



Antioxidative and Antiapoptotic Effect of Sodium Butyrate and Betaine on Broilers Liver Influenced by Dexamethasone

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THIS study was intended to maximize-feed by-products' (betaine and sodium butyrate) benefits on an ecophysiological safe way against stressful conditions induced by dexamethasone. 96 broilers were used and randomly separated into four treatments employed 24 broilers with 3 replications and two age groups of 21 d (1st period) and 42 days (2nd period). G1 was the controlled study, where as DEX was injected at three-day intervals in G2 (Dosage: 1 mg/kg B.W S/C) the dosage was evaluated following preliminary study, then G3 was injected with Dexamethasone (DEX) at three-day intervals and was given sodium butyrate (Dosage: 1.2 g/kg feed), lastly G4 was given DEX injections every three days and was given betaine (Dosage: 2 g/kg feed). The results showed DEX is a nonspecific stress that generates considerable increases in caspase-3, and ALT in the liver tissue and reflected in the circulation, respectively, while SB and B have alleviated a significant feature of the stress ascribed to DEX. On the other hand, AST was extremely statically in the DEX group at 1st period of bird age, although both antiapoptotic agents in G3 and G4 produced cytoprotective impacts to the liver, but in 2nd periods of broiler age, all treated groups significantly differed from the compassion of control. Significantly diminish in Glutathione (GSH) and stress index with raising MAD value in the liver tissue in G2, however G3, and G4 have a fortification effect against liver damage. is concluded that SB and B act to suppress the apoptotic effect influenced by DEX.

Keyword: Betaine, Sodium butyrate, Dexamethasone, Broilers.

Introduction

The competence of feed employment is a very remarkable means of raising profit in any poultry project [1]. Therefore, modern technologies must now be sought to determine the productivity of broiler performance. Animal stress occurs when ecological changes occur and is associated with body responses to reestablish homeostatic conditions [2]. Fowl trade settings are exposed to a variety of stressors, all of which clearly indicate rising oxygen-free radicals' production; thus, oxidative stress is a major sponsor of the negative effects of the most common trade stressors in poultry production [3].

Dexamethasone (DEX) is an artificial

glucocorticoid derivative that has a similar impact to high corticosterone (CORT) levels and activates stress-related signaling pathways, and it is widely used to investigate a variety of non-specific stressor effects in the development of stress in chickens [4]. The liver cell is regarded as a basic metabolic organ with remarkable physiological functions such as biosynthesis, detoxification and clearance. As a result, any production of reactive species in liver cells forces them to commit cellular suicide, which has become a common ailment [5].

Apoptosis is a type of cell suicide regulated by the caspase group, which occurs when cells lose their function and undergo a planned self-destruction system entails cysteine-containing

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aspartic proteolytic enzymes-3 [6]. However, the link between free radical generation, hepatocyte apoptosis and dexamethasone remained obscure.

Sodium butyrate (SB) is a short-chain fatty acid that has effects on the molecular, cellular and tissue levels, once butyric acid starts to lose its H ion, it must be transformed to butyrate ion consequently. In general, sodium salt of butyric acid has an advantage over free acids in that it is odorless and, due to its solid and less volatile nature, makes the feed production process easier to handle [7]. To support the poultry sector, should focusing into the benefits of any supplement containing sodium butyrate that may be used during the growing period because it has the ability to improve the physiological index and the intestinal ecosystem of birds [8]. Not only might sodium butyrate augment serum superoxide dismutase (SOD) with lowering malondialdehyde (MDA) content in typically grown chickens, but it could also alleviate the loss weight gain during surge of corticosterone level [9].

Betaine (B) is a dietary fortification that naturally obtained from beetroot and has been used in a variety of ways to alleviate the inverse effects of distinct types of stress [10]. Furthermore, betaine is the donor of the methyl series (CH₃) in poultry supplements, and it is generated in the mitochondria by choline and glycine, as well as it plays a role in the zwitterionic reaction, acting as an "Osmo" protectant or "osmolyte" that maintains cell water homeostasis [11].

This study scouts the antioxidative and antiapoptotic properties of sodium butyrate and betaine as dietary additives on the imbalanced oxidative status of broilers liver tissue exposed to an array of potential stressors evoked by dexamethasone from hatchability day to market age. There fore, this research contributes to a growing trend of increasing fowl defenses in stressful situations.

