes, so as to neutralize the properties of free radicals [22]. According to Abidah, Flavonoids work as antioxidants by donating electrons and hydrogen ions to superoxide anions so that they become more stable, through this mechanism flavonoids are able to protect lipoproteins and DNA proteins from the oxidation process [23]. Flavonoids also inhibit the action of the enzymes xanthine oxidase and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, and chelate metals (Fe^{2+} and Cu^{2+}) so that they can prevent redox reactions that can produce free radicals [24, 25].

3.1. Effect of Red Ginger Extract on SGPT

In this study the negative control showed the lowest results but was not significantly different from the T3 group. These results were due to the negative control group not being induced by Gentamicin as hepatotoxic. The highest results were shown in the positive control due to the administration of Gentamicin at a dose of 80 mg/kg BW for eight days without giving red ginger extract. Gentamicin can increase the production of superoxide (O_{2+}), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH-) which are part of free radicals [26]. Increased spread of ROS results in peroxidation of monounsaturated fatty acids in the biomembrane, thus causing the production of lipid peroxidation which can disrupt cellular function and cause necrosis [17]. Cell necrosis that occurs in hepatocytes causes swelling of the nucleus and cytoplasm and then breaks, spilling the contents of the cell into the extracellular tissue due to interference with the sodium pump caused by a lack of ATP. If ATP levels are low, intracellular enzymes will exit the cells into the blood so that they can cause an increase in SGPT levels in the blood [27].

Other results from this study showed that red ginger extract at doses of 100, 200, and 400 mg/kg BW could reduce Gentamicin-induced levels of SGPT in white rats of wistar strain. Treatment 3 with a dose of red ginger extract of 400 mg/kg BW could reduce SGPT levels the best and significantly ($p<0.05$) but was not significantly different from the negative control. Treatments 1 and 2 with doses of 100 and 200 mg/kg BW also reduced SGPT levels significantly ($p<0.05$) but not better when compared to treatment 3. This was due to continuous administration of Gentamicin and a lack of sufficient exogenous antioxidants. Based on the results of research conducted by Duppa et al. showed that red ginger extract has a hepatoprotective effect which is characterized by a decrease in SGPT-SGOT levels in white rats induced by Paracetamol [28]. Red ginger contains various antioxidant compounds that play a role in protecting hepatocytes such as gingerols, shogaols, zingerone and phenolic compounds in the form of flavonoids, cinnamic acid derivatives, coumarins, tocopherols and organic acids [29].

Flavonoids are the most effective compounds as scavengers of reactive species, for example super dioxide, peroxyl radicals, and peroxynitrite by transferring H+ atoms [24, 30]. According to Sangeetha et al. the hydroxyl group is believed to play the most role in the process of solving free radicals because it is capable of carrying out the hydrogen donor process [31]. The mechanism that occurs is that flavonoids are oxidized by radicals, producing radicals that are more stable and less reactive. In other words, flavonoids stabilize reactive oxygen species with reactive radicals. The high reactivity of the hydroxyl groups of flavonoids causes the radical bonds to become inactive [32].

4. Conclusion

Red ginger ethanol extract can inhibit the increase in SGOT levels in white rats induced by Gentamicin 80 mg/kg BW with an effective dose of 400 mg/kg BW and can inhibit the increase in SGPT levels in white rats induced by Gentamicin 80 mg/kg BW with an effective dose of 200 mg/kg BW.

Compliance with ethical standards

Acknowledgements

The authors express sincere thanks to the Dean of the Faculty of Veterinary Medicine for providing all necessary facilities and funds for conducting research work.

Disclosure of Conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study was approved by the Faculty of Veterinary Medicine Animal Ethics Committee of Universitas Airlangga. All variables were considered in accordance with the Ethics Committee related to the animal handling to ensure no discomfort or pain was caused to the animals during sampling(certificate registration number: 1. KEH.160.11.2022

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