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Development and Evaluation of Wild-Derived Rats as Potential Experimental Models for Research

[1*]*GITAU L., KANIARU S G., MAINA M G., AGOLA L E*

[1]Kenya Centre for Biotechnology Research and Development

***Corresponding Author**: lugitau75@gmail.com

Abstract

Wild rodents have been used as animal models in experimental studies of cellular aging, cerebral malaria, schistosomiasis, and leishmaniasis. Since they are the reservoirs of these diseases, recent studies have shown that research involving wild rodents is more efficient in giving a mirror image of the disease progression outside the laboratory setting. The study design was an analytic experimental study where observations were made between two groups of animals i.e. the wild-derived and lab-bred rats. The outcome of the intervention was obtained by comparing the two groups. This study sought to determine the usability of wild-derived rats as potential experimental animal models for biomedical research. Wild rats were randomly captured in areas with high transmission of Schistosoma mansoni and Leishmania donovani in Kisumu and Kitui counties, in Kenya and maintained in the animal house at Kenya Medical Research Institute (KEMRI) in Nairobi. Breeding was carried out, and the subsequent generations were used to assess schistosomiasis and leishmaniasis disease progression between the wild-derived, and laboratory-bred rats. We further monitored behavior patterns and food consumption rate for 3 months in a total of 6 experimental trials. The results on feed consumption capacity indicated that consumption was significantly higher in laboratory-bred groups (p=0.001) compared to wild-derived rats. Overall, laboratory-bred rats were significantly heavier than wild rats. In the use of rats to assess schistosomiasis and leishmaniasis disease progression, the wild-derived rats were more susceptible to leishmaniasis and may be considered for S. mansoni compared to wild (worms recovered p=0.031). In conclusion, the study indicated that wild rats are potential reservoir hosts for both schistosomiasis and leishmaniasis and have the potential to maintain cycles of infection until after successful chemotherapeutic intervention. Therefore, wild rats may provide natural means for parasites like S. mansoni and L. donovani to re-infect humans in endemic areas.

Keywords: *Schistosoma mansoni; Leishmania donovani; Wild rats; Neophobia; Reservoirs; Laboratory rats*

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Introduction

Rodents including rats, known to be used in the laboratory today were derived from the brown rat (*Rattus norvegicus*). During the 19th century, they were selectively bred either for their aggression - to be set against terriers - or their coat color. In the 20th century, interest in Mendelian inheritance led to an increase in breeding inbred strains of rats and mice, and with this, large-scale production of specific breeds which are contained in controlled conditions became

common. From these efforts, there were many strains that were produced tailored for specific purposes such as immune-deficient mice and diabetic rats. However, there was the need to reduce genetic heterozygosity to minimize experimental inconsistency. The result was the development of strains of animals that were genetically homogeneous resulting in animal models that are more like a "chemical reagent" element of the equipment of the laboratory (Clause, 1993; Phillips, 1994).

Most of the biomedical research activities that have been conducted use rodents that have been bred in the laboratory having undergone numerous cycles of interbreeding. The inbred stock of rodents has experienced huge selective pressure for many generations, and this has contributed to significantly high rates of growth, fecundity, an excessive amount of food consumed as well as anomalous behaviors. This has resulted in a generation of experimental animals that have characteristics that are different from their ancestral wild rodents where they were first obtained (Harper, 2008). Unlike the inbred rodents that are genetically identical and are homologous at each and every locus, wild-derived rodents are genetically heterogeneous and are a closer representation of the situation in a general population either in humans or other free-living animals (Harper, 2008). The primary advantage of using a wild-derived stock is that the population is composed of genetically heterogeneous individuals whose genetic repertoire has been shaped by "real world" conditions. This is contrary to the stock of rodents that are used in most laboratories

Among the experimental models for studying infectious diseases, mice and rats have been the most widely used animals (Singla *et al.,* 2008). Previously rodents have been used to study the transmission of *Schistosoma mansoni* (Hanelt *et al.,* 2010) and *Leishmania donovani* (Roque & Jansen, 2014), as well as a study of antimalarial drug resistance in rodent malaria parasites (Singla *et al.,* 2008). Laboratory rodents have also been used in aging research. However, as pointed out by Harper (2008), there are a number of consequences of using laboratory-bred rodents in studies such as aging research. Some of these consequences include the fact that there is a loss of naturally occurring alleles some of which might take part in slowing the aging process (Harper *et al.,* 2006; Miller *et al.,* 2000). In a study to determine the factors associated with resistance to murine leukemia virus in wild-derived mice, it was found that feral mice harbored an allele that had never been described in laboratory-bred mice. The identified allele was linked with the observed viral resistance and hence these mice did not suffer from cancer as witnessed in other mice in captivity (Gardner, 1993).

Many laboratory rodents are normally overfed to obesity with minimal physical exercise, which in turn alters their physical development and drug metabolism (Cressey, 2010). Previous studies have described laboratory mice as fat and are characterized by a body mass index (BMI) that is more than 50% of that of the age-matched wild-derived mice (Harper *et al.,* 2005). In addition, the laboratory-bred mice have a significantly higher absolute fat mass when compared with wild-derived mice. These features may have resulted in laboratory-bred mice consuming more food than wild-derived stocks under captive conditions (Austad and Kristan, 2003). Due to these and other factors, laboratory-bred rodents have been reported to give skewed results leading to misinterpretation of findings by researchers, potentially derailing efforts to advance therapeutic drugs. There is, therefore, the need to substantiate the use of wild-derived rodents as alternatives for use in biomedical research where the features of the real world are not significantly modified. The aim of this study was to determine the suitability of wild-derived rats as potential experimental models for biomedical research. Specifically, the study sought to; develop a wild-derived colony of rats, determine the suitability of wild-derived rats as hosts of *Schistosoma mansoni* and *Leishmania donovani* under laboratory conditions, and evaluate the consumption capacity of both laboratory-bred and wild-derived rats.

Materials and Methods

Rodent collection Sites

The rodents were collected in the Kisumu and Kitui counties of Kenya as tabulated in **Table 1**. Kisumu county lies in the Lake Victoria region in

the former Nyanza province in Kenya. The region has numerous water bodies, which include rivers, swamps, and ponds that are perfect for rodent habitats. The Lake Victoria region is characterized by a perennial transmission of *S. mansoni* and the long rains fall between June and July, while the short rains fall during November and December. Kitui is a town in the eastern part of Kenya, 180 kilometers east of Nairobi and 105 kilometers east of Machakos. The town covers an area of approximately 30,496.4 km squared and lies between latitudes 0°10 South and 3°0 South within the longitudes 37°50 East and 39°0 East. In Kitui County, *S. mansoni* is mainly found in Mwingi on the eastern fringes of the central plateau as shown in **Figure 1**. Study sites were randomly selected in these two counties where capture sites were established around areas near water sources and flooded areas with reported schistosomiasis and Leishmaniasis transmission potential. The study aimed at collecting enough females and males of the same species for the purpose of breeding subsequent generations. These areas were also selected because schistosomiasis co-occurs in rodents and humans (Steinauer *et al.,* 2008).

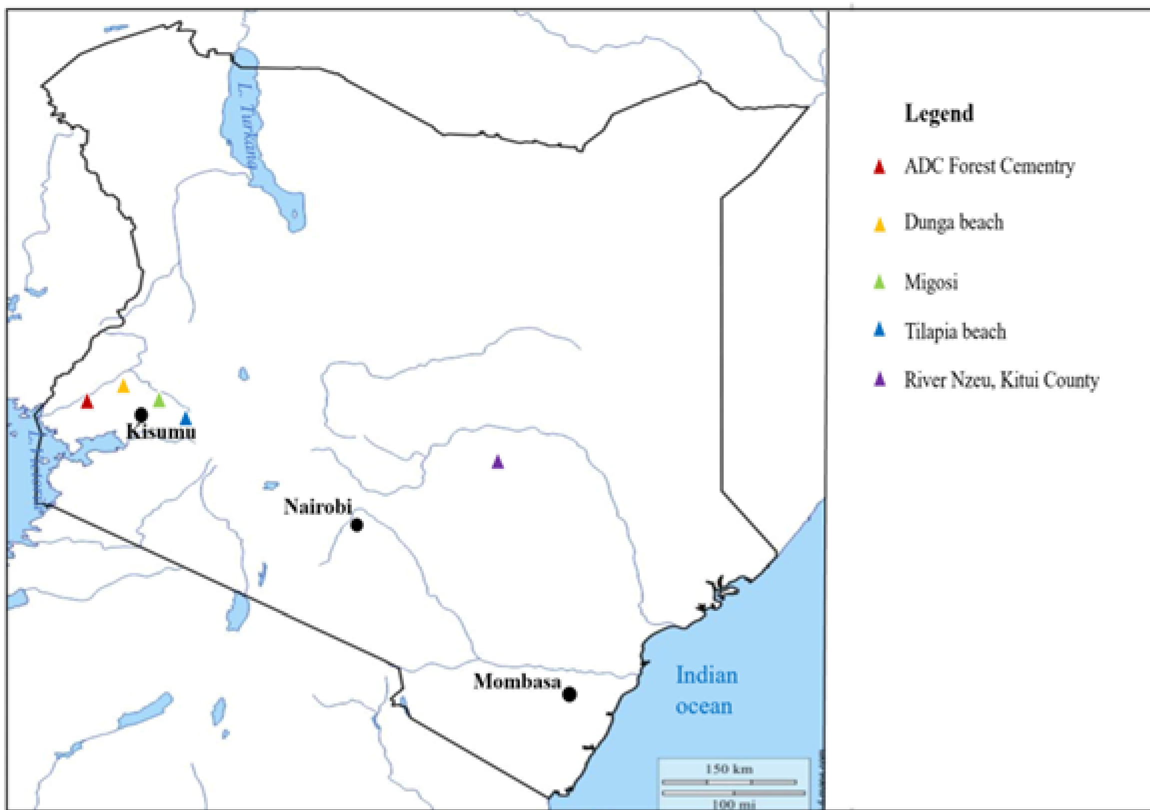

Figure 1. A Map of Kenya showing the rodents collection sites

Table 1. Rodents collection sites, rodent type, number of rodents corrected per site and gender of each collected rodent

Collection site	Rodents collected	No. collected	Sex collected
Dunga beach	*Rattus rattus*	1	Male
Tilapia beach	*Lemniscomys striatus*	1	Male
	Mastomys natalensis	3	Females
ADC forest makaburini	*Lemniscomys striatus*	1	Female
	Mastomys natalensis	1	Female
	Rhabdomys pumilio	3	Males
Migosi wetland	*Aethomys kaiseri*	2	Males
Kitui maize farm	*Acomys wilsoni*	4	Males
	Aethomys kaiseri	2	Females
Along the River Nzeu	*Acomys wilsoni*	1	Female
Totals		19	

Biosafety Measures

In order to create an environment that is safe for the study team to work in, a biosafety training and education session was offered to the study team where potential hazards and safe work practices were discussed. The study investigators were vaccinated against infections such as rabies. Diligent monitoring of the health status of the rats' colony and the use of appropriate personal protective equipment (PPE) such as latex gloves and masks/ respirators were used to prevent the transmission of infective agents to humans. The wild rats were handled with utmost care to avoid bites. Heavy-duty rubber gloves were used during the handling of the rats. The soiled beddings were sprayed with 10% sodium hypochlorite (JIK®) before they were put in disposal bags and incinerated.

Trapping of wild rats

Wild rats were trapped using live traps such as Sherman traps baited with a piece of bread. The traps were placed overnight near houses, garbage dumps, agricultural fields, and in other habitats deemed suitable for rodents. Trapped rats were weighed, evaluated, and separated in different cages according to their sex before being transported to KEMRI-Animal House Nairobi. The transportation method used was designed to reduce the amount of stress that was induced on the captured animals. This was done by ensuring that the animals were not subjected to extreme temperatures, humidity, and noise. The animals were also safeguarded against pathogens and interactions with human beings as well as other animals. Animals were transported in cages that were fastened with binding wire to prevent escape.

Quarantine and Screening

Once the captured rodents were delivered into the laboratory, they were first put in quarantine during which disease screening was done. Disease screening was done to ensure that the captured rodents were pathogen-free and at the same time to prevent the spread of diseases and parasites. Proper quarantine was key in ensuring the pre-existing experimental animals are isolated from infections and/or parasites that wild rats, may carry. Indications of the presence of parasites such as visible worms in the stool, and a hard and/or swollen stomach were monitored. Abnormal secretions from any area of the body were also closely monitored. This included the presence of watery and crusty eyes, signs of bleeding from any orifice, runny nose, anomalous discharge coming from the genital areas, and any form of secretion emanating from

the ears. The body score condition was assessed. The rats were also checked for the presence of visible parasites such as lice, mites/mange, nits, and fleas. The newly acquired animals were housed in an isolated location for a predetermined period (3 months). During this period, the rats were clinically evaluated for signs of illness. The passive approach to quarantine was based on the assumption that infected animals would either develop clinical signs of disease or recover from subclinical illnesses and stop shedding the causative organism during the quarantine interval (Rehg and Toth, 1998).

Breeding, Feeding, and Maintenance of Rats

After quarantine and screening of the rats, harem breeding was performed by putting a group of two female rats in a cage together with one male rat of the same species and the date of mating was noted and marked as the first day. The signs of pregnancy were monitored from the 15th day after the males were introduced. Those rats that were confirmed to be pregnant were put in individual cages where they would give birth. The young ones were weaned at the age of 3 weeks and put separately according to their sexes. The young ones were kept for another 3-5 weeks to attain a maturity age of 6 weeks for females and 8 weeks for males, ready for use in the subsequent experiments. All the cages were kept clean and maintained under standard animal house conditions. Wood shavings were used as bedding materials. The rats were fed with mice pencils and tap water *ad libitum*.

Consumption capacity of wild-derived rats

To determine the rate of food consumption, rats were put into three groups with each group having three rats which were housed one rat per cage. The quantity of feed consumed was monitored daily to determine the consumption capacity of both laboratory-bred and wild rats. Daily intake was estimated by weighing the feeds before feeding every morning. For every group, a total of six trials were performed for both the laboratory-bred and wild-derived strains. For each trial, food consumption was monitored by determining the amount of feeds consumed for a total of 30 days.

Infection of Rats with Schistosoma mansoni Cercaria

Wild-derived and laboratory-bred rats were infected with *S. mansoni* cercariae using the ring method as described elsewhere (Smithers and Terry, 1965). Briefly, each rat was anesthetized using 6% Sodium pentobarbitone, at a dose of 0.001 ml per gram of body mass. The anesthetized rats were shaved on the lower abdomen side using barber's clippers after which the area was rubbed with cotton gauze soaked in snail water. The rats were placed on a timber holding board and a ring was placed over the shaved part. 1 ml of snail water containing a known number of cercariae was put in the ring and the rats were left for 1 hour to allow penetration of the cercariae after which the snail water was removed using a Pasteur pipette. The rats were transferred to a holding cage in a warm room (25°- 30°C) until they recovered from the effects of anesthesia after which they were transferred into well-labeled cages. Rats were monitored by assessing their appearance, activity, and behavior as indications of pain and discomfort. A total of 5 rats were used for both the laboratory-bred and wild rats. 5 Swiss albino mice were used as controls. The rats were monitored for 48 days after which they were assessed for worm burden.

Worm Burden Determination

After 48 days, the worm burden determination was done following a method by Yole *et al.*, (1996) with a few modifications. Briefly, adult worms were recovered through perfusion of the hepatic portal vein. The perfusate was then put in a glass Petri-dish (20 cm in diameter) before it was transferred to urine jars where it was left to settle. After settling, the supernatant was sucked out and the worms were washed with phosphate-buffered saline (PBS) repeatedly until the perfusate became clear. After the final wash, the supernatant was discarded, and cleaned worms moved to a new 10 cm plastic Petri-dish ready for counting. The worms were counted to determine the mean number and the standard error of the mean (SEM) for each group.

Cultivation of Leishmania donovani parasites and infection of rats:

The *Leishmania donovani* (Strain IDUB/94=NLB-065) saline aspirate was taken from an infected Balb/c mouse spleen and parasites were maintained as previously described by Titus *et al*. (1985). Briefly, the parasites were first cultured in Schneider's *Drosophila* medium that had been supplemented with 20% heat-inactivated Fetal Bovine Serum (FBS), glutamine (2mM), Penicillin G (100U/ml), and streptomycin (100µg/ml) at 25^{0}C. The promastigotes were recovered from the culture after which they were washed and purified 3 times in phosphate-buffered saline at 1500 rpm for 15 minutes. To obtain the stationary-phase metacyclic promastigotes, the *L. donovani* (1×10^{6} cells/ml) were cultured for 5 to 7-day-old cultures followed by the isolation of the promastigotes. Subsequent experiments used the stationary-phase metacyclic promastigotes. The rats were inoculated intraperitoneally with 1×10^{6} stationary phase culture of *L. donovani* promastigotes in 40µl phosphate-buffered saline (PBS). Two groups were designed for both the wild-derived and laboratory-bred rats. In each group, 5 rats were used.

The rats were monitored for 21 days after which they were screened for infection. For controls, 2 Balb/c mice were infected by inoculation of mice with the parasite intradermally. Balb/c mice were used since they are highly susceptible to *L. donovani.*

Waste disposal

The disposal of waste materials that were generated during the study was done following the KEMRI waste disposal protocols as outlined in the KEMRI Health Safety and Environment Policy. The dead animals were first put in biosafety bags before they were incinerated at the KEMRI incinerator.

Data Analysis

Statistical analysis of the experimental results was conducted using Statistical Package for Social Sciences (SPSS) version 26.0 (SPSS, Inc., Chicago, IL, USA). The student's t-test was used to compare the means between two groups that we had in our experiment. In this study, a comparison was done between lab-bred rats and wild-derived. The test was also used to compare postoperative changes in body weight between the wild-derived groups and the laboratory-bred groups. Measurements with $p \leqslant 0.05$ were considered significantly different.

Ethical Considerations

The study was ethically approved by the KEMRI Scientific and Ethics Review Unit (SERU Protocol 169/3496), KEMRI Animal Care and Use Committee (ACUC), and the National Museum of Kenya (NMK). Local authorities and household heads were also informed about the study and permission to access the areas was sought before the study commenced. The rats were handled with proper care and regarding the guidelines of the animal care and use committee.

Results

From the different sites, a total of 19 rodents were collected comprised of 57.9% male and 42.1% female (Table 1). In terms of the number of rats collected, Kitui maize farm had the highest number (n=6) followed by ADC forest Makaburini with 5 rats. A total of six distinct species were collected from the different collection sites. The most abundant rodent species that were captured were *Acomys* (26.3%), *Mastomys* (21.1%), and *Aethomys* (21.1%).

Consumption capacity of wild-derived rats and laboratory-bred rats

Overall laboratory-bred rats (n=18) were significantly heavier than the wild-derived rats (lab vs wild) ($t(14)=5.047$, $p<0.001$)). The mean weight of the laboratory-bred rats was 189.4 mg (SD=8.26) while that of the wild-derived rats was 136.8 mg (SD=11.88). The amount of food consumption per rat was calculated using (A/B x1000g) as previously described (Modlinska *et al*., 2015) (where A, was the amount in grams of food taken during the experiment and B, was the body weight of the rat). A student's t-test was used to carry out a comparative analysis of the amount of food eaten by individual rat types was done and significant differences between the groups were detected. The results indicate that food consumption in laboratory-bred rats was higher than in wild rats ($p=0.001$) (Figure 2).

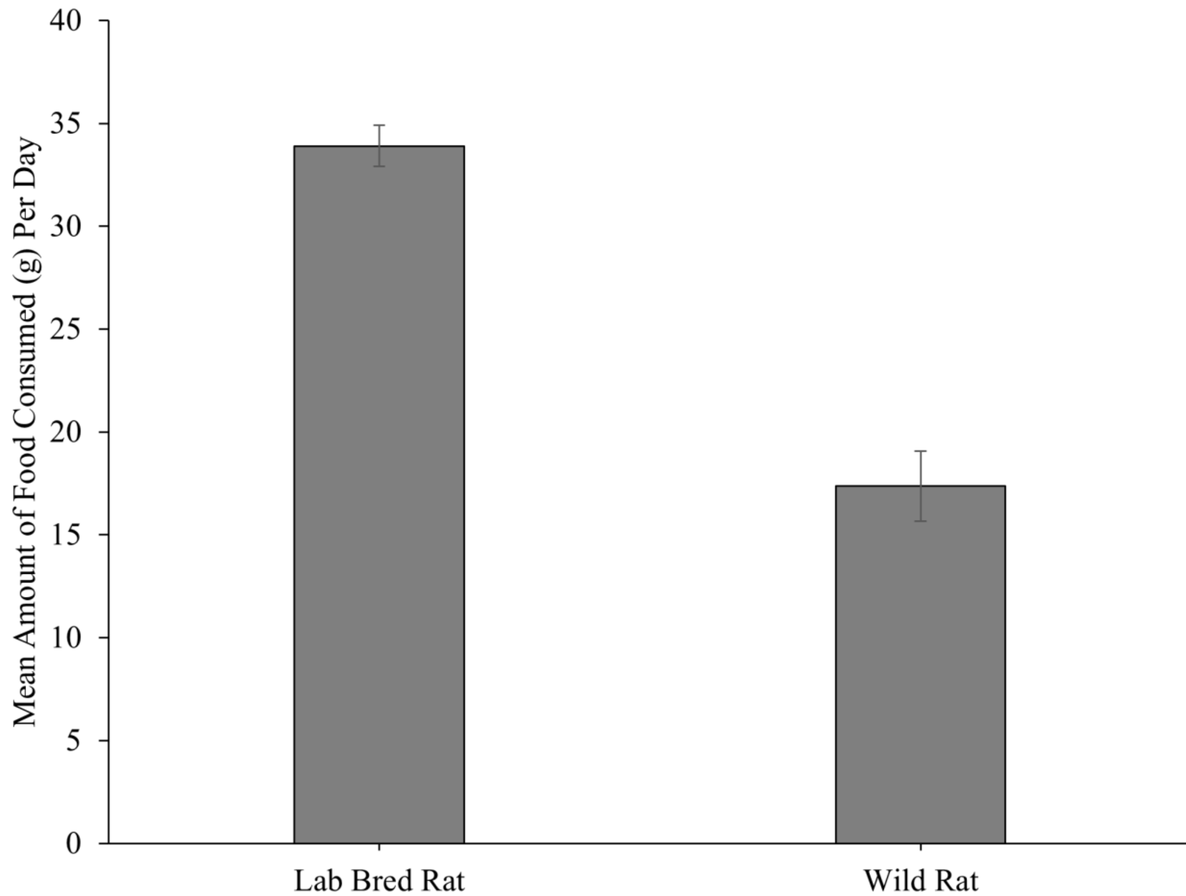

Figure 2. Graph showing average food consumption in wild and laboratory-bred rats

Schistosoma Worm Burden
Laboratory-bred rats seemed better hosts (worms recovered, t=9.467, p=0.031) for *S. mansoni* with a mean of 9 (SD=3.0) parasites per rat recovered in laboratory-bred groups compared to a mean of 7 (SD=4.0) parasites per rat in wild-derived groups.

The reservoir of Leishmania donovani
The results indicate that wild-derived rats were more susceptible to Leishmaniasis due to a highly significant mean count of recovered amastigotes 1563 (SD=108.60) versus lab-bred 583.3 (SD =70.95) (t= 13.087, p<0.001) compared to laboratory-bred rats (Figure 3). The splenic index of infected rats was also observed to be significantly (p=0.002) higher in wild-derived rats 0.61 (SD= 0.097) than in laboratory-bred rats 0.27 (SD =0.04) as shown in Figure 4.

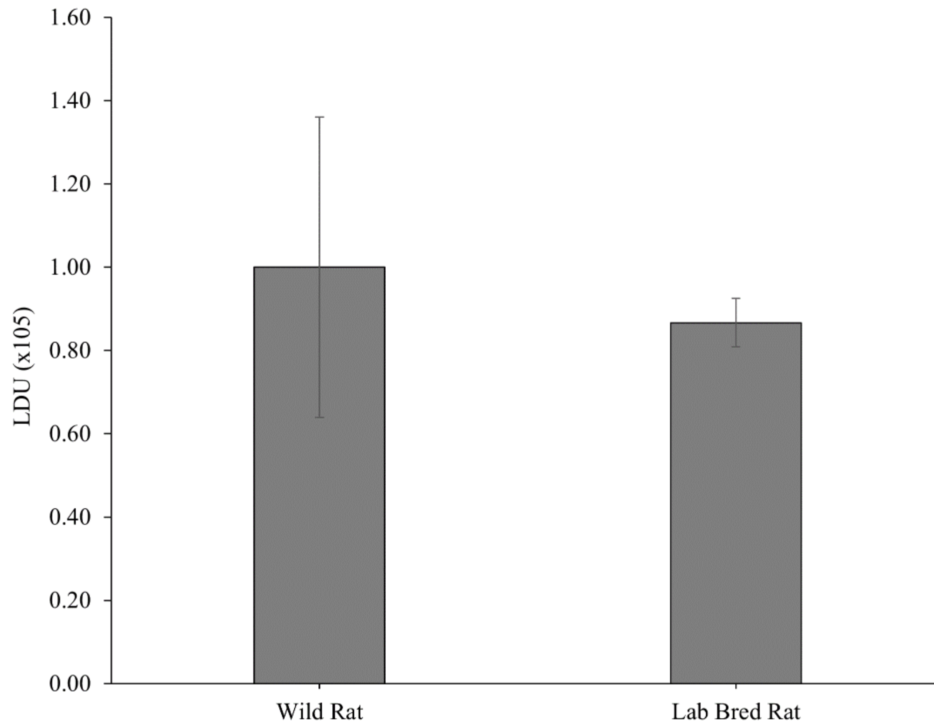

Figure 3. Susceptibility of wild and laboratory-bred Rats to Leishmaniasis

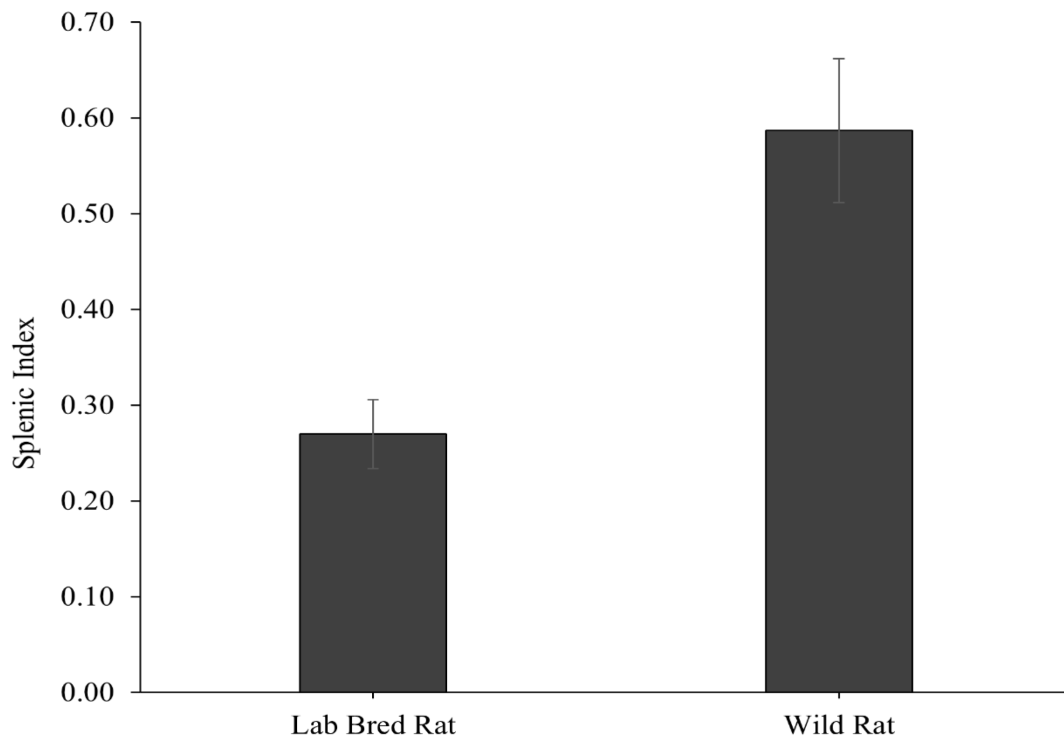

Figure 4. Comparison of the Splenic Index of wild rats and laboratory-bred rats

Discussion

The current study aimed to determine the suitability of wild-derived rats as potential experimental models for biomedical research. Wild-derived rats were captured from the wild and tested for their suitability as hosts of *Schistosoma mansoni* and *Leishmania donovani* under laboratory conditions. There are different species of rodents that freely roam in the wild. In Ethiopia, previous studies have identified more than 40 species of rodents with some of the commonest genera found in the wild being *Acomys, Mastomys, Arvicanthis* and *Mus* (Bekele and Leirs, 1997). In this study, the most common genera that were collected were *Acomys*, *Mastomys*, and *Aethomys*. These results are in agreement with previous studies conducted in Ethiopia where *Acomys, Mastomys,* and *Arvicanthis* were the three main genera of rodents collected from the wild (Kassahun *et al*., 2015).

From this study, laboratory-bred rats were significantly heavier than the wild-derived rats. The difference in the weight between the strains could be attributed to the genetic differences between the two strains. Similar findings have been reported between two rat strains obtained from different sources (Brower *et al.,* 2015). In addition, selection pressure imposed by adaptations that laboratory-bred rats must undergo may favor them resulting in strains that are more efficient. Studies have shown that relative to the laboratory-bred rodents, wild-derived rodents are slower to reach sexual maturity and are characterized by smaller litters (Harper *et al*., 2006; Miller *et al.,* 2000, 2002). Due to the positive correlation between litter size and body mass, laboratory-bred rodents may, therefore, tend to be larger and grow rapidly compared with the wild-derived rodents (Brower *et al.,* 2015).

Food consumption studies indicated that laboratory-bred rats consumed more food than wild-derived rats. Analysis of these results also showed that similar responses were observed when food was introduced to both strains. In addition, food intake behavior took a similar trend for the two strains although the amount of food that was consumed by the laboratory-bred strain was always higher than the amount taken by the wild-derived strain. Similar findings were reported by Modlinska *et al.,* (2015) who observed eating latency during the first trial of food consumption in both wild-derived and laboratory-bred rats. The rats also showed a decreased eating pace even though the number of times the rodents samples the food before eating was high. These observations were in contrast to the claims of Barnett (2017), who reported that wild-derived rats do not stop eating completely when presented with a novel food but only temporarily limit their food intake.

In this study, the role of rats as reservoir hosts for *S. mansoni and L. donovani* was established. We recorded high infection rates with *S. mansoni* in the laboratory-bred rats and wild rats. Approximately 60% of the tested rats harbored *S. mansoni*, and nearly a third of these were infections consisting of both male and female worms. However, considering the number of parasites recovered, laboratory-bred rats seemed better hosts for *S. mansoni* compared to wild rats. This variation may be attributed to the concomitant immunity of the wild rodents as they are constantly overexposed to *schistosome* infections in the field unlike the domesticated rats which are naïve (Chabé *et al.,* 2010; Ng-Hublin *et al.,* 2013). Thus, wild rats cannot be ruled out as potential reservoir hosts in experimental studies. In experiments with Leishmaniasis specifically *L. donovani* infection, wild-derived rats demonstrated that indeed parasites can be recovered from the spleens. Significantly, a high number of amastigotes were recovered in wild rats compared to domesticated ones suggesting high susceptibility to *L. donovani*. The role of laboratory rats as reservoir hosts for Leishmaniasis has been reported in previous studies (De Mendonça *et al.,* 2011; Navea-Pérez *et al.*, 2015; Papadogiannakis *et al.,* 2010; Singh *et al.,* 2013; Zanet *et al.,* 2014). Thus, this result suggests that wild-derived rats may also be considered as a satisfactory host for Leishmaniasis parasites in empirical research. This is the first study in Kenya reporting the suitability of wild-derived rats as potential reservoir hosts for *S. mansoni* and *L. donovani* in experimental models.

Previous studies reported that limiting the preference to most laboratory strains that are commonly used, without considering their specific physiological or even behavioral profiles,

may result in making the wrong conclusions. This may be due to either procedure that is specific to a certain experiment (Modlinska *et al.*, 2015) or unsuitable breeding conditions (Casellas, 2011; Festing, 1999, 2010). Current quantitative studies that are putting emphasis on the role of rodents in serving as a source for parasitic infections are needed now that large-scale control programs are underway (Fenwick and Jourdan, 2016). Wild rats which act as the natural reservoir hosts may sustain transmission until after interventions with chemotherapeutics are successfully taken, thus providing means for parasites like *S. mansoni* and *L. donovani* to re-infect humans (Gentile *et al.,* 2012; Hanelt *et al.,* 2010).

Conclusion

Considering the high variability among domesticated strains, if good research practices are put in place to minimize any health risk factors or aspects that induce stress in breeding wild-derived rats and experimental procedures their role in research may prove to be essential. This is because they reflect the real nature of disease transmission in the specific area where they originate due to constant exposure to infections. This study has demonstrated that wild-bred rats can be maintained in a laboratory setup and their food consumption was significantly lower than in laboratory-bred rats. This shows that they might be cheaper to maintain compared with the currently used laboratory-bred rodents. Wild-derived rats also showed to be better hosts for *S. mansoni* than laboratory-bred rats and have a higher splenic index than the laboratory-bred rats. Although the laboratory-bred rats seemed to be better hosts for *S. mansoni* based on the number of parasites, wild-bred rats still offer a better alternative overall and may need to be examined for use in a variety of African transmission settings. It is recommended that studies that investigate the suitability of different strains of wild rats in comparison with their laboratory-bred conspecifics in sub-Saharan Africa are needed, especially in areas with active schistosomiasis and Leishmaniasis control programs.

Study Limitations

As much as the wild rodents have the advantage of being shaped by 'real world' conditions and present a mirror image of the natural infections, with time wild-derived rats would fall into the same pitfalls as the laboratory-bred rats as they will be subjected to captivity. They will therefore eventually be overfed to obesity with minimal physical exercise.

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Data availability

The data that support the findings of this study are available from the corresponding author, [LG], upon reasonable request.

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