Jurnal Riset Veteriner Indonesia
Journal of the Indonesian Veterinary Research
P-ISSN: 2614-0187, E-ISSN:2615-2835
Volume 3 No. 1 (Januari 2019), pp. 1-9
journal.unhas.ac.id/index.php/jrvi/

Review Article

Bats Oxidative Stress Defense
(Pertahanan Stres Oksidatif pada Kelelawar)

Desrayni Hanadhita[1], Aryani Sismin Satjaningtyas[1], Srihadi Agungpriyono[1]*
[1]Department of Anatomy Physiology and Pharmacology, Faculty of Veterinary Medicine, IPB University
Jl. Agatis, Kampus IPB Dramaga, Bogor 16680, Indonesia

*Corresponding authors: Srihadi Agungpriyono (ysrihadi@apps.ipb.ac.id)

Abstract

Antioxidants and free radicals have long been known to be the main factors in the occurrence of degenerative diseases. Various studies related to antioxidants and free radicals which have implications for oxidative stress have increased in the last decade. Knowledge of stress oxidative physiology in various animals help in understanding the pathophysiology of diseases associated with oxidative stress. Bats are claimed to be the best known animals in term of survival compared to other mammals. Bats are reported to produce low reactive oxygen species (ROS) but high endogenous antioxidants that can prevent oxidative stress. Bats high defense against oxidative stress has implications for their extreme longevity, the role as a reservoir of viruses, and the potential as experimental animals.

Key words: *aging, animal model, antioxidant, comparative physiology, free radical*

Introduction

Oxidative stress has been a scourge for the health world for more than three decades (Sies, 2015). Research on oxidative stress status related to disease pathogenesis is increasing every year. The knowledge of the oxidative stress process in the species other than human is very important in order to understand the process of oxidative stress associated with the homeostasis process. Bats are the most successful mammals regarding survival and have an outstanding defense mechanism against oxidative stress (Brunet-Rossinni & Austad, 2004; Hanadhita, Rahma, Prawira, Sismin Satyaningtijas, & Agungpriyono, 2018; Wang, Walker, & Poon, 2011; Wilhelm Filho, Althoff, Dafré, & Boveris, 2007). Bats are scattered all over the world with various latitude, climates, and habitats. There are 1240 species of bats in the world that represent more than 20% of mammal species (Calisher, Childs, Field, Holmes, & Schountz, 2006; Wang et al., 2011). Bats (Chiropteran order) is traditionally divided into two suborders based on their morphology, Megachiroptera which consists of frugivorous bats and distributed only in the old world, and Microchiroptera which includes of other bats and can be found both in the old world and new world (Simmons, 2000). Megachiropteran or megabats have a large body size (20-1500 grams), while Microchiroptera or microbats usually small-sized (1.5-150 grams) (Altringham, 2011). Classification of the taxonomy of bats based solely on morphology is no longer relevant, nowadays the order of Chiroptera consists of two suborders Yinpterochiroptera and Yangochiroptera (M. Lei & Dong, 2016; Teeling et al., 2005).

Yinpterochiroptera unites Pteropodidae families that do not have echolocation ability with the Rhinolophoidea family that has excellent echolocation abilities (M. Lei & Dong, 2016).

Bats, as the only flying mammal, experience a daily metabolic surge of up to 10-17 times (O'Shea et al., 2014). As stated in the free radical theory of aging, high metabolic rate will induce high free radicals production. High amounts of free radicals that are not balanced by antioxidants neutralization can cause damage to several cells components such as lipids, proteins, and DNA and often lead to cancer and degenerative diseases (Buffenstein, Edrey, Yang, & Mele, 2008; Harman, 2006). However, bats have a unique mechanism for preventing oxidative stress. This paper will discuss the uniqueness of oxidative stress defenses in bats and their implications for their life history.

Oxidative Stress Defense of Bats

Bats have flying behavior to forage and roaming around the area from dusk to night (Basri et al., 2017; Hengjan et al., 2018). Bats have an extensive home range and can fly relatively far, up to hundreds of kilometers in one time (Breed, Field, Smith, Edmonston, & Meers, 2010; Hengjan et al., 2018; Norquay, Martinez-Nunez, Dubois, Monson, & Willis, 2013; Roberts, Catterall, Eby, & Kanowski, 2012). Large bat species such as the flying foxes can even travel between continents (Breed et al., 2010). Their flying behavior makes bats have experience with high metabolic spikes than same-sized terrestrial mammals (O'Shea et al., 2014).

In bats metabolism, energy production in the form of adenine triphosphate (ATP) also produces by-products in the form of reactive oxygen species (ROS) (Figure 1). Increased metabolic rate will have a direct impact on increasing ROS production. A radical form of ROS can cause damage to cellular components related to the aging process, degenerative diseases, and even cancer formation (Birben, Sahiner, Sackesen, Erzurum, & Kalayci, 2012; Buffenstein et al., 2008). Intracellular ROS is mainly produced by electron transport metabolism in the inner membrane of mitochondria. Besides, intracellular ROS comes from the metabolic processes of long fatty acids and proteins in peroxisomes and endoplasmic reticulum (ER), as well as other enzymes such as NADPH oxidase, xanthine oxidase, nitric oxide synthase, cyclooxygenase, cytochrome P450 enzymes, and lipoxygenase (Holmström & Finkel, 2014).

Despite high metabolism, bats are reported to have minimal adverse effects due to oxidative stress (Brunet-Rossinni, 2004; Brunet-Rossinni & Austad, 2004; Podlutsky, Khritankov, Ovodov, & Austad, 2005; Ungvari et al., 2008). Oxidative stress is a condition of imbalance between ROS and antioxidants which can be caused by a lack of antioxidants or too high ROS production (Birben et al., 2012). MDA is one of the metabolic products of lipid peroxidation by ROS (Figure 1). MDA is often used as a biological marker of stress oxidative (Grotto et al., 2009; Ho, Karimi Galougahi, Liu, Bhindi, & Figtree, 2013; Kwiecien et al., 2014; Wresdiyati et al., 2007). SOD is one of the endogenous antioxidant enzymes that function as superoxide (O_2^-) scavenger.

Superoxide is one of radical ROS formed from electron transport. SOD along with other antioxidant enzymes such as catalase, glutathione peroxidases, and peroxiredoxins become common defenses to detoxify free radicals into less radical forms (Figure 1) (Fukai & Ushio-Fukai, 2011; X. G. Lei et al., 2016). Hanadhita et al. (2017) analyzed malonaldehyde (MDA) and superoxide dismutase (SOD) levels in the spleen and liver organ of the lesser short-nosed bat (*Cynopterus brachyotis*). *C. brachyotis* spleen was reported to have higher levels of MDA than liver, even though the liver is generally the largest ROS producing organ. These results are thought to be related to cellular activity in the spleen that might be associated with the active immune activity (Hanadhita, Rahma, et al., 2018). Comparison between liver and spleen levels

of MDA and SOD in *C. brachyotis* and *R. norvegicus* showed that *C. brachyotis* produced less MDA and SOD compared to *R. norvegicus* although *C. brachyotis* had a higher basal metabolism rate than *R. norvegicus* (Hanadhita, Rahma, Prawira, Satjaningtyas, & Agungpriyono, 2017). Other researchers have also reported low production of ROS by bats. Little Brown Bat (*Myotis lucifugus*) was reported produce less than half the amount of free radical per unit of oxygen consumed compared to the short-tailed shrew (*Blarina brevicauda*) and white-footed mice (*Peromyscus leucopus*) (Brunet-Rossinni, 2004). Ungvari et al. (2008) also stated that endothelial cells from the arteries of *M. lucifugus* generate fewer ROS and are more resistant to oxidative damage than *P. leucopus* cells. Study of comparison of the ROS releasement by the Big Brown Bat (*Eptesicus fuscus*), house sparrow (*Passer domesticus*), and mice (*Mus musculus*) also shows that *E. fuscus* produce the lowest ROS up to 67% below the mice (Brown, McClelland, Faure, Klaiman, & Staples, 2009).