Materials and Methods

Broilers

To perform this investigation, 96 Rose-type broiler chicks were brought from hatchery and maintained under standard conditions in the animal's house/College of Veterinary Medicine. The birds were then divided into four groups, each with 24 birds with three replications. The hall was fitted with heaters and air vacuums to manage the temperature (The temperature at 1st day was 32-33 degrees Celsius, then decreased 1

degree Celsius after the 4th day of age, and then continued dropping 1 degree Celsius every 3 days of bird age) and appropriate ventilation. During the first 7 days of life, the birds were exposed to natural lighting accompanied by artificial lighting (60-watt lamps), which was gradually reduced by 2 hours each week until it was reduced to 16 hours per day at the end of the rearing. The water was provided freely *ad libitum* throughout the trial, whereas ingredients and nutrient levels in the basic diet are provided in accordance with to National Research Council (NRC) [12].

Design of Experiment

After three days of acclimation, 96 chicks were randomly separated into four groups (24 birds/group) each set has 3 replicates and two age periods of 21 and 42 days were taken for sampling. Five treatment comprises: (G1) represented untreated group, while, (G2) injected with DEX at 3 day intervals (dosage: 1 mg/kg B.W. S/C) (after a preliminary trials, the dosage was determined and melted with Propylene glycol), and (G3) injected with DEX at 3 day intervals and receiving sodium butyrate (SB) (dosage: 1.2 g/kg feed) [13]. Finally G4 injected with DEX at 3 day intervals and receiving betaine (B) (dosage: 2 g/kg feed) [14]. Both sodium butyrate and betaine were added to poultry diet throughout the trial period (3-42 day of bird's age)

Materials utilized

The dose was prepared with dexamethasone obtained from (Pioneer company- Slemani) and dissolved with propylene glycol (Laboratory reagent- India), and the dose was determined based on dexamethasone solubility as follows: every 1 mg of dexamethasone dissolved in 1 ml of propylene glycol. Sodium Butyrate and Betaine were supplied by (biopoint company- Poland). All of the materials subjected in the recent project were provided as a 99.9% pure product.

Blood samples

Blood samples were collected from the jugular vein of the birds in the groups mentioned above, on the day before the date of slaying. The blood sample was placed in tubes and centrifuged at 3000 rounds/min for 15 minutes, after which the serum was separated and distributed to small volumes in Eppendorf tubes and kept in the freezer at -20 C° until the ALT and AST as liver biomarkers were measured.

While blood with anticoagulant was used for differential leukocytic count (DLC) and stress index using Wright stain [15].

Liver samples

To carry out the trials, the birds were slain between the ages of 21 and 42 days, the liver was taken and divided into three sections, each of which was wrapped in aluminum foil and frozen at -20 °C until the tests were carried out on it.

Parameters utilized

Initially estimated Caspase-3 (cysteine-containing aspartic proteolytic enzymes-3) ELISA kit(Solarbio, China), ALT & AST spectrophotometric kits(BioLabo, France)[16]. The concentration of GSH in liver tissue was measured by the modified Ellman method [17], while [18] method was used to measure MDA in the tissue.

Statistical analysis

The data were statistically evaluated with a two-way analysis of variance by sigma plot to see if there was a significant difference at probability ($P < 0.05$) between groups and between the two birds age (21 and 42 days)[19].

Results

The trial data are logged in Table 1 of the ongoing study at 21 and 42 days of age, indicating a highly significant value ($P < 0.05$) of caspase in G2 compared to resting groups, although no statistical difference was observed between them in the 1st period, but then in the 2nd period graduated from G3, then G4 and differed statically from G1 which showed a lower level of caspase. When the statistical analysis was done to see if there were any significant differences between the two times (21 and 42 day), it was discovered that there were none, except in G2

at 21 days, which exhibited a substantial drop compared to the G2 at 42 days of age.

When compared to other groups, injecting DEX (G2) at first period resulted in significantly massive of ALT and AST, whereas G1, G3, and G4 showed no significant difference between them. However, at 42 days, the ALT value was statistically higher in G2 compared to the remaining groups, with the exception of G3, which did not differ with all groups, whereas the AST enzyme level at the second period was clearly higher in G2 compared to G1 but not the other groups. When the total groups in the two analyses were compared to each other for both periods, there was no significant difference ($p > 0.05$) (Table 2).

The data in Table 3 show that after estimating the value of GSH in the liver at two different times, the greatest value was identified in G1 when comparison to the resting treatment, while G2 led to a significant in statically reduced, but G2 was shown to be at the same level as G4. When the statistical analysis was performed between the two age periods, a notable increase was observed in the groups 4 at 42 days compared to 21 days.

In the same table, the results of MDA in the liver revealed that groups G3, and G4 were not statistically significant between them ($p > 0.05$), but G2 showed a substantial increase in significance compared to control at both time periods. When the treated groups were compared for MDA analysis over two periods, the only two groups that have shown significance presented in G1 and G2, which recorded a higher level at 21 days of age than at 42 days of age.

TABLE 1. Influence of the DEX, SB, and B on broiler's caspase-3.

Groups	Mean ± Standard error	
	21 days of age (1 st period)	42 days of age (2 nd period)
	Caspase-3 μMol/L	Caspase-3 μMol/L
G1	1.16 ± 0.10 ^{ba}	1.01 ± 0.07 ^{ca}
G2	1.68 ± 0.05 ^{ab}	1.98 ± 0.08 ^{ab}
G3	1.33 ± 0.08 ^{ba}	1.29 ± 0.08 ^{ba}
G4	1.23 ± 0.04 ^{ba}	1.35 ± 0.07 ^{ba}

*Values in the column with small letters are different significantly at ($p < 0.05$) between groups

**Values in the column with capital letters are different significantly at ($p < 0.05$) between two period of age (21 and 42 day).

TABLE 2. Influence of the DEX, SB, and B on broiler's ALT and AST enzyme as a liver biomarker.

Groups	Mean ± Standard error			
	21 days of age (1 st period)		42 days of age (2 nd period)	
	ALT IU/L	AST IU/L	ALT IU/L	AST IU/L
G1	35.91 ± 2.67 ^{ba}	202.1 ± 27.01 ^{ba}	36.39 ± 2.97 ^{ba}	208.6 ± 25.12 ^{ba}
G2	50.15 ± 3.63 ^{aa}	321.7 ± 33.74 ^{aa}	52.33 ± 4.08 ^{aa}	291.6 ± 28.68 ^{aa}
G3	36.94 ± 2.18 ^{ba}	225.1 ± 17.16 ^{ba}	44.17 ± 1.33 ^{abA}	248.0 ± 14.85 ^{abA}
G4	36.35 ± 3.25 ^{ba}	228.7 ± 18.85 ^{ba}	42.01 ± 1.52 ^{ba}	241.8 ± 19.53 ^{abA}

*Values in the column with small letters are different significantly at (p< 0.05) between groups

**Values in the column with capital letters are different significantly at (p< 0.05) between two period of age

TABLE 3. Influence of the DEX, SB, and B on broiler's GSH and MDA in the liver.

Groups	Mean ± Standard error			
	21 days of age (1 st period)		42 days of age (2 nd period)	
	GSH μMol/L	MDA μMol/g	GSH μMol/L	MDA μMol/g
G1	0.41 ± 0.04 ^{aa}	2.30 ± 0.24 ^{ba}	0.50 ± 0.04 ^{aa}	1.00 ± 0.31 ^{bb}
G2	0.17 ± 0.02 ^{ca}	7.36 ± 0.67 ^{aa}	0.25 ± 0.01 ^{ca}	2.76 ± 0.37 ^{ab}
G3	0.31 ± 0.01 ^{ba}	2.26 ± 0.27 ^{ba}	0.35 ± 0.03 ^{ba}	1.32 ± 0.28 ^{ba}
G4	0.24 ± 0.02 ^{bcB}	2.00 ± 0.24 ^{ba}	0.34 ± 0.02 ^{bcA}	1.16 ± 0.18 ^{ba}

*Values in the column with small letters are different significantly at (p< 0.05) between groups

**Values in the column with capital letters are different significantly at (p< 0.05) between two period of age

After checking and counting the WBCs at first period of age, it was noted that the number of lymphocytes and monocytes in G2 and G3 did not differ significantly from G1, whereas in G3 groups showed a high statistical value relative to other groups, but the heterophils were obviously raised when doing stactical analysis in G2 compared to rest groups, but groups including G3 and G4 from G1 showed no significant difference. All treated groups didn't influence basophile and eosinophil count. The result is shown in the same table. The stress biomarker was obtained by dividing the percent of lymphocytes to heterophils indicated stress index, in the G2 mark with high statistical variance as compared to other groups, while G3 and G4 did not differ between them and with G1 (Table 4).

Table 5 shows that the birds in Group G2 have a significantly lower percentage of lymphocytes with a higher heterophil percentage when compared to other treatments at 42 d of age as well as monocyte statically decreasing when compared to G1, while G3 and G4 did not differ between them and G1. Also, this table clarified no any statically variation in basophile and eosinophil between treated groups. Whereas the stress index becomes a statically significant value in G2 relative to control and resting treatment, the stress index in G3 and G4 is similar to G1 but variable between them.

The influence of the 2 periods on DLC and stress index were not mentioned I mean no any value different statically (Tables 4 and 5).

TABLE 4. Influence of the DEX, SB, and B on broiler's differential leucocytic count (DLC) and stress index at 1st period of age.

Groups	Mean ± Standard error					
	21 days of age (1 st period)					
	Lymphocyte %	Heterocyte %	Monocyte %	Basophil %	Eosinophil %	Stress index
G1	36.20 ± 1.53 ^{abA}	37.20 ± 1.35 ^{bcA}	24.60 ± 1.50 ^{abA}	1.00 ± 0.31 ^{aA}	1.00 ± 0.31 ^{aA}	1.02 ± 0.06 ^{bcA}
G2	31.20 ± 1.62 ^{ba}	47.00 ± 2.02 ^{aA}	20.60 ± 0.81 ^{ba}	0.60 ± 0.40 ^{aA}	0.60 ± 0.40 ^{aA}	1.55 ± 0.14 ^{aA}
G3	40.20 ± 2.03 ^{aA}	33.00 ± 1.22 ^{cA}	25.80 ± 1.02 ^{aA}	0.60 ± 0.40 ^{aA}	0.40 ± 0.24 ^{aA}	0.82 ± 0.06 ^{cA}
G4	35.40 ± 2.56 ^{abA}	40.00 ± 1.37 ^{ba}	22.80 ± 1.39 ^{abA}	0.80 ± 0.20 ^{aA}	1.00 ± 0.31 ^{aA}	1.17 ± 0.14 ^{ba}

*Values in the column with small letters are different significantly at (p< 0.05) between groups

**Values in the column with capital letters are different significantly at (p< 0.05) between two period of age.

TABLE 5. Influence of the DEX, SB, and B on broiler's differential leucocytic count (DLC) and stress index at 2nd period of age.

Groups	Mean ± SE					
	42 days of age (2 nd period)					
	Lymphocyte %	Heterocyte %	Monocyte %	Basophil %	Eosinophil %	Stress index
G1	35.80 ± 1.06 ^{aA}	35.20 ± 1.88 ^{cA}	27.60 ± 1.91 ^{aA}	1.00 ± 0.44 ^{aA}	0.40 ± 0.24 ^{aA}	0.97 ± 0.07 ^{bcA}
G2	27.00 ± 1.41 ^{ba}	49.80 ± 1.39 ^{aA}	21.60 ± 0.92 ^{ba}	0.80 ± 0.37 ^{aA}	0.80 ± 0.37 ^{aA}	1.73 ± 0.05 ^{aA}
G3	38.60 ± 2.29 ^{ba}	35.40 ± 1.63 ^{cA}	24.80 ± 1.59 ^{abA}	0.60 ± 0.40 ^{aA}	0.60 ± 0.40 ^{aA}	0.83 ± 0.07 ^{cA}
G4	35.20 ± 0.91 ^{aA}	40.00 ± 0.70 ^{ba}	23.60 ± 1.07 ^{abA}	0.40 ± 0.24 ^{aA}	0.80 ± 0.37 ^{aA}	1.13 ± 0.04 ^{ba}

*Values in the column with small letters are different significantly at (p< 0.05) between groups

**Values in the column with capital letters are different significantly at (p< 0.05) between two period of age

Discussion

Dexamethasone causes cellular damage in hepatocytes, indicating that apoptosis is triggered, according to this study evidence of increased caspase-3 in the DEX-injected group (as nonspecific stress) supports this hypothesis by Tonomura et al. [20] which approved because of the different intracellular signalling pathways, glucocorticoids or analogs (DEX) are thought to stimulate apoptosis and limit cell growth by increasing oxidative stress (H₂O₂), and the generation of mitochondrial cytochrome C which eventually leads to the induction of apoptosis, as a result, apoptotic circuits are disrupted, and unwanted, defective, or infected cells cannot be completely removed. Furthermore, other researchers continued their investigation into

the impact of glucocorticoids (GCs), which skew path physiological function by impairing cytokine expression at the signalling pathway and causing apoptotic developments such as caspase initiation and mitochondrial malfunction [21]. According to the current findings, it appears that betaine alleviated the effect of DEX and this complied with [22], debunked betaine boosted glutathione and glutathione peroxidase (GPx), catalase (CAT), and superoxide-dismutase (SOD) efficiency, which enhanced cytoprotective of the liver against oxidants. In line with the outcomes Furthermore, our research has optimized the attributed ability of SB to restore the negative impact of DEX in accordance with the finding [23] that butyric acid or its sodium salt may play a more efficient role on broilers preserved in a more stressful environment, and

the potential benefits may be attributed in part to its ability to alleviate the circulating CORT level increase possibly induced by different stresses.

The liver is the body's largest gland, responsible for filtering harmful poisons from the bloodstream as well as vitamin / mineral production. A spectrophotometric liver function tests were performed using serum biomarkers such as ALT and AST, which are regarded specific markers of liver cellular damage. As a results of our research, Group 2 had a higher level of these two enzymes on Day 21 of the trial when compared to the other groups, whereas all treated animals in first bird age differ only from control birds later in the time. This agreement with Sultana et al.[23]. The fact that DEX certainly changes hepatic enzymes in broiler circulation at 14 days of age could be due to necrosis of the liver cells, or it could be due to disrupted hepatocyte permeation, resulting in a gradual decrease in total hepatic ALT, due to the ALT molecule's size "114 kDa", therefore DEX is hepatotoxic, which can lead to an increase in hepatic enzymes. The own research found that SB halved AST and ALT serum levels, this line with Lan et al.[13] suggests that SB administration in the different birds age (1-35 day) restored liver function in the face of adversity therefore, the possible explanation could be due to the increased antioxidant of the broilers in the SB-supplemented groups, indicating a positive effect induced with butyric acid or sodium salts by reduced H₂O₂-induced DNA damage, and increased CAT activity. As a result, betaine aids in the reestablishment of liver function and the reduction of enzymes. This result corresponds with Veskovcic et al.[22] and the reason that betaine fortification to mice restricts the appearance of TNF and IL-6 mRNA as well as Bax mRNA (proapoptotic mediator) even as raising to that Bcl-2 mRNA (antiapoptotic).

In our research DEX was accountable for disrupting the redox equilibrium, which is dependent on the output of radicals, the data revealed a drop in glutathione levels together with an increase in lipid oxidation". Prior studies back this up with [24] between 19 and 41 days of broiler age, exogenous DEX "20 mg/L" downregulated SOD enzyme activity as well as glutathione peroxidase, resulting in a decrease in the "GSH/GSSG" ratio with a constant induce phospholipids peroxidation in the broiler liver cells.

Aside from SB and Bamended antioxidant status in contrast with the effect of DEX. Prior articles offer additional support that found [25] SB in a protected from improves "antioxidant balance." That indicate by ratio of total antioxidant capacity (TAC) to (MDA) denoted as "TAC/MDA" of the small bowel mucus layer in broiler chicken at 21 day of age. In addition, count that B exerts antioxidant properties by raising quantities of "S-adenosylmethionine" and "methionine" which are required for the creation / excretion of very-low-density lipoproteins VLDL and hepatic β -oxidation, which inhibits both oxidative stress and pathological apoptosis[26]. Under physiological homeostasis or low lipid peroxidation thresholds, cells spur their survival via antioxidant protection systems in response to a stressor, but when lipid oxidation peaks, the severity of oxidative overwhelms repair capabilities, resulting in prompt apoptosis. As a result, in reply to membrane lipid peroxidation, add some additive to help the biological system overcome cell suicidal tendencies[27].

In a recent study, stress biomarkers, including the stress index, showed a statistically significant shifts in group 2 when treated with dexamethasone due to a decrease in lymphocytes with an increased heterophil percentage but not in G3 and G4, which cause an modify effect of the stress index. The researchers[28] were sure to regularly estimate the proportion of H:L to an assessment of stress in poultry, and they demonstrated that addition of CORT or dexamethasone analog results in massive increases in the H:L ratio. This suggests that giving dexamethasone in the diet may be an appropriate method of glucocorticoid delivering to chickens. It reproduces stress and causes intestine inflammation, as well as changes in intestinal mucosa mucosal permeability. The intestinal permeation is implicated in the pathogenesis translocation in the portal or circulatory system, leading to increasing bacterial infections and, ultimately, a shift in the stress index [29]. Because of the role of betaine as an antistress and consequence antiapoptotic additives, betaine reinforcement (0.1 %) during the thermal challenged minimized the detrimental impact on performance and enhanced production with improvement stress index throughout the first 18 days of broiler age [30]. Another notable benefit of (β -hydroxy β -methylbutyrate) was a significant rise in white blood cell count, including lymphocytes, with a reduction in Heterophil

as well as H: L rates at day 21 compared to control treatment, indicating an advancement in the immunity responses in birds fed butyrate supplemented diets [31].

Conclusion

dexamethasone, which causes apoptosis as well as oxidative damage. The antiapoptotic properties of sodium butyrate and betaine on liver tissue can help to reduce the deleterious effects of dexamethasone and worsened hepatic apoptosis.

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Conflict of interest

There are no conflicts of interest declared by the authors.

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تأثير بيوتاريت الصوديوم والبيتاين المضاد للاكسدة ولموت الخلايا في كبد الدجاج اللاحم المتأثر بالديكساميثازون

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كان الهدف من الدراسة هو تحديد الاستفادة من اضافة بيوتاريت الصوديوم والبيتاين بطريقة فسيولوجية آمنة وتوفير بيئة فسلجية ضد الاجهاد المحدث بالديكساميثازون. تم استخدام ٩٦ فروج، قسمت عشوائيا إلى ٤ مجاميع لكل منها ٢٤ فرخة وبواقع ٣ مكررات وفترتين عمريتين ٢١ و ٤٢ يوم. كانت المجموعة G1 (السيطرة)، بينما تم إعطاء DEX لمدة ٣ أيام متتالية في المجموعة G2 وبجرعة ١ ملغم/كغم من وزن الجسم/ تحت الجلد حيث تم حساب الجرعة وفقا لدراسة أولية مسبقة. المجموعة G3 تم حقنها بال DEX لثلاث أيام متتالية ومن ثم أعطيت بيوتاريت الصوديوم بجرعة ٢ غم/كغم مع العلف. وأخيرا المجموعة G4 تم حقنها بال DEX وبنفس الجرعة والفترة أعلاه لكن غوملت بالبيتاين بجرعة ٢ غم/كغم مادة علفية. أظهرت النتائج بأن DEX هو عامل محدث للاجهاد غير المتخصص وأدى الى زيادة ملحوظة في ٣-caspase ورفع من مستوى ALT في الكبد والدورة الدموية على التوالي. بينما قل كل من SB وB من الاجهاد المحدث بواسطة ال DEX. ومن جهة أخرى، كان AST ثابتاً في المجموعة G2 في الفترة الأولى، على الرغم من أن كل من SB وB في المجموعتين G3 و G4 أحدثا تأثيرات واقية في الخلايا الكبدية، ولكن في الفترة الثانية اختلفت المعايير في المجاميع المعاملة بشكل كبير عن مجموعة السيطرة. وحدث انخفاض معنوي ف GSH ومؤشر الكرب مع زيادة قيمة MAD في أنسجة الكبد للمجموعة G٢، ولكن المجموعتين G3 وG4 ظهر فيهما تأثير محسن ضد تلف الكبد. وهنا نستنتج بأن SB و B يعملان على الحد او التقليل من تأثير موت الخلايا المبرمج المحدث بـ DEX.