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Effect of Long Term Administration of *Solanum Nigrum* Extracts in Female Swiss White Mice Infected with *Trypanosoma Brucei Rhodesiense*

Serem, Erick Kibichiy[1]. Ngure, Raphael M[2]. Chome, Jonathan[1]. Korir, Scolastica C[1]. Mdachi, Raymond E.[3] and Mburu, Jane N.[4]

[1]Department of Biological Sciences, Egerton University, P. O Box 536-20115 Egerton.

[2]Biochemistry and Molecular Biology Department, Egerton University. P. O Box 536-20115 Egerton.

[3]Kenya Agricultural Research Institute- Trypanosomosis Research Centre, Pharmacology and Chemotherapy Division. P.O Box 362- 00902, Kikuyu.

[4] Animal Sciences Department, Egerton University, P. O Box 536-20115 Egerton.

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Abstract

Trypanosomosis progression and prognosis in female mice varies on the concentrations of the drug used due to the differences in which metabolites are accumulated or excreted from their bodies. Female Swiss white mice were infected with *Trypanosoma brucei rhodesiense* and treated with different concentrations of *Solanum nigrum* extract (SNE). The results indicated that mice treated with 10g/L and 6.7g/L of SNE had significantly lower survival time probably due to the accumulation of metabolites to toxic levels while mice treated with 3.3g/L had a longer survival time due to the beneficial effect of the extract. The mice treated with 3.3g/L SNE also had lower parasitaemia levels and significantly higher PCV, body weights and albumin levels compared to the infected mice treated with dexamethasone and higher concentrations of SNE. In summary, lower concentrations of SNE should be used in the treatment of female mice to avoid accumulated SNE metabolites to toxic levels.

Keywords: Survival time, Mice, Females, Toxicity, Metabolite accumulation, Chronic therapy

Introduction

Chemotherapy in males and females differs due to the differences in the pharmacokinetics and pharmacodynamics of the chemotherapeutic agents. For the efficacy of a drug it is necessary to maintain certain drug concentrations so as to improve the therapeutic effect and minimize the adverse effects (Hamburg and Collins, 2010). The differences in sex, influences how a drug will be metabolized or accumulated in the body (Soldin et al., 2011). Moreover, the length of time in which the drug is administered may have an effect on the prognosis of the disease especially due to the toxicity. Short term toxicity studies of a drug may not reveal the long term toxic effects of a therapeutic agent (Pellegatti and Pagliarusco, 2011).

Water extracts of *S. nigrum* have been shown to contain active compounds such as tanins, alkaloids, phytosterols, flavonoids and coumarins (Ravi *et al.,* 2009). Different phytochemicals in *S. nigrum* have different effects. It has been shown to be protective in carbon tetrachloride induced liver damage in rats (Lin et al., 2008), inhibit thioacetamide induced liver fibrosis in mice (Hsieh et al., 2008), be cytoprotective in Gentamicin induced kidney cell damage *in vitro* (Kumar et al., 2001) and also in preventing trypanosome induced liver damage thus increasing the survival time of mice infected with *T. b. rhodesiense* (Serem et al., 2013). In India a *S. nigrum* formulation, Liv 52, is used for the treatment of liver diseases (Sandhir and Gill, 1999). Despite its beneficial effects *S. nigrum* may have some toxic effects. *S. nigrum* contains two main cytotoxic glycoalkaloids, solanine and solasodine, thus are poisonous when taken in large quantities with the highest concentrations of solanine occurring in the immature fruit but decreases on ripening (Defelice, 2003). Glycoalkaloids clearance takes more than 24 hours, which implicates that the toxicants may accumulate in case of daily consumption (Mensinga *et al*., 2005) a condition that may be more marked during liver damage since glycoalkaloids concentrate mainly in the liver (Friedman, 2006).

This study therefore investigated the effect of long term administration of *Solanum nigrum* in female mice infected with *Trypanosoma brucei rhodesiense* parasites.

2.0 Materials and Methods

2.1 Collection and extraction of plants

The *S. nigrum* plants were collected from Kapchuriai village in Chepkunyuk Location of Nandi County in Kenya and extracted as described by Serem et al., (2013). The resulting freeze dried extract was stored in closed vials ready for use.