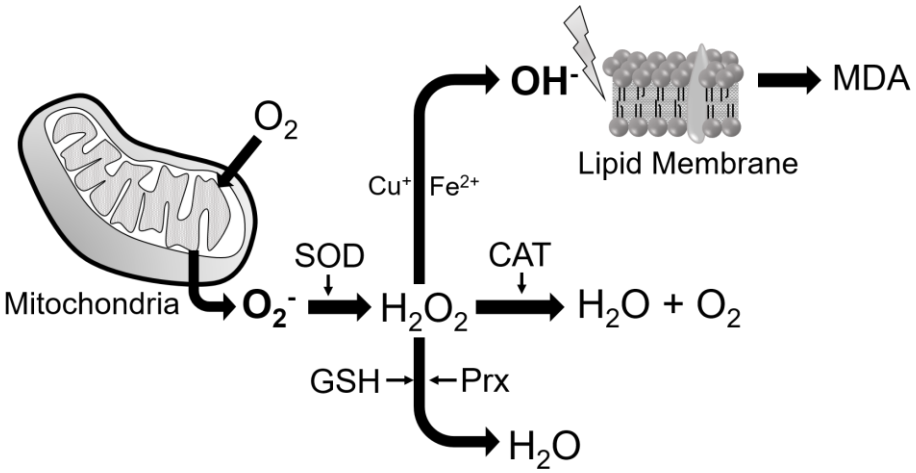

Figure 1 Production of reactive oxygen species (ROS) from cell respiration and antioxidants neutralization pathway. Superoxide (O_2^-) produced by mitochondrial respiration, is converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). H_2O_2 is converted by catalase (CAT), glutathione peroxidase (GSH), and peroxiredoxins (Prx). H_2O_2 can be converted spontaneously to hydroxyl radical (OH^-) when interacting with reduced transition metal (Cu^+ / Fe^{2+}). OH^- is very radical and can oxidize cells lipid membranes and produce secondary metabolites such as aldehyde and malondialdehyde (MDA) (modified from Fukai and Ushio-Fukai 2011; X. G. Lei *et al.* 2016).

Besides producing low ROS, bats are reported to bring high endogenous antioxidants. Bats deliver endogenous antioxidants such as SOD, glutathione peroxidases, catalase, α-tocopherol, and β-carotene that are higher than sheep, rats, and mice (Filho, Althoff, Dafré, & Boveris, 2007; Reinke & O'Brien, 2006). The high yield of endogenous antioxidants protects red blood cells from oxidative damage that might occur when flying (Reinke & O'Brien, 2006). One species of bat, white bat Honduran (*Ectophylla alba*), has a unique ability which is not found in other mammals. They can store carotenoid antioxidants on its skin. Therefore it appears as a bright yellow color (Galván et al., 2016).

Low production of ROS in bats is a result of mitochondrial DNA (mtDNA) evolution that prevents oxidative stress. Bats mitochondrial genes that play a significant role in energy metabolism (e.g., cytochrome B and oxidative phosphorylation gene) experience adaptive evolution with a high evolutionary rate compared to other mammals. Bats also have a low mtDNA mutation rate which allows low ROS production (Nabholz, Glémin, & Galtier, 2008). The concentration of bats endogenous antioxidant was closely related to hibernation and feeding habits. Hibernating bats have higher antioxidants than non-hibernating bats (Yin et al., 2016) and frugivorous bats have the highest antioxidants followed by omnivorous and

animalivorous species (Schneeberger, Czirják, & Voigt, 2014). Redox status balance between free radicals and antioxidants is essential to prevent a surge in oxidative stress levels (Birben et al., 2012). Low generation of free radicals and high production of antioxidants are two critical powers of bats in fighting against oxidative stress.

Implications of Stress Oxidative Defense

Extreme Longevity

The dispossable soma theory at the cellular levels predicts that cellular maintenance and repair processes will directly impact longevity (Thomas B L Kirkwood & Austad, 2000). This factor can be related to the mitochondria function that produces fewer free radicals, or the body produces or acquires more antioxidants, which of these two factors occur in bats (Harman, 2006; T. B.L. Kirkwood, 1989; Thomas B L Kirkwood & Austad, 2000). Bats have 3-10 times greater lifespan than other mammals with similar size (Tabel 1) (Ball, levari-Shariati, Cooper, & Aliani, 2018; Podlutsky et al., 2005; Wilkinson & South, 2002). The most extended lifespan reported in *Myotis brandtii* with recorded longevity for more than 40 years (Podlutsky et al., 2005). Hibernation behavior that has an impact on increasing endogenous antioxidant production and minimal production of ROS seems to have implications for the long lifespan of bats (Podlutsky et al., 2005; Yin et al., 2016). However, homeothermic bats that do not have the habit of hibernation also have a longer life than same sized mammals (Jürgens & Prothero, 1987; Wilkinson & South, 2002). Extreme survival compared to other mammals with the same body size makes bats placed above the regression line in studies that link body mass and durability in mammals and birds (Healy et al., 2014).

Table 1 The maximum lifespan of bats

Bats Species	Maximum Lifespan (years)	Reference
Plecotus auritus[1]	> 30	Wilkinson & South, (2002)
Myotis lucifugus[1]	> 30	Wilkinson & South, (2002)
Rhinolopus ferrumequinum[1]	> 30	Wilkinson & South, (2002)
Pteropus giganteus[2]	>30	Wilkinson & South, (2002)
Myotis brandti[1]	>40	Podlutsky et al. (2005)

[1)]Heterothermic [2)]Homeothermic

Bats as Reservoir Virus

Bats have been known to be a reservoir of various viruses that are harmful to humans but not damaging to bats (Anindita et al., 2015; Dharmayanti & Sendow, 2015; Kobayashi et al., 2015; Sasaki et al., 2016, 2014, 2012, Sendow et al., 2010, 2013; Wada et al., 2018). Bats have a unique immune component that prevents damage due to viral infections (Hanadhita, Satyaningtijas, & Agungpriyono, 2018; Pavlovich et al., 2018; Schountz, Baker, Butler, & Munster, 2017). The high production of antioxidants in bats can also support their resistance to viruses. Antioxidants treatment can significantly reduce replication of flavivirus in vitro studies (Gullberg, Steel, Moon, Soltani, & Geiss, 2015). An understanding of oxidative stress status in bats can help reveal the pattern of transmission of the virus from bats to other vulnerable hosts. Exposure to toxins, ectoparasites, weather changes, and physiological cycles can interfere with bat oxidative homeostasis and result in oxidative stress (Lilley et al., 2013; Oliveira et al., 2018; Ruiz, Eeva, Kanerva, Blomberg, & Lilley, 2019). The use of pesticides (e.g., Deltamethrin) on fruit plantations impacts the increase in stress oxidative markers in fruit bats (Oliveira et al., 2018). Heavy metal contamination in bat habitat also impact on decreasing endogenous antioxidants and increasing ROS in bats (Ruiz et al., 2019). Stress on bats due to the infection of white-nose syndrome, which is highly pathogenic to bats, can causes increased viral replication and viral shedding from bats (Davy et al., 2018). Environmental stressors and

changes in the ecological habitat of bats may have a contribution to the spread of the virus and the incidence of zoonotic outbreaks.

The Potential Use as Animal Model

The bat's barrier to oxidative damage can be used as creature models of various degenerative diseases, including cardiovascular degeneration (Ungvari et al., 2008). Induction of oxidative stressors against animal models often increases cancer risk. Wang et al. (2011) have conducted extensive research to identify the presence of tumors in bats on the Australia, Asia, and Africa continent then failed to find cancer incidence. It is suspected that the bat's mitochondrial defense against oxidative damage results in a decrease of cancer cells formation. *E. alba*, the only mammal that can store carotenoids, has the potential to be an animal model for the study of macular degeneration therapy in humans (Galván et al., 2016).

Bats can be maintained in captivity despite the need for long acclimatization (Crichton & Krutzsch, 2000). The breeding of bats in captivity is difficult, although it is not impossible (Brunet-Rossinni & Austad, 2004). In vitro experiments using cell lines from bats have also been developed by several researchers. Crameri et al. (2009) have established a method for making cell lines from various bat organs *Pteropus alecto* which is expected to be applied to other bat species. Commercial bats cell line Tb 1 Lu (ATCC® CCL-88TM) has also been available and accessible for interested researchers.

Conclusion

Bats produce low free radicals but high antioxidants which allow them to be resistant to oxidative stress. High resistance to oxidative stress has implications for their long lifespan, role as reservoir virus, and potential as animal models. The mechanism of bat's resistance on oxidative stress is expected in understanding the pathophysiology of degenerative diseases, aging processes, and zoonotic diseases originating from bats.

Acknowledgment

The authors thank Directorate of Research and Community Services, Directorate General of Research and Development, Ministry of Research, Technology, and Higher Education for financial support of this paper through Penelitian Pendidikan Magister Menuju Doktor untuk Sarjana Unggul (PMDSU) grant. The author states there is no conflict of interest with the parties concerned in this research.

References

Altringham, J. D. (2011). *Bats from Evolution to Conservation* (Second Edi). Oxford: Oxford University Press.

Anindita, P. D., Sasaki, M., Setiyono, A., Handharyani, E., Orba, Y., Kobayashi, S., … Kimura, T. (2015). Detection of coronavirus genomes in Moluccan naked-backed fruit bats in Indonesia. *Archives of Virology*, *160*(4), 1113–1118. https://doi.org/10.1007/s00705-015-2342-1

Ball, H. C., levari-Shariati, S., Cooper, L. N., & Aliani, M. (2018). Comparative metabolomics of aging in a long-lived bat: Insights into the physiology of extreme longevity. *PLoS ONE*, *13*(5), 1–20. https://doi.org/10.1371/journal.pone.0196154

Basri, C., Arifin, E. M. Z., Takemae, H., Hengjan, Y., Iida, K., Sudarnika, E., … Hondo, E. (2017). Potential risk of viral transmission from flying foxes to domestic animals and humans on the southern coast of West Java, Indonesia. *Journal of Veterinary Medical*

Science, *79*(9), 1615–1626. https://doi.org/10.1292/jvms.17-0222
Birben, E., Sahiner, U. M., Sackesen, C., Erzurum, S., & Kalayci, O. (2012). Oxidative Stress and Antioxidant Defense. *World Allergy Organization Journal*, *5*(1), 9–19. https://doi.org/10.1097/WOX.0b013e3182439613
Breed, A. C., Field, H. E., Smith, C. S., Edmonston, J., & Meers, J. (2010). Bats without borders: Long-distance movements and implications for disease risk management. *EcoHealth*, *7*(2), 204–212. https://doi.org/10.1007/s10393-010-0332-z
Brown, J. C. L., McClelland, G. B., Faure, P. A., Klaiman, J. M., & Staples, J. F. (2009). Examining the mechanisms responsible for lower ROS release rates in liver mitochondria from the long-lived house sparrow (Passer domesticus) and big brown bat (Eptesicus fuscus) compared to the short-lived mouse (Mus musculus). *Mechanisms of Ageing and Development*, *130*(8), 467–476. https://doi.org/10.1016/j.mad.2009.05.002
Brunet-Rossinni, A. K. (2004). Reduced free-radical production and extreme longevity in the little brown bat (Myotis lucifugus) versus two non-flying mammals. *Mechanisms of Ageing and Development*, *125*(1), 11–20. https://doi.org/10.1016/j.mad.2003.09.003
Brunet-Rossinni, A. K., & Austad, S. N. (2004). Ageing studies on bats: A review. *Biogerontology*, *5*(4), 211–222. https://doi.org/10.1023/B:BGEN.0000038022.65024.d8
Buffenstein, R., Edrey, Y. H., Yang, T., & Mele, J. (2008). The oxidative stress theory of aging: Embattled or invincible? Insights from non-traditional model organisms. *Age*, *30*(2–3), 99–109. https://doi.org/10.1007/s11357-008-9058-z
Calisher, C. H., Childs, J. E., Field, H. E., Holmes, K. V, & Schountz, T. (2006). Bats: Important reservoir hosts of emerging viruses. *Clinical Microbiology Reviews*, *19*(3), 531–545. https://doi.org/10.1128/CMR.00017-06
Crameri, G., Todd, S., Grimley, S., McEachern, J. A., Marsh, G. A., Smith, C., … Wang, L. F. (2009). Establishment, immortalisation and characterisation of pteropid bat cell lines. *PLoS ONE*, *4*(12). https://doi.org/10.1371/journal.pone.0008266
Crichton, E. G., & Krutzsch, P. H. (2000). *Reproductive Biology of Bats*. (E. G. Crichton & P. H. Krutzsch, Eds.). London: Academic Press. https://doi.org/10.1017/CBO9781107415324.004
Dharmayanti, N., & Sendow, I. (2015). Ebola : Penyakit Eksotik Zoonosis yang Perlu Diwaspadai. *Wartazoa*, *25*(1), 29–38. https://doi.org/10.14334/wartazoa.v25i1.1126
Filho, D. W., Althoff, S. L., Dafré, A. L., & Boveris, A. (2007). Antioxidant defenses, longevity and ecophysiology of South American bats. *Comparative Biochemistry and Physiology - C Toxicology and Pharmacology*, *146*(1–2 SPEC. ISS.), 214–220. https://doi.org/10.1016/j.cbpc.2006.11.015
Fukai, T., & Ushio-Fukai, M. (2011). Superoxide Dismutases: Role in Redox Signaling, Vascular Function, and Diseases. *Antioxidants & Redox Signaling*, *15*(6), 1583–1606. https://doi.org/10.1089/ars.2011.3999
Galván, I., Garrido-Fernández, J., Ríos, J., Pérez-Gálvez, A., Rodríguez-Herrera, B., & Negro, J. J. (2016). Tropical bat as mammalian model for skin carotenoid metabolism. *Proceedings of the National Academy of Sciences*, *113*(39), 10932–10937. https://doi.org/10.1073/pnas.1609724113
Grotto, D., Santa Maria, L., Valentini, J., Paniz, C., Schmitt, G., Garcia, S. C., … Farina, M. (2009). Importance of the lipid peroxidation biomarkers and methodological aspects for malondialdehyde quantification. *Quimica Nova*, *32*(1), 169–174. https://doi.org/10.1590/S0100-40422009000100032
Gullberg, R. C., Steel, J. J., Moon, S. L., Soltani, E., & Geiss, B. J. (2015). Oxidative stress influences positive strand RNA virus genome synthesis and capping. *Virology*, *475*, 212–229. https://doi.org/10.1038/jid.2014.371
Hanadhita, D., Rahma, A., Prawira, A. Y., Satjaningtyas, A. S., & Agungpriyono, S. (2017). Comparison of Oxidative Stress Status between Lesser Short Nosed Bat (Cynopterus brachyotis) and Laboratory Rat (Rattus Norvegicus) Related to Their Longevity. In

International Scientific Symposium (pp. 17–18). Bogor.
Hanadhita, D., Rahma, A., Prawira, A. Y., Sismin Satyaningtijas, A., & Agungpriyono, S. (2018). Morfometri Limpa Berkaitan dengan Produksi Radikal Bebas dan Antioksidan pada Kelelawar Pemakan Buah Codot Krawar (Cynopterus brachyotis). *Jurnal Veteriner*, *19*(1), 62–70. https://doi.org/10.19087/jveteriner.2018.19.1.62
Hanadhita, D., Satyaningtijas, A. S., & Agungpriyono, S. (2018). Bats As A Viral Reservoir: A Short Review Of Their Ecological Characters And Immune System. In *Proceedings of the 1st International Conference in One Health (ICOH 2017)* (pp. 124–128). Atlantis Press. https://doi.org/10.2991/icoh-17.2018.25
Harman, D. (2006). Free radical theory of aging: An update - Increasing the functional life span. *Annals of the New York Academy of Sciences*, *1067*(1), 10–21. https://doi.org/10.1196/annals.1354.003
Healy, K., Guillerme, T., Finlay, S., Kane, A., Kelly, S. B. A., McClean, D., … Cooper, N. (2014). Ecology and mode-of-life explain lifespan variation in birds and mammals. *Proceedings of the Royal Society B: Biological Sciences*, *281*(1784). https://doi.org/10.1098/rspb.2014.0298
Hengjan, Y., Saputra, V., Mirsageri, M., Pramono, D., Kasmono, S., Basri, C., … Hondo, E. (2018). Nighttime behavioral study of flying foxes on the southern coast of West Java, Indonesia. *Journal of Veterinary Medical Science*, *80*(7), 1146–1152. https://doi.org/10.1292/jvms.17-0665
Ho, E., Karimi Galougahi, K., Liu, C. C., Bhindi, R., & Figtree, G. A. (2013). Biological markers of oxidative stress: Applications to cardiovascular research and practice. *Redox Biology*, *1*(1), 483–491. https://doi.org/10.1016/j.redox.2013.07.006
Holmström, K. M., & Finkel, T. (2014). Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nature Reviews Molecular Cell Biology*, *15*(6), 411–421. https://doi.org/10.1038/nrm3801
Jürgens, K. D., & Prothero, J. (1987). Scaling of maximal lifespan in bats. *Comparative Biochemistry and Physiology -- Part A: Physiology*, *88*(2), 361–367. https://doi.org/10.1016/0300-9629(87)90498-1
Kirkwood, T. B. L. (1989). DNA, mutations and aging. *Mutation Research DNAging*, *219*, 1–7. https://doi.org/10.1016/0921-8734(89)90035-0
Kirkwood, T. B. L., & Austad, S. N. (2000). Why do we age? *Nature*, *408*(6809), 233–238. https://doi.org/10.1038/35041682
Kobayashi, S., Sasaki, M., Nakao, R., Setiyono, A., Handharyani, E., Orba, Y., … Sawa, H. (2015). Detection of novel polyomaviruses in fruit bats in Indonesia. *Archives of Virology*, *160*(4), 1075–1082. https://doi.org/10.1007/s00705-015-2349-7
Kwiecien, S., Jasnos, K., Magierowski, M., Sliwowski, Z., Pajdo, R., Brzozowski, B., … Brzozowski, T. (2014). Lipid peroxidation, reactive oxygen species and antioxidative factors in the pathogenesis of gastric mucosal lesions and mechanism of protection against oxidative stress - induced gastric injury. *Journal of Physiology and Pharmacology : An Official Journal of the Polish Physiological Society*, *65*(5), 613–622.
Lei, M., & Dong, D. (2016). Phylogenomic analyses of bat subordinal relationships based on transcriptome data. *Scientific Reports*, *6*(May), 1–8. https://doi.org/10.1038/srep27726
Lei, X. G., Zhu, J.-H., Cheng, W.-H., Bao, Y., Ho, Y.-S., Reddi, A. R., … Arnér, E. S. J. (2016). Paradoxical Roles of Antioxidant Enzymes: Basic Mechanisms and Health Implications. *Physiological Reviews*, *96*(1), 307–364. https://doi.org/10.1152/physrev.00010.2014
Lilley, T. M., Ruokolainen, L., Meierjohann, A., Kanerva, M., Stauffer, J., Laine, V. N., … Nikinmaa, M. (2013). Resistance to oxidative damage but not immunosuppression by organic tin compounds in natural populations of Daubenton's bats (Myotis daubentonii). *Comparative Biochemistry and Physiology - C Toxicology and Pharmacology*, *157*(3), 298–305. https://doi.org/10.1016/j.cbpc.2013.01.003
Nabholz, B., Glémin, S., & Galtier, N. (2008). Strong variations of mitochondrial mutation

rate across mammals - The longevity hypothesis. *Molecular Biology and Evolution*, *25*(1), 120–130. https://doi.org/10.1093/molbev/msm248
Norquay, K. J., Martinez-Nunez, F., Dubois, J. E., Monson, K. M., & Willis, C. K. (2013). Long-distance movements of little brown bats (Myotis lucifugus). *Journal of Mammalogy*, *94*(2), 506–515. https://doi.org/10.1644/12-MAMM-A-065.1
O'Shea, T. J., Cryan, P. M., Cunningham, A. A., Fooks, A. R., Hayman, D. T. S., Luis, A. D., … Wood, J. L. N. (2014). Bat flight and zoonotic viruses. *Emerging Infectious Diseases*, *20*(5), 741–745. https://doi.org/10.3201/eid2005.130539
Oliveira, J. M., Losano, N. F., Condessa, S. S., de Freitas, R. M. P., Cardoso, S. A., Freitas, M. B., & de Oliveira, L. L. (2018). Exposure to deltamethrin induces oxidative stress and decreases of energy reserve in tissues of the Neotropical fruit-eating bat Artibeus lituratus. *Ecotoxicology and Environmental Safety*, *148*(July 2017), 684–692. https://doi.org/10.1016/j.ecoenv.2017.11.024
Pavlovich, S. S., Lovett, S. P., Koroleva, G., Guito, J. C., Arnold, C. E., Nagle, E. R., … Palacios, G. (2018). The egyptian rousette genome reveals unexpected features of bat antiviral immunity. *Cell*, *173*(5), 1098–1110.e18. https://doi.org/10.1016/j.cell.2018.03.070
Podlutsky, A. J., Khritankov, A. M., Ovodov, N. D., & Austad, S. N. (2005). A new field record for bat longevity. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *60*(11), 1366–1368. https://doi.org/10.1093/gerona/60.11.1366
Reinke, N. B., & O'Brien, G. M. (2006). High activity antioxidant enzymes protect flying-fox haemoglobin against damage: An evolutionary adaptation for flight? *Journal of Comparative Physiology B: Biochemical, Systemic, and Environmental Physiology*, *176*(8), 729–737. https://doi.org/10.1007/s00360-006-0094-7
Roberts, B. J., Catterall, C. P., Eby, P., & Kanowski, J. (2012). Long-distance and frequent movements of the flying-fox Pteropus poliocephalus: Implications for management. *PLoS ONE*, *7*(8), 23–25. https://doi.org/10.1371/journal.pone.0042532
Ruiz, S. R., Eeva, T., Kanerva, M., Blomberg, A., & Lilley, T. M. (2019). Metal and metalloid exposure and oxidative status in free-living individuals of Myotis daubentonii. *Ecotoxicology and Environmental Safety*, *169*(May 2018), 93–102. https://doi.org/10.1016/j.ecoenv.2018.10.083
Sasaki, M., Gonzalez, G., Wada, Y., Setiyono, A., Handharyani, E., Rahmadani, I., … Sawa, H. (2016). Divergent bufavirus harboured in megabats represents a new lineage of parvoviruses. *Scientific Reports*, *6*(April), 1–8. https://doi.org/10.1038/srep24257
Sasaki, M., Setiyono, A., Handharyani, E., Kobayashi, S., Rahmadani, I., Taha, S., … Kimura, T. (2014). Isolation and characterization of a novel alphaherpesvirus in fruit bats. *Journal of Virology*, *88*(17), 9819–9829. https://doi.org/10.1128/JVI.01277-14
Sasaki, M., Setiyono, A., Handharyani, E., Rahmadani, I., Taha, S., Adiani, S., … Kimura, T. (2012). Molecular detection of a novel paramyxovirus in fruit bats from Indonesia. *Virology Journal*, *9*, 1–7. https://doi.org/10.1186/1743-422X-9-240
Schneeberger, K., Czirják, G. Á., & Voigt, C. C. (2014). Frugivory is associated with low measures of plasma oxidative stress and high antioxidant concentration in free-ranging bats. *Naturwissenschaften*, *101*(4), 285–290. https://doi.org/10.1007/s00114-014-1155-5
Schountz, T., Baker, M. L., Butler, J., & Munster, V. (2017). Immunological control of viral infections in bats and the emergence of viruses highly pathogenic to humans. *Frontiers in Immunology*, *8*(SEP). https://doi.org/10.3389/fimmu.2017.01098
Sendow, I., Field, H. E., Adjid, A., Ratnawati, A., Breed, A. C., Darminto, … Daniels, P. (2010). Screening for Nipah virus infection in West Kalimantan Province, Indonesia. *Zoonoses and Public Health*, *57*(7–8), 499–503. https://doi.org/10.1111/j.1863-2378.2009.01252.x
Sendow, I., Ratnawati, A., Taylor, T., