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The adverse impact of *Aloe Vera* gel extract and *Aloe Vera*-fortified yogurt on hepatic and renal functions

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Abstract

Aloe Vera gel is used to ameliorate medical complications such as inflammation, wounds, and diabetes. It is utilized as a dairy products supplement to potentiate its nutritive value. However, *Aloe Vera* was reported as a potential irritant for hepatic and renal tissues. In this study, we investigated the impact of different concentrations of *Aloe Vera* gel extract alone or as a supplement to yogurt on hepatic and renal functions. Thirty-six male albino rats were randomly divided into six groups (n = 6). The groups received either oral administration of distilled water (DW/Control), *Aloe Vera* gel 10% in DW (AV10), *Aloe Vera* gel 20% (AV20), plain yogurt (Y), yogurt supplemented with 10% *Aloe Vera* gel extract (Y+AV10), or yogurt supplemented with 20% *Aloe Vera* gel extract (Y+AV20). Treatment was carried out daily for one week. Renal and hepatic biochemical parameters were assessed. ALT was significantly increased in the AV20 group compared to the control and AV10 groups. AST level was significantly high in Y+AV20 compared to Y+AV10, Y, and DW groups. No changes were observed in creatinine and urea. Hepatic micrographs showed vacuolar degeneration of hepatocytes in the AV20 group, while the Y+AV20 group showed necrosis of parenchyma and individualization of hepatocytes. No significant tissue changes were observed in the kidney. In conclusion, *Aloe Vera* gel extract, especially with higher concentrations, is irritant to the liver of rats with no prominent impact on the kidney. Moreover, yogurt failed to ameliorate the drastic impact of *Aloe Vera* on hepatic functions.

Keywords:

Aloe Vera, Kidney, Liver, Yogurt.

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Introduction

Aloe Vera is a widely used herbal succulent plant for targeting various medical and cosmetic purposes. It is an alternative medical agent for the amelioration of wounds (Atiba et al., 2011) (Khan et al., 2013), type 2 diabetes (Kim et al., 2009), tumors (Karpagam et al., 2019), and obesity (Misawa et al., 2012), as well as the stimulation of immune response (Im et al., 2010). *Aloe Vera* constitutes various bioactive components that might induce a deleterious effect if not used responsibly (Fogleman et al., 1992).

Literature documented various protective influences of *Aloe Vera* on the liver (Nahar et al., 2013; Werawatganon et al., 2014; Cui et al., 2014) and kidney (Chatterjee et al., 2012; Saada et al., 2003). Nevertheless, it might also exert undesirable effects on both organs at specific doses and preparations. The consumption of *Aloe Vera* pills can elevate alanine aminotransferase (ALT) in subjects without a previous history of hepatic disorders (Parlati et al., 2017). Moreover, *Aloe Vera* gel administration is reported to induce toxic hepatitis either in male or female subjects (Curciarello et al., 2008; Lee et al., 2014).

Aloe Vera constitutes bioactive components such as acemannan, and mucopolysaccharides which can induce pyelonephritis, bleeding, and enlargement of rat kidneys (Fogleman et al., 1992). Renal toxicity is more likely to occur with higher doses and chronic administration of *Aloe Vera* (Nalimu et al., 2022). Moreover, oral administration of *Aloe Vera* can induce pigmentation of the kidney and thickness of the colon (Chen et al., 2017).

Aloe Vera is provided as a supplement to yogurt to enhance the physicochemical properties of yogurt (Govindammal et al., 2017) and to improve the viability of starter bacterium (Raghunath et al., 2020). Adding *Aloe Vera* to yogurt can ameliorate oxidative stress (Hussein et al., 2021), and reduce the angiotensin-converting enzyme responsible for high blood pressure (Basannavar et al., 2014). However, the literature elucidating *Aloe Vera*-fortified yogurt impact on hepatic and renal functions are scarce.

The method used to extract, and dissolve *Aloe Vera* can modulate the drastic impact of *Aloe Vera* on the liver. For instance, oral administration of *Aloe Vera* dissolved in soya bean oil can induce degenerative changes in hepatic tissue and congestion in central hepatic veins (Kosif et al., 2010) and the irritation of hepatic and renal tissues is also more associated with whole leaf extract of *Aloe Vera* rather than gel extracts (Boudreau et al., 2013).

This investigation aims to the clarification of the potentially drastic impact of *Aloe Vera* gel extract on the liver and kidney and for assessing the safety of *Aloe Vera* at different concentrations either alone or in combination with yogurt.

