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Effects of ivermectin and albendazole on some liver and kidney function indices in rats

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Evaluation of repeated administration of ivermectin and albendazole separately and in combination on some hepatic and renal function indices were examined in albino rats (*Rattus novergicus*). The experimental animals were randomly divided into four groups: those administered distilled water (control), those administered 0.4 mg/kg bodyweight of ivermectin (Iver), those administered 15 mg/kg body weight of albendazole (Alb) and those administered the two drugs concurrently (Iver+Alb). The animals were administered, the drugs daily for fifteen days after which venous blood, liver and kidney were collected. The separate administration of ivermectin and albendazole significantly elevated (P<0.05) the concentrations of serum potassium and bicarbonate ions. Also, their co-administration caused a significant elevation (P<0.05) of serum phosphate ion concentration. Administration of ivermectin and/or albendazole led to significant increase (P<0.05) in serum urea, creatinine, glucose and cholesterol concentrations while albumin was significantly reduced (P<0.05). Generally, activities of ALP, ACP, LDH, AST, ALT, Na^+-K^+ ATPase and Ca^{2+}-Mg^{2+} ATPase of liver and kidney were significantly altered (P<0.05). These observations may be suggestive of deranged membrane structures and functions. Thus the combined administration of the two drugs may be exerting more deleterious effects on both renal and hepatic functions than when administered individually.

Key words: Ivermectin, albendazole, liver function, kidney function.

INTRODUCTION

Onchocerciasis and lymphatic filariasis are major public health problems in several tropical countries including Nigeria (Ottesen and Ramachandran, 1995). Lymphatic filariasis was rated as the highest of all tropical disease after malaria (Ottesen et al., 1997). It is the world's second leading cause of long term disability. Also, ocular-onchocerciasis has been found in more than one million individuals in Nigeria (WHO, 1995). Due to altered immune cell characteristics, infection with filarial worms could enhance the replicative capacity of HIV (WHO, 2006). In addition to severe sexual dysfunction, these infections can also have a significant economic impact in endemic communities, since some of the disabilities may lead to reduced productivity (WHO, 1997).

The two main drugs used for the treatment of onchocerciasis and lymphatic filariasis are ivermectin and albendazole. Ivermectin is a macrocyclic lactone while albendazole is derived from benzimidazole. The coendemicity of onchocerciasis and lymphatic filariasis (Molyneux and Zagaria, 2002) and development of ivermectin resistance in nematodes (Harder et al., 2003) have brought about generous ivermectin and albendazole donation programmes since 1998 (Molyneux and Zagaria, 20 02). Combination therapy involving these drugs has been carried out in some countries with reports of high efficacy in the treatment of onchocerciasis and lymphatic filariasis (Ismail et al., 1998; Awadzi et al., 2003).

Separate administration of the two drugs has been reported to interfere with normal functioning of the heart as seen in a few cases of tachycardia and deaths recorded in animals repeatedly treated with ivermectin and albendazole separately (Gardon et al., 1997). Ahern et al. (19 99) reported that ivermectin increased Ca^{2+} release from sarcosplasmic reticulum vesicles and from endosplasmic reticulum by inhibiting Ca^{2+} uptake by the Ca^{2+}-Mg^{2+} ATPase. A minimal transient elevation of serum createnine following repeated administration of albendazole has been described by Ismail et al. (1998). Ivermectin is also known to cause decrease in the activity of lactate dehydrogenase (LDH) *in vitro* (Mattei and Rodrigues,

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Table 1. Effects of ivermectin and albendazole on the concentrations of some serum electrolytes[1] in rats.