2.2 Trypanosomes and Ethical approval

A trypanosome strain, KETRI 2537, was obtained from the trypanosome bank of Kenya Agricultural Research Institute-Trypanosomiasis Research Centre (KARI-TRC). All protocols involving the use of the laboratory animals were approved by the research ethics committee of TRC.

2.3 Experimental mice

Female Swiss white mice were obtained from the Kenya Medical Research Institute (KEMRI) small animal breeding unit and acclimatized for a period of two weeks in the laboratory. The mice were treated with Ivermectin® at a dose of 300µg/kg and maintained on mice pellets (Unga feeds Kenya) throughout the period of study.

2.4 Toxicity studies

Female Swiss white mice weighing between 22 to 25g were randomly divided into 5 groups of 5 mice each and each mouse marked with picric acid. Each group was housed separately and treated with increasing concentrations of *S. nigrum* extract daily for a period of 10 days and monitored further for four days for evidence of toxicity. The mice were

Corresponding Author: Serem, Erick Kibichiy
Department of Biological Sciences, Egerton University, P. O Box 536-20115 Egerton.
Email:erickserem06@gmail.com

treated as follows: Group i; 250mg/kg body weight (bwt), Group ii; 500mg/kg bwt, Group iii; 1000mg/kg bwt and Group iv 2000mg/kg bwt. Group v was given water only as a negative control. During the period of the toxicity studies the packed cell volume (PCV) and the body weights of the mice were monitored every two days and changes in these parameters recorded. After the experimental period of toxicity the mice were euthanized and disposed off.

2.5 Experimental design

This experiment on the female mice was carried out at the same time and in the same way as that of the males described in Serem et al., (2013). The experimental mice were randomly divided into six groups of five mice, marked and housed separately. Two donor mice were immunosupressed with cyclophosphamide and according to Kagira et al., (2005) and the parasites collected on the first peak of the parasitaemia. Each experimental mouse was infected with 10^4 trypanosomes intraperitoneally and the groups treated with decreasing concentrations of the SNE extract as follows: Group i; 10g/l, Group ii; 6.7g/l, Group iii; 3.3g/l, Group iv; 0.2mg of dexamethasone every two days Group v; infected untreated Group vi; uninfected untreated. The mice were then monitored for parasitaemia, bwt and PCV every two days for the entire period of the study. Any deaths that occurred were recorded and the survival time calculated.

2.6 Data analysis

The data for parasitaemia, bwt and PCV in different groups of mice were presented as mean ± standard error of the mean (mean ± SEM). The data was analysed for statistical differences using the GenStat® statistical programme. The significance of difference between the means of different groups were determined by ANOVA and considered significantly different at $p < 0.05$. The survival distribution of the groups was determined by Kaplan-Meier method Rank statistics for testing homogeneity of survival curves using Graphpad®

3.0 Results

3.1 Toxicity

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The results of the body weighs and the PCV of the mice in the toxicity studies are shown in figure 1. The data on the PCV showed that the there was no significant change in the levels of the PCV from the normal values of healthy mice during the entire period of the toxicity study. In addition there was continual increase in the body weights of the mice on toxicity studies throughout the entire period of toxicity study. Furthermore, no mouse died or showed signs of overt toxicity during the toxicity study.

3.0 Packed cell volume

Figure 3 shows the packed cell volume of the infected experimental mice during the period of the study. The PCV levels of the infected mice treated with 10g/L and 6.7g/L of SNE decreased significantly ($p<0.05$) compared to mice treated with 3.3g/L SNE immediately after the infection. It was also noted that the PCV of dexamethasone and the infected untreated declined gradually and the decline was statistically significant. The PCV of mice treated with 3.3g/L SNE however remained at the normal levels throughout the entire period of the study.

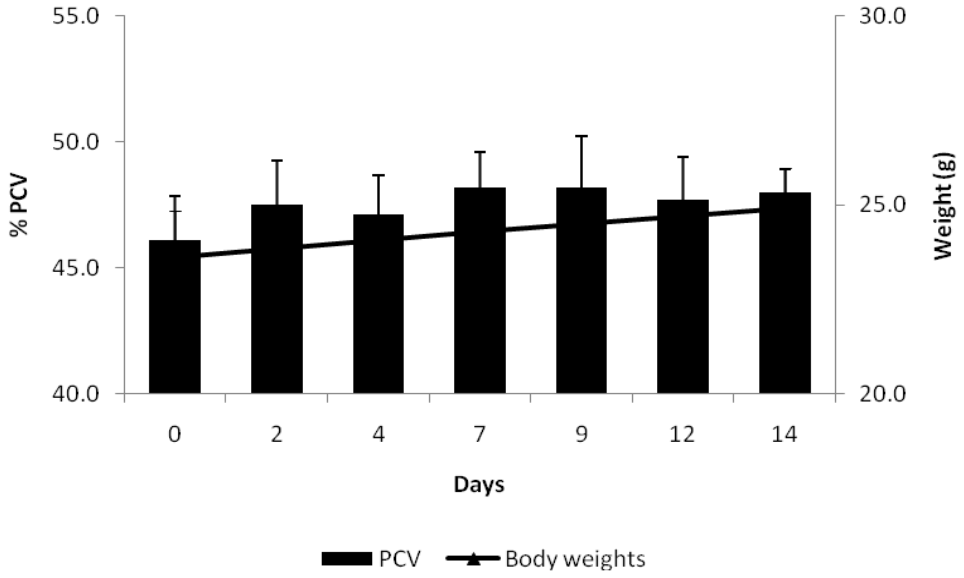

Figure 1: Mean PCV and body weight changes of female mice in toxicity studies

3.2 Parasitaemia

The prepatent period of KETRI 2537 in the female mice ranged from 3 to 4 days. The parasites multiplied rapidly and the first peak of the parasitaemia was observed by day 6 post infection. Thereafter, there was fluctuation of the parasitaemia levels till the end of the study. Figure 2 shows the levels of parasitaemia in different groups of mice. From the graph it is evident that mice treated with 3.3g/L of SNE had lower parasitaemia levels compared to all the other groups though not statistically significant.

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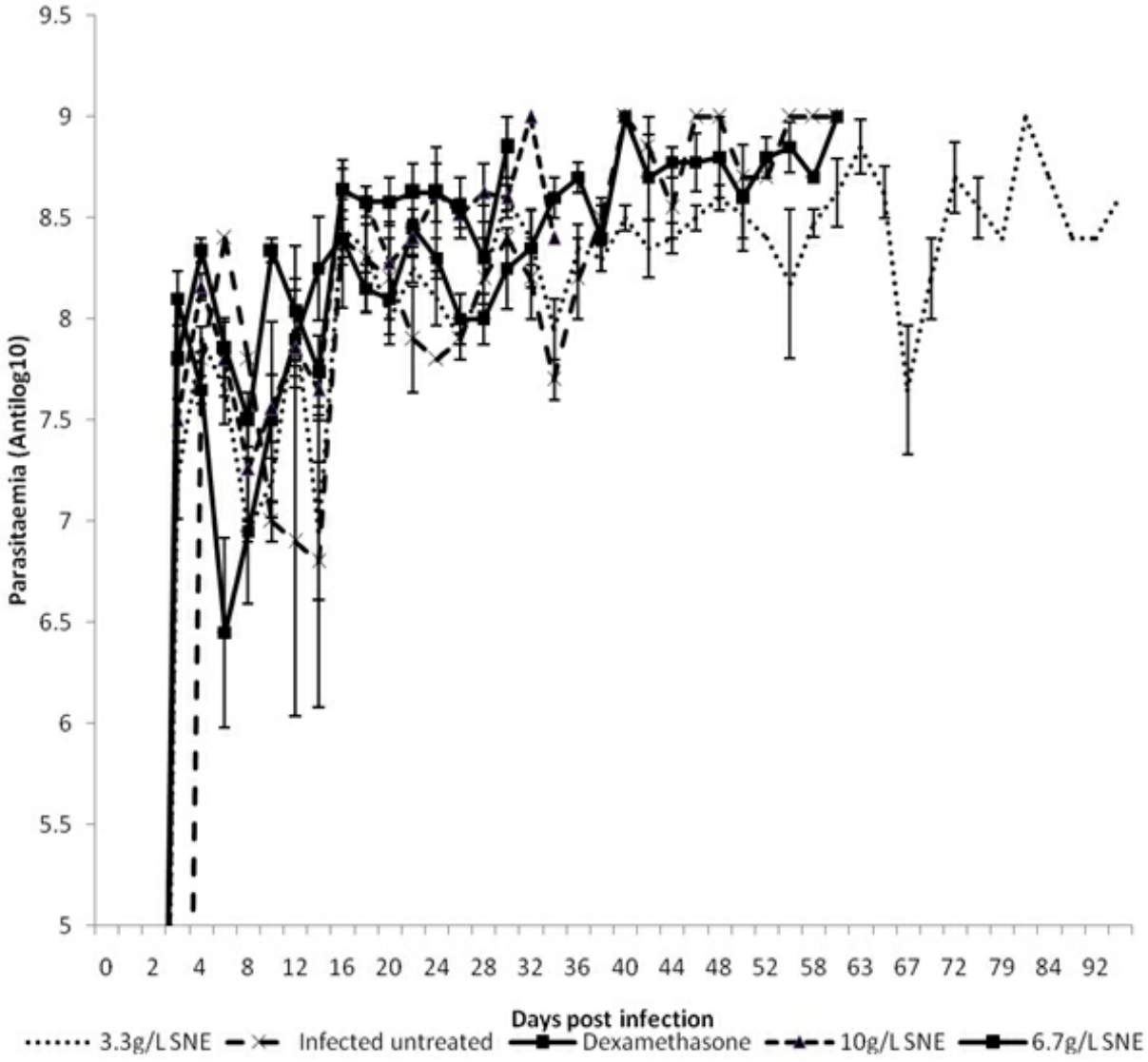

Figure 2: Mean parasitaemia levels (antilog$_{10}$ ± S.E.M) of *T. b. rhodesiense* infected female mice, untreated or treated with either SNE or dexamethasone.

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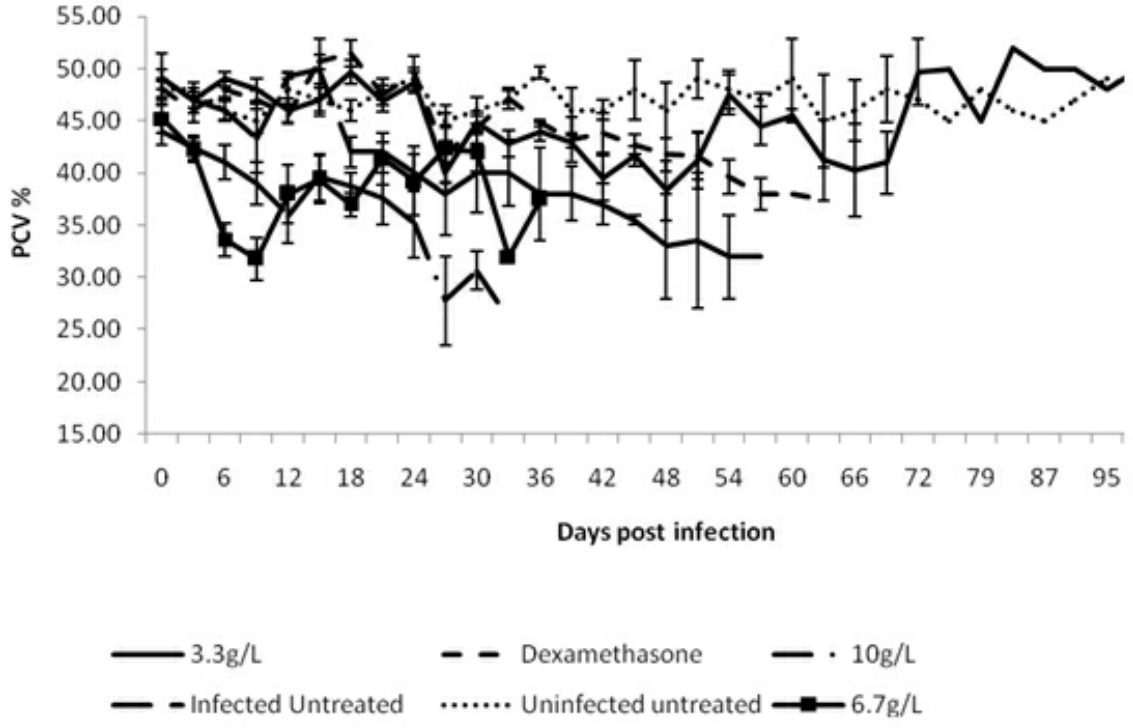

Figure 3: Changes in PCV level of uninfected untreated, infected untreated and *T. b. rhodesiense* infected female mice treated with different concentrations of SNE or dexamethasone

3.4 Body weights

Body weights were measured as a general parameter for the health state of the mice. Mice treated with 10g/l and 6.7g/l of SNE had a significant decline in the body weights during the study period. The decline in the body weights began at the first peak of the parasitaemia. However, mice treated with 3.3g/l SNE had a continual increase in body weights throughout the entire period of the study. The body weights of mice treated with dexamethasone and the infected untreated mice decreased significantly ($p<0.05$) as from day 45 post infection until death of all the mice.

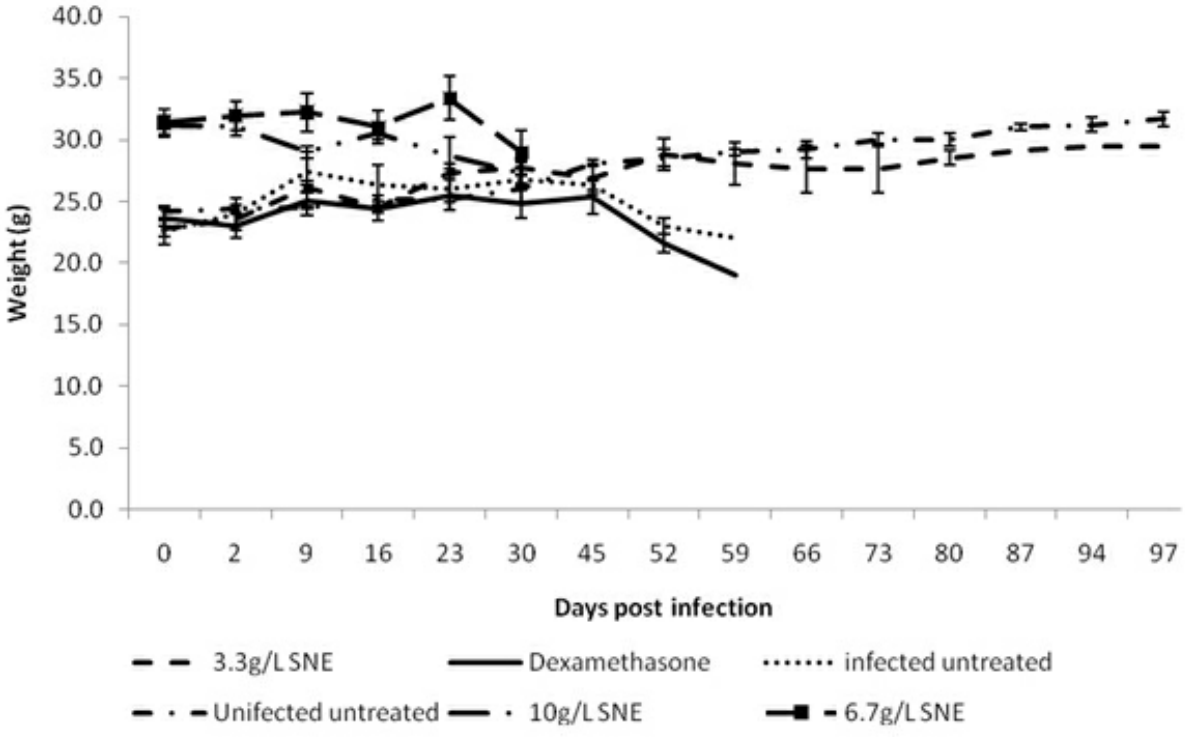

Figure 4: Changes in the body weights of uninfected, infected untreated and *T. b. rhodesiense* infected female mice treated with different concentrations of SNE or dexamethasone

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3.5 Albumin levels

There was a general reduction in the levels of albumin concentrations among the infected mice during the experimental period. Mice treated with 10g/L and 6.7g/L SNE had a significantly higher decline in the albumin concentrations over time ($p<0.05$). However, the mice treated with 3.3g/L had a slight decline in the albumin concentrations which however was statistically significantly different ($p<0.05$) when measured at day 50 post infection. The decline in the concentrations of albumin in dexamethasone treated mice and untreated mice was also significantly lower when compared to those treated with 3.3g/L but higher when compared to the mice treated with 6.7g/L and 10g/L SNE.

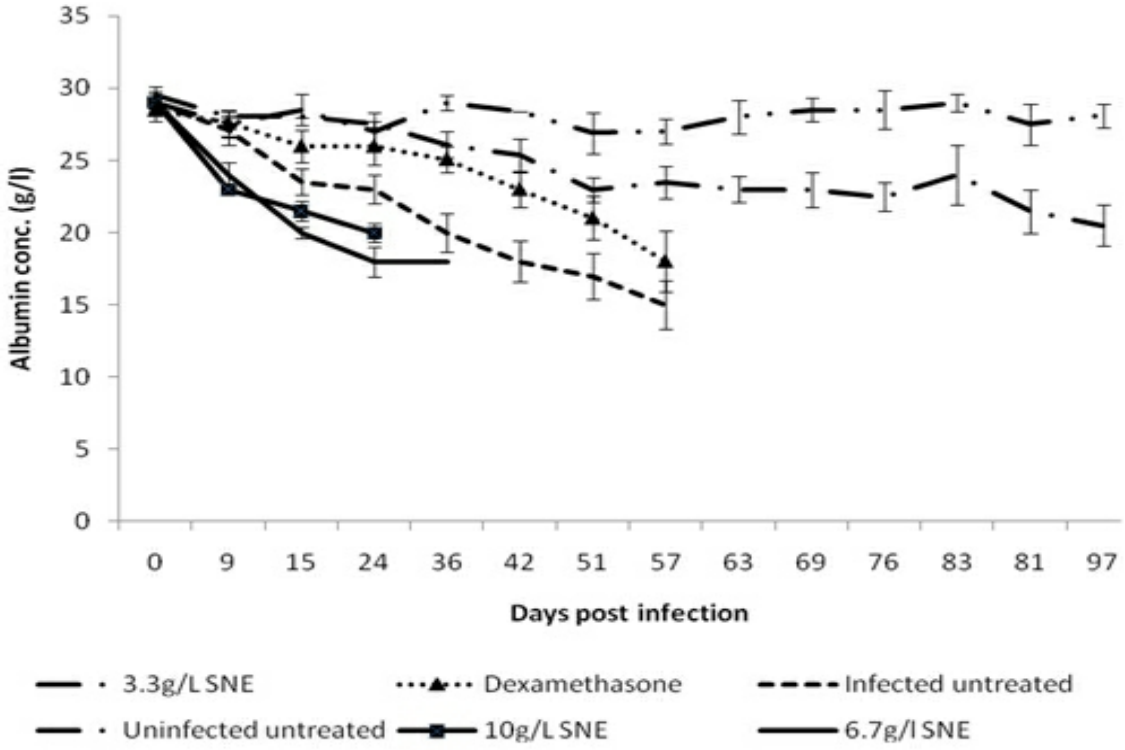

Figure 5: Changes in albumin concentrations of uninfected and *T. b. rhodesiense* infected female mice untreated or treated with different concentrations of SNE or dexamethasone.

3.6 Survival time

Figure 6 below shows the survival distribution of the female mice treated with different concentrations of SNE. Mice treated with 10g/L and 6.7g/L SNE had a shorter survival time and 100% of them died in less than 36 days post infection. The result of the group treated with 3.3g/L is consistent throughout this experiment because in addition to the beneficial effects of this concentration on PCV, body weights, parasitaemia and albumin concentrations, it provided the highest survival with 20% of the mice surviving till the end of the experiment at day 97 post infection. The infected untreated control mice however had a maximum survival of 63 days. This depicts that the mice treated with 10g/L and 6.7g/L probably died due to accumulation of the extract to toxic levels. No protection was provided by the anti-inflammatory drug dexamethasone since the survival time for the infected untreated was similar to that of dexamethasone.

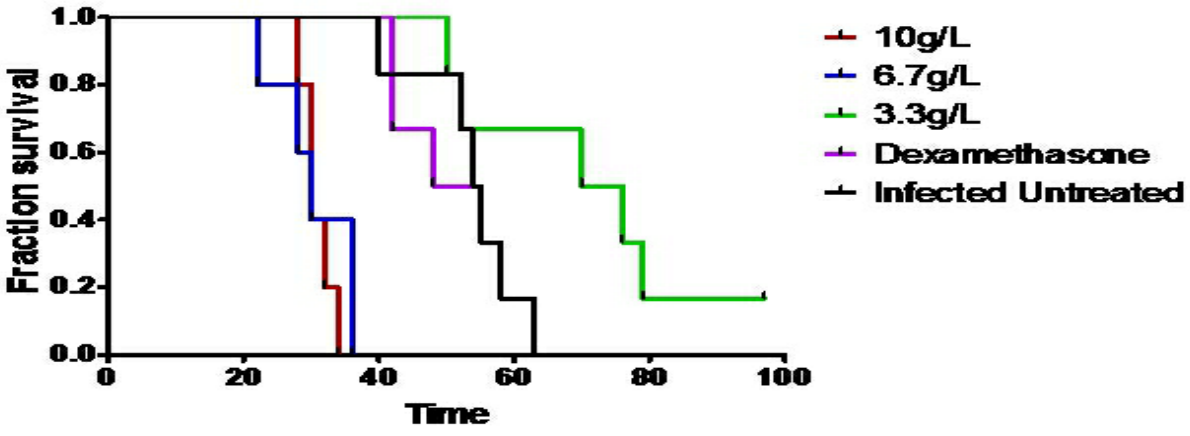

Figure 6: Survival distribution function of *T. b. rhodesiense* infected male mice treated with different concentrations of SNE or dexamethasone and infected untreated controls

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4.0 Discussion

Oral toxicity study of upto 2000mg/kg body weight of mice for a period of two weeks did not show any signs of overt toxicity in the mice. However, the highest dose used in the main experiment was reduced to 10g/L equivalent to 1500mg/kg body weight. Dose reduction was done on the basis that death can occur due to metabolite accumulation in tissues during chronic therapy (Swanson *et al*., 1997). Most drugs are administered not as a single dose but as a sequence of repetitive doses and usually result in accumulation of the drug in the body (Brocks and Mehvar, 2010). A study by Pellegatti and Pagliarusco (2011), found out that long term repeat dose toxicity studies in rats and dogs gave evidence of myocardial necrosis, degeneration and inflammation which were never detected in the previous shorter toxicity studies. Therefore compounds chronically administered may accumulate in target tissues and may be one of the potential causes of long-term toxicity. *S. nigrum* contain different phytochemicals including alkaloids, flavonoids, saponins, tannins, phytic acid and hydrocyanic acid (Potawel et al., 2008) which have been implicated to their activity. Clearance of glycoalkaloids usually takes more than 24 hours, which implicates that the toxicants may accumulate in case of daily consumption (Mensinga *et al*., 2005). The test mice were therefore given decreasing doses of the extract in different groups to determine any possible anti-inflammatory activity and the effect of accumulation of the drug and possible toxicity.

The protective activity of *S. nigrum* due to its antioxidant and anti-inflammatory activity in trypanosome infected male mice has been shown in earlier studies by Serem et al., (2013). Two saponins, nigrumin I and II, have also been shown to have hepatoprotective effects (Ikeda *et al*., 1978). The current study showed that female mice treated 3.3g/L of SNE obtained better protection than those treated with 10g/L and 6.7g/L of the extract. From this study it is evident that *S. nigrum* at 3.3g/L provided protection to infected mice than all the other concentrations of the extract or even dexamethasone, a known anti-inflammatory drug which was used as a control. The extract did not eliminate the parasites from the infected mice but it reduced the level of parasitaemia in those treated with 3.3g/L SNE. This was also observed in the levels of PCV in that this concentration of the extract limited parasite induced PCV reduction in infected mice.

This is in agreement with the study by Serem et al. (2013) on male mice infected with *T. b. rhodesiense* except for the concentrations of the extract used. The study on males showed that the extract provided dose dependent protection of the infected mice with 10g/L SNE giving the highest protection. The 3.3g/L which gave good activity on the females however gave the poorest activity on the males.
The difference observed in these two studies (males and females) could be attributed to the differences in intrinsic factors related to sex such as differences in metabolism and clearance of metabolites since male mice have a higher rate of metabolism and renal clearance (Soldin *et al.,* 2011). Females have a higher fat content than males due to the high levels of oestrogen in females which mediate the association between fat patterning and lipoproteins (Freedman *et al.,* 1990). The antioxidant protective activity of water extracts of *S. nigrum* have been attributed to the polyphenols in the extract (Ravi et al., 2009). Polyphenols interact with phospholipids and lipophilic polyphenol derivatives resulting from enzymatic esterification with fatty acids in plasma (Manach *et al.,* 2004). Polyphenols have been detected by high performance liquid chromatography (HPLC) analysis in a wide range of tissues in mice and rats, including brain endothelial cells, heart, kidney, spleen, pancreas, prostate, uterus, ovary, mammary gland, testes, bladder, bone and skin (Dalta *et al.,* 2001; Mullen *et al.,* 2002).

Since polyphenols are lipophilic the accumulation in females could be higher due to their high fat content. Data from animal studies indicate that some polyphenol metabolites may accumulate in certain target tissues rather than just equilibrating between blood and tissues (Manach *et al.,* 2004). This could explain the difference in the results observed. The females treated with 10g/L and 6.7g/L SNE possibly accumulated polyphenol metabolites in the tissues and caused toxicity hence the early death of mice getting this treatment. On the other hand mice treated with 3.3g/L accumulated the extract in concentrations that were not toxic and thus provided protection to the mice.

The SNE limited parasite induced decline in the parasitaemia. This could be attributed to the antioxidant activity of the extract which reacted with the free radicals preventing the peroxidation of erythrocyte membranes (Igbokwe, 1994). Plant phenolics may however interfere with iron utilization by reducing the intracellular storage form of serum ferritin to its ferrous state (Boyer et al., 1988) while some phenolic compounds prevent non-heme iron absorption in mammalian small intestines (Tuntawiroon et al., 1991). Phenolics from *S. nigrum* such as tannins and flavonoids bind iron in a dose dependent manner (Tuntawiroon et al., 1991; Kell, 2009). It has also been shown that these phenolics can interfere with physiological activities of the body such as disrupting enzymatic and cellular function and thus decreasing the availability of protein, iron and calcium upon oral consumption (Afsana et al., 2004). Therefore the type and dose of phenolic compound consumed can provide beneficial activity or deleterious effects. Sustained inflammatory responses during trypanosomiasis lead to the damage of vital organs including the liver, kidney, heart and the gut. The rapid decline in the concentration of albumin in mice treated with 10g/L and 6.7g/L SNE could be due to the inflammatory kidney damage leading to increased permeability of the glomerulus (Agu and Egbuji, 2002) in addition to the use of albumin as an antioxidant due to its free thiol groups (Pupim et al., 2004) and decreased synthesis due to liver damage (Limdi and Hyde, 2003). Polyphenols are not transported as free components but are bound extensively to albumin (Manach et al., 2004). Therefore decreased levels of albumin may lead to less extracts being transported to tissues where it is needed to accomplish the anti-inflammatory role.

From this study it can be noted that the concentrations of SNE at 10g/L and 6.7g/L in females were probably accumulated at toxic concentrations by females which interfered with intracellular serum ferritin, a storage form of iron in the body, in addition to binding non-heme iron sources and therefore interfered with its absorption in the body. The collective damage of iron unavailability and breakdown of red blood cells in the body by the parasite

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induced peroxidation of erythrocyte plasma membranes probably contributed to anemia which is known as the main cause of death in mice infected with trypanosomes (Igbokwe et al., 1994). This was evident due to the rapid decline in the PCV levels of mice treated with 10g/L and 6.7g/L SNE.

5.0 Conclusion

There is an obvious difference in the way in which different metabolites are accumulated and metabolized between males and females. This study showed that phenolic compounds are toxic to females at lower concentrations than males mainly due to the lipophillic nature of these compounds and thus are accumulated more by females than males. Due to the long time of clearance of some phytochemicals by the kidneys of more than 24 hours, these compounds could accumulate to toxic levels and have deleterious effects such as reducing iron utilization leading to development of anemia which can cause death.

Competing interests

The author(s) declare that they have no competing interests.

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