Materials and methods

Ethical approval:

All experimental procedures in the present study were performed and approved in accordance with the Ethical Research Committee of the Faculty of Veterinary Medicine, South Valley University, Qena, Egypt. The protocols of the animal experiment have complied with the approved institutional animal care and use committee (IACUC#: 12-214). The experiments were also following the Egyptian welfare laws.

Animals

Male albino rats weighing 250-300 g were used to carry out the current study. All animals were distributed randomly into the treatment groups. Animals were maintained in plastic cages and allowed for *ad-libitum*

access to food and water in a 12 h light/dark cycle of room temperature.

***Aloe Vera* gel extraction:**

Aloe Vera leaves were collected from Qena Governorate, Egypt, and the gel was extracted as described before with slight modification (Noor et al., 2008). Leaves were washed with tap water and care was taken to avoid contamination with leaf latex and exudate. Spines along the leaf were removed. A knife was used to cut the green skin, and the top rind was removed. Gel content was collected and cut into pieces. The gel was diluted in distilled water to get the final concentration of 10% or 20%.

Yogurt preparation:

Yogurt preparation was carried out as described before (Lee and Lucey, 2010). Fresh cow's milk was pasteurized at 90ºC for 20 min then cooled to 42ºC and inoculated with 3% (v/v) Yogurt's starter culture (YC-X11). The plain yogurt was prepared without the addition of *Aloe Vera* gel extract and was used as a control. *Aloe Vera* fortified yogurts were prepared by mixing milk and starter with different concentrations (10% and 20%) of *Aloe Vera* extract (v/v), which was previously pasteurized (90ºC for 20 min). Plain and *Aloe Vera* fortified yogurt samples were incubated at 42ºC for 4 h until complete coagulation, cooled to refrigerator temperature (~6±1ºC), and then stored for 14 days.

Preparation of yogurt/*Aloe Vera* gel mixture:

Aloe Vera extract was added to raw cow milk (10 or 20 gm *Aloe Vera* / 100 ml of raw milk). Afterward, the new mixture was pasteurized at 90–95 °C, then cooled to 40-42 °C, followed by adding of bacterial starter. Consequently, yogurt was conveyed to plastic cubs and incubated at 40–42 °C tell Ph is 4.6. Finally, Yogurt was refrigerated at 4–5 °C. *Aloe Vera* gel extract/ yogurt mixture was administered orally at (2 ml/100 gm. b.wt)

Experimental Design

Animals were divided randomly into six treatment groups (n = 6). The first group was kept as control and received an oral administration of distilled water (DW group). The second group received 10% *Aloe Vera* gel extract diluted in distilled water (AV10 group). For the third group, animals received *Aloe Vera* gel extract of 20% (AV20 group). The fourth group received plain yogurt (Y group). The fifth group received *Aloe Vera* 10% fortified yogurt (Y+AV10), and finally, the sixth group received *Aloe Vera* 20% fortified yogurt (Y+AV20). The oral administration was done daily using a stomach tube for one week.

Measurement of body and organs weights:

At the start of the experiment, initial body weights were recorded. Afterward, body weights were measured after one week of the experiment for each treatment group. Livers and kidneys were weighed after animal sacrifice and the organ/body weight ratio was calculated.

Samples collection:

Rats were sedated with diethyl ether; individual blood samples were collected from retro-orbital venous plexus from each group in plain test tubes one week after the initial treatment. Blood samples were centrifuged at 3000 rpm for 15 minutes then sera were separated and collected in Eppendorf tubes. Sera samples were placed at -20 ºC tell being used.

Biochemical analysis:

The assessment of the biochemical parameters was done using sera samples and the related kinetic and colorimetric kits. Alanine Aminotransferase (ALT; CAT. NO. 292002) and Aspartate Aminotransferase (AST; CAT. NO.

291002) kinetic enzyme activity was assessed to evaluate the hepatic functions in different treatment groups. Creatinine (CAT. NO. 234001) and urea (CAT. NO. 318001) were measured for evaluation of renal functions. All kits were purchased from Spectrum, Egypt. All procedures were done according to manufacturer instructions and as previously described (Swaminathan, 2011). All tests were performed using a T80 spectrophotometer (PG Instruments, UK).

Histopathological examination:

The liver and Kidney of all rats in the experimental groups were removed, weighed, and quickly fixed in neutral buffered paraformaldehyde (PFA) 4%. Afterward, organs were processed through the conventional paraffin embedding technique (Bancroft and Gamble, 2007) then sectioned at 5 µm thick and stained with Hematoxylin and Eosin (H & E).

Statistical analysis:

Results were presented as (mean ± SEM). A two-way ANOVA test followed by Tukey's post hoc test was used for multiple comparisons of mean differences. A *P*-value less than 0.05 is considered significant. All statistical tests were done using GraphPad Prism version 8.

Result

Hepatic functions assessment:

After one week of *Aloe Vera* gel extract treatment, ALT serum level was significantly increased in AV20 group (40.67 + 3.21a) when compared to DW (19.32 + 4.34, $P < 0.05$) and AV10 (20.25 ± 7.35, $P< 0.05$) groups (Fig. 1a). However, animal groups Y, Y+AV10, and Y+AV20 showed no significant differences when compared to the DW group.

For AST serum level, Y+AV20 group (156.70 + 12.90) was significantly increased when compared to Y+AV10 (62.13 + 15.05, $P < 0.01$), Y (75.08 ± 7.30, $P < 0.05$), and DW (87.74 + 5.04, $P < 0.05$) groups. However, AV10 and AV20 groups AST was not significantly different compared to DW group (Fig. 1b).

Renal functions assessment:

Serum creatinine showed no significant change in different treatment groups (Fig. 2a). However, serum urea was significantly high in the Y group when compared to the Y+AV10 group (41.78 + 2.28, $P < 0.05$), and without any significant differences from the DW group (Fig. 2b).

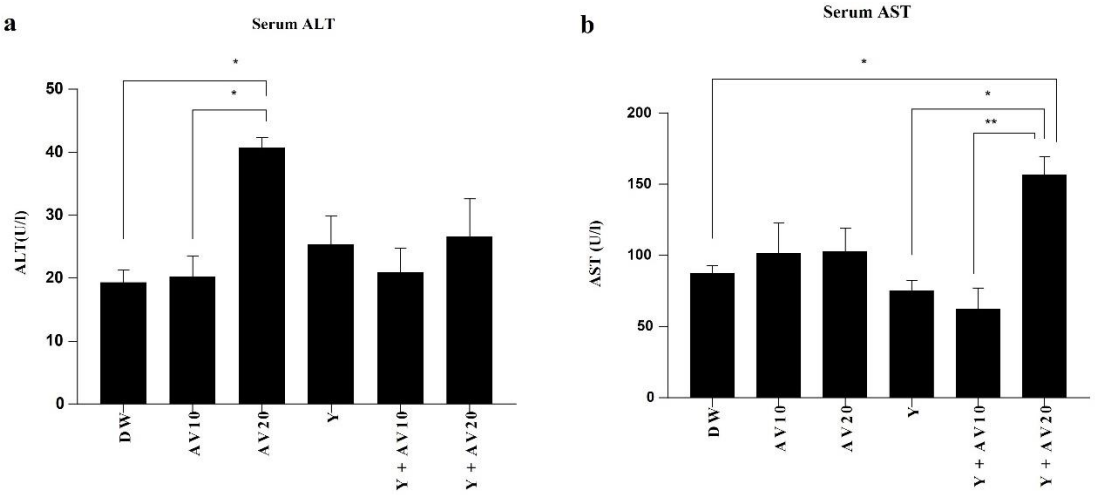

Fig. 1. **Hepatic functions at different groups one week after treatment. (a)** Serum level of ALT (U/l) and **(b)** serum level of AST (U/L) in different treatments. Data are presented as mean ± SEM (n = 6). *$p < 0.05$, **$p < 0.01$.

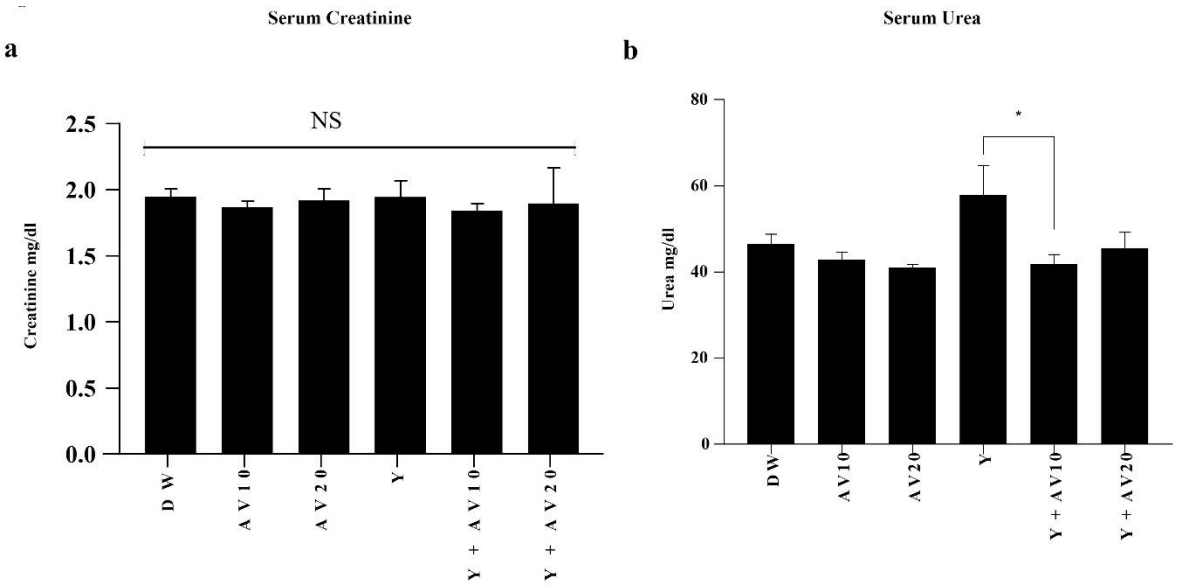

Fig. 2. Colorimetric estimation of renal functions at different groups one week after treatment. (a) Serum level of creatinine (mg/dl) and **(b)** serum level of urea (mg/dl) in different treatments. Data are presented as mean ± SEM (n = 6). *$p < 0.05$.

Body Weights and relative liver and kidney weights:

After one week of treatment, body weights showed no significant differences in all treatment groups. Likewise, the relative liver weight (liver weight/ body weight) (Fig. 3a) and the relative kidney weight (Kidney weight/ body weight) (Fig. 3b) did not show any significant differences one week after initial treatment.

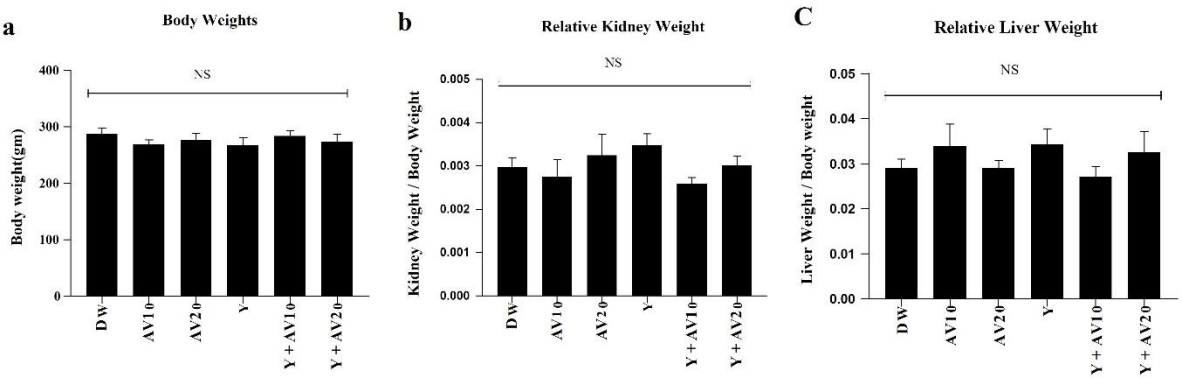

Fig. 3. Body weights and relative liver and kidney weights. (a) Total rats' body weights, **(b)** liver/ body weight ratio, and (c) kidney/body weight ratio at different treatment groups. Data are presented as mean ± SEM (n = 6). NS = no significance.

Histopathological Examination:

The histopathological examination was done for the hepatic tissue after one week of treatment. For DW and Y groups, hepatic tissue revealed a normal hexagonal lobular pattern of hepatic tissue with normal size and shape (polygonal) of hepatocytes that exhibited granulated eosinophilic cytoplasm and centrally located basophilic, uniform, and round nuclei. Hepatocytes were arranged in well-organized radiating hepatic cords around the central vein and separated by narrow blood sinusoids with a normal appearance. Portal areas were histologically normal (Fig. 4A). For the AV10 group, hepatic tissue revealed multiple necrotic foci (Fig. 4B). AV20 group showed vacuolar degeneration with

the signet-ring appearance of almost all involved cells which may indicate a fatty change (Fig. 4C). Y+AV10 group showed focal replacement of some necrotic foci with mononuclear inflammatory cells and congestion of hepatic and portal vessels (Fig. 4D). The hepatic tissue in of Y + AV20 group showed necrosis of hepatic parenchyma and individualization of hepatocytes (Fig. 4E). Kidney did not show any significant lesions.

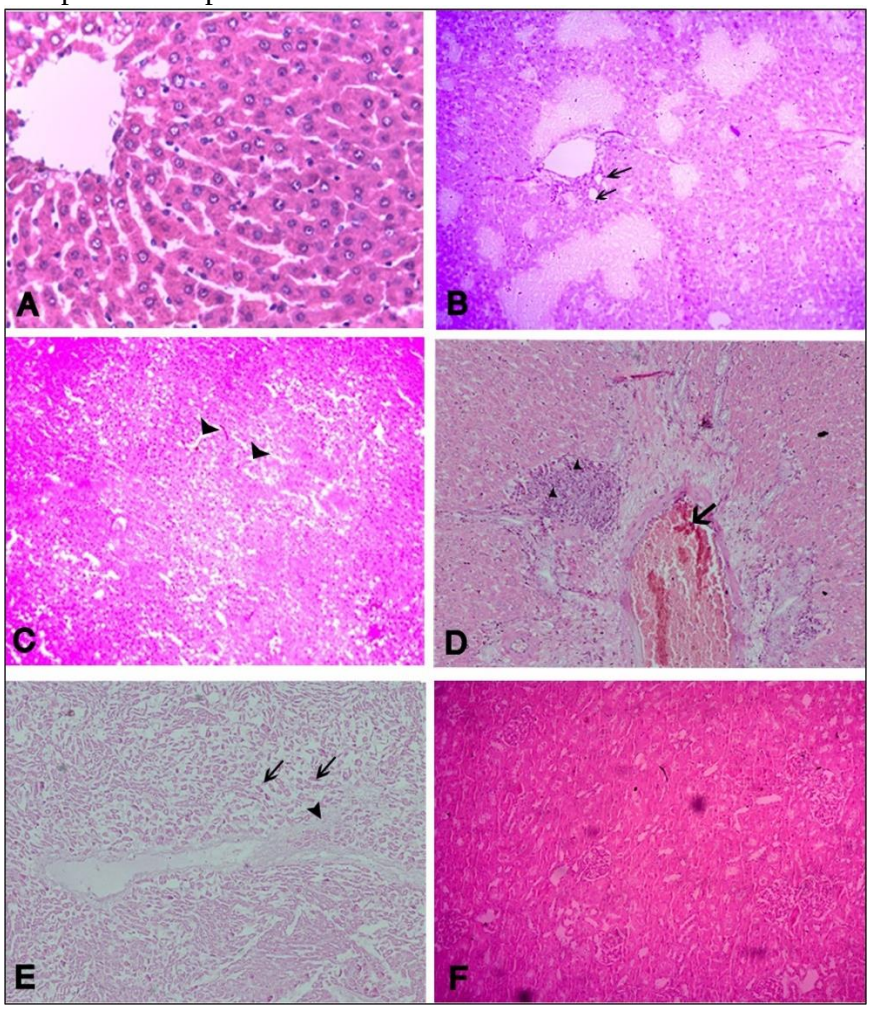

Fig. 4. Liver micrographs showing histopathological structures in different treatments. (A) A randomly selected micrograph for the normal structure of the liver in the DW group and yogurt group. The image shows the normal size and shape of hepatocytes with granulated eosinophilic cytoplasm and centrally located basophilic round nuclei (H&E stain, X300). **(B)** Hepatic micrograph of AV10 group showing multifocal necrosis of hepatic parenchyma (Arrows) (H &E stain, X300). **(C)** Hepatic micrograph of AV20 group showing vacuolar degeneration with signet ring appearance, which may indicate fatty change (Arrow Heads) (H &E stain, X 300). **(D)** Hepatic micrograph of Y+AV10 group showing focal replacement of some necrotic foci with mononuclear inflammatory cells, inflammatory cells in the portal area (Arrow Heads), and congestion of portal vessels (Arrow) (H &E stain, X 300). **(E)** Hepatic micrograph of group Y+AV20 showing necrosis of hepatic parenchyma (Arrow Heads) and individualization of hepatocytes (Arrows) (H &E stain, X300). **(F)** A random representative micrograph showing the normal renal structure of the kidney (H &E stain, X300).

Discussion

Aloe Vera pulp extract is a commonly used product for targeting several health troubles including type 2 diabetes, wound healing, and promoting general health conditions through the antioxidant, anti-inflammatory, and anti-cancer properties. In the current study the impact of Aloe Vera as a sole treatment, or as a supplement to yogurt was estimated on the functional parameters of the liver and kidney. Several reports showed a promising protective impact of Aloe Vera on hepatic (Nahar et al., 2013; Saito et al., 2012; Werawatganon et al., 2014) and renal tissues (Chatterjee et al., 2012; Saada et al., 2003; Sumi et al., 2019). However other reports showed that Aloe Vera or its constituents might exert an irritant effect in renal (Fogleman et al., 1992; Nalimu et al., 2022) and hepatic tissues (Curciarello et al., 2008; Lee et al., 2014; Parlati et al., 2017). For more elucidation of the Aloe Vera effect, the current study focused on the impact of Aloe Vera's gel extract after one-week oral administration in albino rats as well as its impact as an enrichment to yogurt.

We showed here that various aloe vera treatments had no impact on the body weights of naïve rats which adheres to previous literature that showed an anti-obesity effect of *Aloe Vera* on obese rat models but not on normal rats (Lasker et al., 2019; Misawa et al., 2012). Accordingly, it is suggested that *Aloe Vera* owns a therapeutic effect on obese models without further interference with normal body weights. However, other reports showed that *Aloe Vera* might enhance body weight gain during the growth stage in broilers when *Aloe Vera* is used as a diet supplement (Mmereole, 2011). Yogurt can exert the same impact on body weight without interfering with the level of triglycerides and cholesterol in the blood (Haque et al., 2017). The influencing impact of *Aloe Vera* on weight gain is a result of the inhibition of pathogenic coliforms and enhancement of commensal bacteria growth (Shokraneh et al., 2016).

For assessment of *Aloe Vera's* safety on the liver, ALT and AST enzymes were measured. The current findings showed that administration of Aloe *Vera* gel extract at 20%, but not 10% could induce an irritant effect through the elevation of ALT. However, this impact was attenuated when *Aloe Vera* 20% was ingested in combination with yogurt. These findings were supported by previous reports which showed an influencing impact of *Aloe Vera* gel administration on serum ALT in the old (Parlati et al., 2017), and also young subjects (Curciarello et al., 2008; Lee et al., 2014). Therefore, it is concluded that it is safer for *Aloe Vera* to be ingested with yogurt rather than distilled water. These findings are in line with previous reports that showed the ameliorative effect of yogurt on hepatic functions as a result of its antioxidant impact on hepatic tissue and prevention of fat accumulation in the liver, moreover, yogurt was also reported to decrease ALT and AST levels in hepatotoxic models (Asadi et al., 2010; Nabavi et al., 2014). We also showed that AST levels were significantly increased in animals that received yogurt with *Aloe Vera* 20% when compared to DW, yogurt with *Aloe Vera* 10%, and yogurt groups. Although AV20 and AV10 groups tend to have a higher level of AST, the changes were not significant. However, ALT is more specific to the hepatic function than AST, therefore, the elevation of AST might indicate dysfunction in other organs such as the heart, skeletal muscles, and kidney which might justify the relatively elevated urea level in the yogurt group (Giannini et al., 2005).

Assessment of renal function showed no significant changes in the serum levels of creatinine. Likewise, the literature showed that administration of *Aloe Vera* had a desirable impact on the kidney including the reduction of creatinine in nephrotoxicity models (Chatterjee et al., 2012) and relief of oxidative stress in renal tissue via elevation of antioxidant levels without additional changes in normal rats (Saada et al., 2003).

We showed that yogurt administration does not have a drastic impact on renal or hepatic biochemical functions. However, urea level was significantly decreased in Y+AV10 when compared to yogurt, this might be a result of yogurt's high protein content and the ability of aloe vera to downregulate elevated serum urea (Tanomand et al., 2018).

The group which received yogurt supplemented with *Aloe Vera* 20% showed vacuolar degeneration with the signet-ring appearance of almost all involved cells which may indicate a fatty change and coincides with the current biochemical findings of elevated ALT serum level. However, the group of yogurts supplemented with the higher concentration of AV (20%) showed necrosis of hepatic parenchyma and individualization of hepatocytes which is correlated with the high level of AST in the same group.

Conclusion

Oral administration of high concentrations of *Aloe Vera* alone or in combination with yogurt could induce a drastic impact on hepatic functions represented by high levels of ALT and AST enzymes without notable effect on the kidney. Moreover, the administration of yogurt could not ameliorate the undesirable effect of *Aloe Vera*.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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