Concentration of serum electrolytes	Control	Iver	Alb	Iver+Alb
Na^+(mmol/l)	142.20±1.12[a]	146.40±1.72[b]	142.80±1.32[a]	142.80±1.64[a]
K^+ (mmol/l)	5.70±0.16[a]	6.0±0.16[b]	7.40±0.88[c]	5.98±0.28[a]
Ca^{2+}(mmol/l)	2.22±0.057[a]	2.49±0.07[b]	2.21±0.014[a]	2.23±0.04[a]
PO_4^{2-}(mmol/l)	0.97±0.02[a]	0.98±0.03[a]	0.71±0.02[c]	1.94±0.10[d]
HCO_3 (mmol/l)	22.00±1.32[a]	27.10±0.79[b]	29.50±1.30[c]	22.60±1.24[a]

[1]Values are means ± S.D. Values with different superscript (a, b, c or d) in each row are significantly different at P<0.05.

1994). Studies have also revealed minimal transient increase in serum and liver aminotransferase activities following separate administration of ivermectin and albendazole (Ismail et al., 1998; Arise and Malomo, 2005).

The paucity of information on the biochemical effects of these drugs especially when used in combination prompted this study with a view to providing data and information on the effects of this regimen on some liver and kidney function indices in rats.

MATERIALS AND METHODS

Drugs and reagents

Ivermectin (Iver) and albendazole (Alb) were products of Merck and Co., England and Glaxo Smithkline Beecham, Netherlands respecttively. All the reagents used for this study were of analytical grade, prepared in all-glass distilled water.

Animals and treatments

The rats were maintained on normal rat chow and water *ad libitum* and were housed in wooden cages. Animal husbandry and experimentation were consistent with the Guiding Principles in the Use of Animals in Toxicology (Derelanko, 2000).

Twenty (20) male albino rats (*Rattus novergicus*) weighing between 155 and 160g were randomly divided into four groups of five rats each. Group I (control) received an appropriate volume of distilled water. Group II (Iver) received a human therapeutic dose of 0.4 mg/kg body weight (b.w.) ivermectin; Group III (Alb) received a human therapeutic dose of 15 mg/kg body weight albendazole while group IV (Iver + Alb) received a dose of 0.4 mg/kg body wei-ght ivermectin co-administered with 15 mg/kg body weight albendazole. The administration was done orally on a daily basis for fifteen (15) days. This duration was based on the clinical trial conducted by Ismail et al. (1998) to evaluate the potency of the combination therapy. The animals were sacrificed 24 h after the fifteenth day administration.

Sample preparation

At the end of the experimental period, approximately 5 ml of venous blood was collected from each of the experimental animals according to the method of Narayanan et al. (1984) . The serum was prepared by centrifuging the blood samples at 3000 rpm for 5 min (Ogbu and Okechukwu, 2001) and serum collected with a Pasteur pipette. The animals were thereafter quickly dissected and the liver and kidneys removed. The decapsulated kidneys and liver were suspended in ice-cold 0.25 M sucrose solution (1:5 w/v) and homogenized. The homogenates were kept frozen overnight to ensure maximum release of the enzymes (Adebayo et al., 2003).

Assay of biochemical parameters

Concentrations of serum sodium and potassium ions were determined by flame photometry using the Jenway clinical PFP7 flame photometer as described by Tietz et al. (1994). Serum urea concentrations were estimated by the diacetylmonoxime assay (Veniamin and Varkirtzi-Lemonias, 1970). Serum creatinine concentration was determined using Jaffe's reaction as described by Cook (1975). Serum albumin concentration was estimated using the albumin-bromolcresol green reaction described by Grant and Kachmar (1987). The glucose oxidase method (Chawla, 1999) was used to estimate serum glucose concentration while serum cholesterol concentration was estimated by the method described by Stroev and Makarova (1989). Serum inorganic phosphate and calcium ion concentrations were estimated by the method of Ray-Sarkar and Chanhan (1967). The back titration procedure as described by Tietz et al. (1994) was used in the estimation of serum bicarbonate concentration. Alkaline phosphatase (ALP) activity was determined by the method of Ahamed and King (1959) while the activities of aspartate and alanine aminotransferases (AST and ALT respectively) were determined by the method of Reitman and Frankel (1957). The activities of Na^+-K^+ and Ca^{2+}-Mg^{2+} ATPases were determined by the method of Ronner et al. (1977).

Statistical analysis

All data are presented as mean ±standard deviation. Statistical analyses were carried out using Duncan Multiple Range test (Montgomery, 1976). In all cases probability level of 95% was taken as significant.

RESULTS

The effects of ivermectin and/or albendazole on the concentrations of some serum electrolytes are shown in Table 1. Ivermectin significantly elevated (P<0.05) the concentrations of serum sodium, potassium, calcium and bicarbonate ions compared to controls. Ivermectin did not bring about any significant change (P> 0.05) in serum phosphate concentration. Also, albendazole significantly increased (P<0.05) the concentrations of serum potassium and bicarbonate ions. The co-administration of the two drugs caused significant elevation (P<0.05) in the concentration of serum inorganic phosphate, suggesting synergistic interaction, while there were no significant

Table 2. Effects of ivermectin and albendazole on the concentrations of some serum biomolecules[1] in rats.

Serum Parameters	Control	Iver	Alb	Iver+Alb
Glucose (mmol/l)	9.8±0.53[a]	18.22±0.19[b]	7.36±0.32[c]	8.60±0.26[d]
Urea (mmol/l)	5.52±0.39[a]	6.92±0.49[b]	8.31±0.30[c]	9.20±0.16[d]
Albumin (mmol/l)	60.81±4.39[a]	49.90±2.18[b]	54.12±4.11[c]	54.93±2.99[c]
Creatinine (mg/dl)	67.96±0.75[a]	76.80±1.21[b]	84.75±1.20[c]	90.36±1.56[d]
Cholesterol ($x10^2$mmol/l)	0.20 ± 0.01[a]	1.5 ±0.01[b]	1.40 ±0.01[b]	1.9 ± 0.01[c]

[1]Values are means ±S.D. Values with different superscript (a, b, c or d) in each row are significantly different at P<0.05.

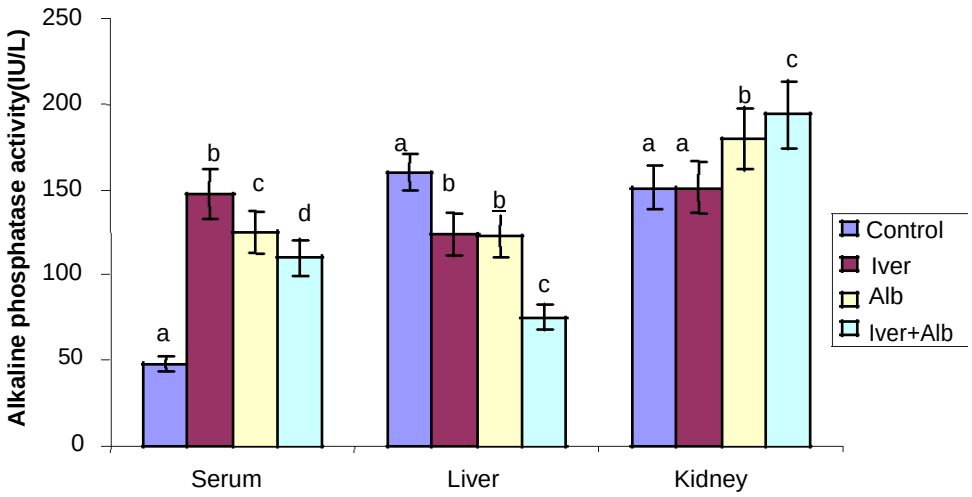

Figure 1. Effects of ivermectin and albendazole on alkaline phosphatase activities in selected rat tissues.
[1]Values are means (n=5) ±S.D (bars with different superscripts a, b, c or d are significantly different at P<0.05).

differences (P>0.05) in the concentrations of other serum electrolytes.

Shown in Table 2 are the effects of ivermectin and/or albendazole administration on the concentration of some serum biomolecules. Administration of ivermectin and/or albendazole for 15 days led to significant increase (P< 0.05) in the concentrations of all the biomolecules except the significant reduction (P<0.05) observed in serum albumin concentrations in all the treatment groups and serum glucose concentration in albendazole, and ivermectin plus albendazole administered rats when compared with control.

Figures 1-6 show the effects of ivermectin and/or albendazole administration on the respective activities of ALP, LDH, ALT, AST, Na^+-K^+ ATPase and Ca^{2+} -Mg^{2+} ATPase in the tissues studied. The drugs and their combination significantly increased (P<0.05) serum ALP activity while there was significant reduction (P<0.05) in liver ALP activity compared to controls. Albendazole and its co-administration with ivermectin significantly (P<0.05) elevated kidney ALP activity.

There was a significant increase (P<0.05) in serum LDH activity while liver LDH activity was significantly reduced (P<0.05) in all treatment groups, compared to controls. However, separate administration of ivermectin and albendazole significantly elevated (P<0.05) kidney LDH activity while their co-administration significantly lowered (P<0.05) the enzyme activity, compared to controls. There was a significant elevation (P<0.05) in serum ALT activity and a significant reduction (P<0.05) in both liver and kidney ALT and AST activities in all the treatment groups compared to controls. However, there was a significant elevation (P<0.05) in the serum AST activity following the administration of ivermectin and its co-administration with albendazole. Separate administration of albendazole had no significant effect (P>0.05) on serum AST activity.

Separate and combined administration of ivermectin and albendazole significantly elevated (P<0.05) liver Na^+-K^+ ATPase and Ca^{2+}-Mg^{2+} ATPase activities compared to controls. The separate administration of ivermectin and albendazole did not significantly (P>0.05) affect kidney

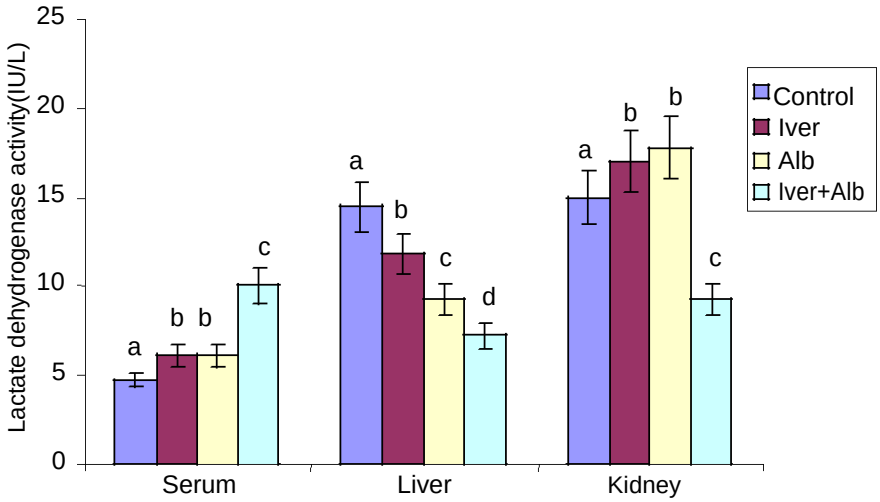

Figure 2. Effects of ivermectin and albendazole on lactate dehydrogenase activities in selected rat tissues.
[1]Values are means (n=5) ± S.D (bars with different superscripts a, b, c or d are significantly different at P<0.05).

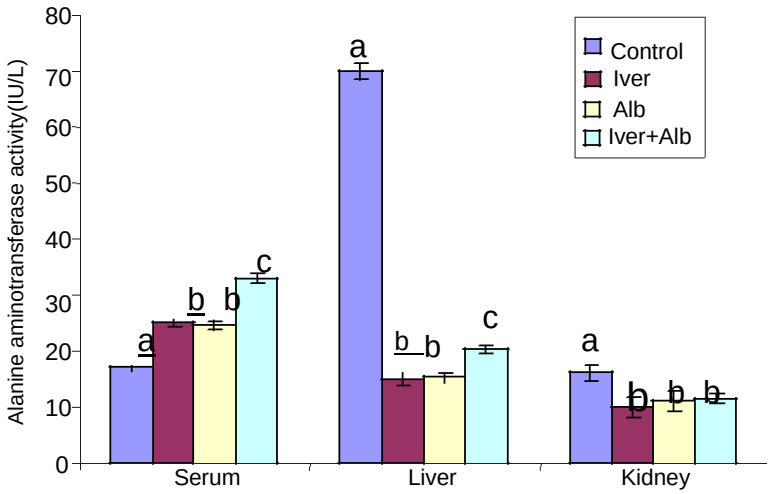

Figure 3. Effects of ivermectin and albendazole on alanine aminotransferase activities in selected rat tissues.
[1]Values are means (n=5) ± S.D (bars with different superscripts a, b or c are significantly different at P<0.05).

Na^+ -K^+ ATPase activity but the co-administration of the two drugs significantly elevated (P<0.05) the enzyme activity in the kidney compared to control. Moreover, Ca^{2+}-Mg^{2+} ATPase activity was significantly lowered (P< 0.05) in the kidney following separate administration of ivermectin, and albendazole. Their combined administration resulted into a significant increase (P<0.05) in kidney Ca^{2+}-Mg^{2+} ATPase activity compared to control.

DISCUSSION

The functional capacity of the kidney can be assessed by determining the serum concentration of electrolytes and excretory constituents (Whelton et al., 1994). Inorganic electrolytes occur in large quantities in both extracellular and intracellular fluids of the body. Due to their ability to dissociate readily into their constituent ions or radicals, they constitute the most important factors in the transfer of electrolytes between the extracellular and intracellular compartments.

The elevated serum glucose level observed may have resulted from increased mobilization of glucose for metabolism or may be due to reduced glucose uptake into cells (Bray et al., 1999) caused by ivermectin. This is also suggestive of a possible modulation of the capacity of the renal tubule by the drug to reabsorb glucose actively from

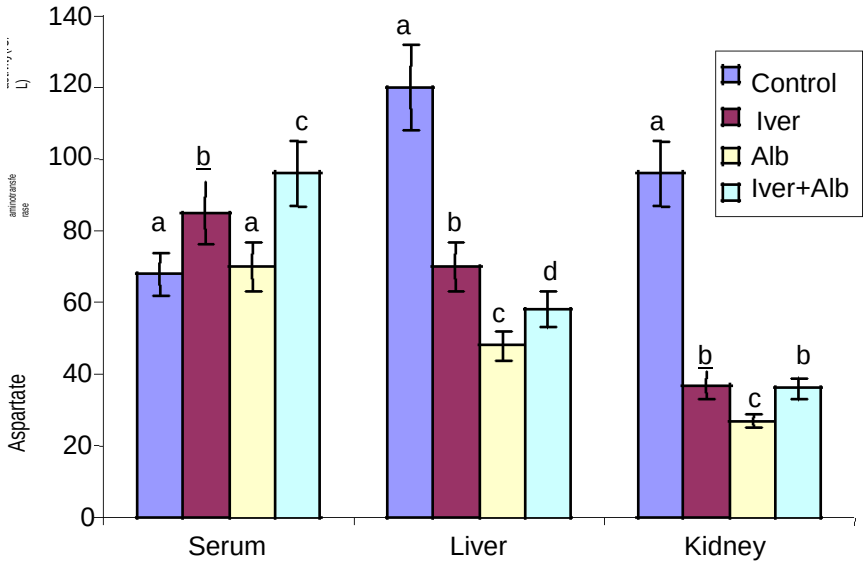

Figure 4. Effects of ivermectin and albendazole on aspartate aminotransfe-rase activities in selected rat tissues.
[1]Values are means (n=5) ± S.D (bars with different superscripts a, b, c or d are significantly different at P<0.05).

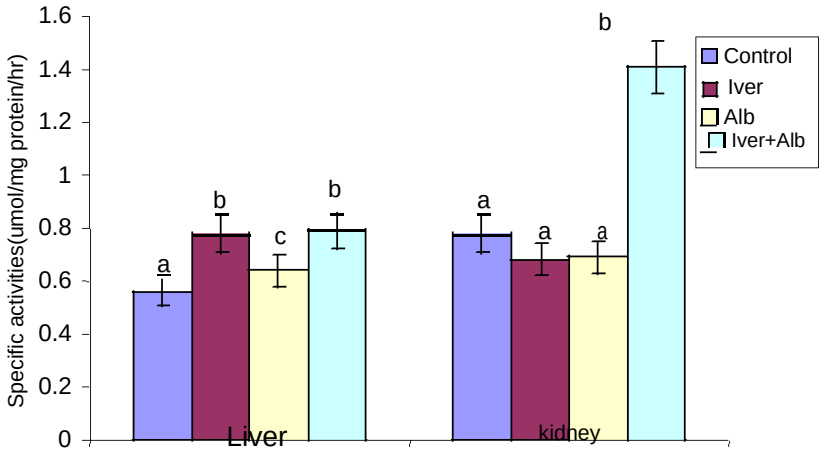

Figure 5. Effects of ivermectin and albendazole on activities of Na^+-K^+ ATPase in selected rat tissues.
[1]Values are means (n=5) ±S.D (bars with different superscripts a, b or c are significantly different at P<0.05).

the blood (Bray et al., 1999). The reduction in serum glucose concentration following the administration of albendazole and its combination with ivermectin may be due to inhibition of the uptake and transport of glucose by albendazole (Strote et al., 1990). Albendazole has been reported to exert its effect on tubulin polymerization leading to loss of cytoplasmic microtubles and the ability to take up and transport glucose (Strote et al., 1990).

The significant increase in the serum Na^+ concentration following the administration of ivermectin repeatedly for 15 days may be attributed to increased production of aldosterone (which has been reported to stimulate membrane aldosterone receptor) and other mineralocorticoids which increase the tubular reabsorption of Na^+ (Tietz et al., 1994) . The significant increase in serum K^+ concentration in rats administered ivermectin or albendazole may be due to increased sensitivity of the nephron to aldosterone and other mineralocorticoids responsible for reabsorption and retention of electrolytes respectively.

The significant increase in serum Ca^{2+} and inorganic phosphate ion levels following ivermectin and its combined administration respectively may be due to cell

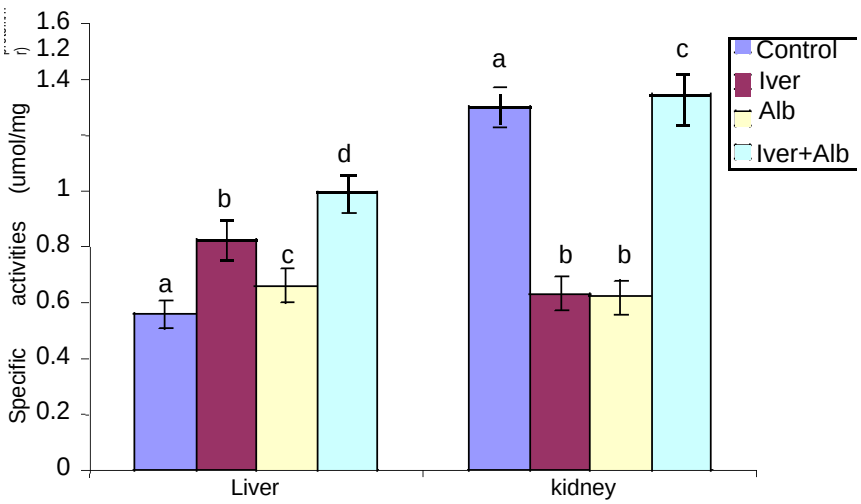

Figure 6. Effects of ivermectin and albendazole on activities of Ca^{2+}-Mg^{2+} ATPase in selected rat tissues.
[1]Values are means (n=5) ± S.D (bars with different superscripts a, b, c or d are significantly different at P<0.05).

membrane damage as a result of exposure to these drugs or inhibition of uptake by cells and tissues. Alterations in Ca^{2+} uptake and release may explain both the po-sitive and negative side effects of ivermectin. Positively, ivermectin may be protective against glutamate excitoto-xicity partly mediated by altered Ca^{2+} level (Manev et al., 1993). Increased serum phosphate concentration after combined administration of ivermectin with albendazole may be due to failure of the kidney to excrete phosphate into the urine, causing phosphate accumulation in the blood. Ivermectin is known to cause inhibition of renal ex-cretion of substances that are substrates of *p*-glyco-protein (Fricker et al., 1999).

Increase in serum bicarbonate level in the ivermectin or albendazole administered rats may imply that either of the drugs overwhelmed the pH regulatory mechanism of the blood. The pH of the mammalian system depends on the ratio of (HCO_3^-) to the partial pressure of exhaled CO_2 (pCO_2) (Bray et al., 1999). While bicarbonate concentra-tion is controlled by the kidney, pCO_2 is rapidly controlled by the lung (Bray et al., 1999). Thus, the increase in bicarbonate concentration or metabolic acidosis suggests compromise of the renal cell integrity and function as relates to re-absorption at the proximal tubule (Ganong, 1991).

Reduced renal blood flow associated with higher serum urea concentration may impair the secretory function of the kidney (Whelton et al., 1994). Malfunction in the glomerular filtration results in the retention of substances including urea and creatinine, and this may be responsible for their high serum levels in all the treatment groups. A minimal transient elevation of serum creatinine following repeated administration of albendazole has been described by Ismail et al. (1998). Reduction in serum albumin level has adverse consequences. Albumin in conjuction with other plasma proteins (being large colloidal molecules) cannot diffuse through the thin capillary wall membranes as most other plasma solutes. Thus they are entrapped in the vascular system and exert a colloiddal osmotic pressure, which serves to maintain a normal blood volume and normal water content in the interstitial fluid and tissues (Malomo et al., 2007). The albumin fraction is the most important in maintaining this normal colloidal osmotic or oncotic pressure in blood. Thus decreese in serum albumin concentration to low levels implies that water will diffuse from the blood vessels and enter interstitial fluid and the tissues, leading to the accumulation of water in such tissues (Malomo et al., 2007).The significant increase in the serum cholesterol concentration in all the treatment groups compared to control may be due to nephritis. High serum cholesterol level has been implicated as a factor in degenerative renal tubular epithelial cells. Alterations in cholesterol level are often used as an index of renal damage (Whealton et al., 19-94). On the other hand, this increase may be due to derangement of tissue plasma membrane (Whealton et al., 1994) caused by the drugs and their combination, thus leading to leakage of cholesterol into the extracellular fluids (Popishil and Tatiana, 1996). Cholesterol is an essential component of animal cell membranes and also of myelin sheath of nerves and outer sheaths of plasma lipoproteins (Whealton et al., 1994).

The significant increase in serum ALP activity of all the treatment groups is suggestive of a possible damage to tissue cell plasma membrane by the combined administration with albendazole either singly or in combination, thus leading to leakage of membrane components into the extracellular fluid (Akanji et al., 1993). This was further supported by a corresponding reduction in liver ALP activities. This may be attributed to loss of membrane

and cytosolic components (Akanji et al., 1993) including ALP. The significant increase in kidney ALP activity following administration of albendazole and its combination with ivermectin may be as a result of increased enzyme synthesis to offset the stress imposed by albendazo-le and its combination with ivermectin (Malomo et al., 1995).

The significant reduction in the kidney LDH activity following the co-administration of ivermectin and albendazole is also suggestive of plasma membrane derangement by the drugs leading to excessive leakage of cytosolic materials including LDH into extracellular fluids (Huang et al., 2009). This may be due to possible tissue plasma membrane labilization by the drugs singly or in combination, inhibition of the enzyme molecule by either drug or both, or probably the inactivation of the enzyme molecule *in situ* (Copeland, 2005). This corroborates the work of Mattei and Rodrigues (1994) in which they reported decrease in the activity of LDH *in vitro* in the presence of ivermectin. The plasma membrane derangement resulting from the combination of the two drugs seems plausible in the light of over 100% increase in the serum LDH activity. Ivermectin and albendazole are very soluble in fat-a major component of the plasma membrane (Redondo et al., 1999) and this would aid the accumulation of the two drugs and/or their metabolites in the cell, causing injury. The increase in kidney LDH activity following separate administration of the two drugs may be due to response of the cellular systems to offset the stress imposed as a result of exposure to either of the two drugs. Malomo et al., (1995) observed increased activities of various enzymes under varying conditions of stress.

Alanine aminotransferase activity in the blood are increased in conditions in which cells are damaged or dead (Jimoh and Odutuga, 2001). Elevation in the activities of serum ALT and AST as observed in this study may have been due to leakage from the organs into extracellular fluids due to change in endothelial permeability as earlier stated. High serum levels of AST and ALT have been used as indicators for some forms of hepatic diseases. The significant reduction in the liver and kidney ALT and AST activities in all the treatment groups is suggestive of damage to the plasma membrane of these tissues at the cellular level, leading to increased efflux of these enzymes into the extracellular fluid (Huang et al., 2009).

The significant increase in Na^{+}-K^{+} ATPase in all the treatment groups revealed that ivermectin, albendazole or their combination may have imposed some form of stress on liver cells, thus increasing the synthesis of the enzyme molecule to offset the stress (Malomo et al., 1995). The concentration of Ca^{2+} in extracellular fluid is four times higher than that of cytosol (Anderson et al.
1993). This gradient is maintained by the active transport, of Ca^{2+} across the plasma membrane. The significant increase in the hepatic activity of Ca^{2+}-Mg^{2+} ATPase in all the treatment groups may be due to increased production of the enzyme to conteract the stress imposed by the drugs. The significant reduction in the kidney Ca^{2+}-Mg^{2+} ATPase activity following ivermectin and albendazole administra-tion may be attributed to membrane derangement or inhibition of the enzyme by the drugs. Ahern et al. (1999) reported that ivermectin increased Ca^{2+} release from sarcosplasmic reticulum vesicles and from endosplasmic reticulum by inhibiting Ca^{2+} uptake by Ca^{2+} -Mg^{2+} ATPase. This may also be the reason for the reduced activity of Ca^{2+}-Mg^{2+} ATPase in the kidney as observed here. This reduction in Ca^{2+} -Mg^{2+} ATPase activity in the kidney may lead to an increase in intracellular Ca^{2+} concentration which may in turn, lead to leakage of potassium ions out of the cells with corresponding loss of cell water (Hebbel, 1991). The consequent effect of this is inhibition of Na^{+}-K^{+} ATPase activity. Also these may affect the osmoregu-latory role of the kidney. However, the combination thera-py displayed negative synergism by significantly increa-sing the enzyme activity.

The results obtained from this study suggest that the repeated administration of ivermectin and/or albendazole may compromise the integrity of the kidney and the liver and thereby adversely affect their normal functions. Also recipients with renal and hepatic disorders may have their ill health compounded with the co-administration of the two drugs. It therefore implies that the combined therapy, despite its reported efficacy, may possess the potential of adversely affecting liver and kidney functions.

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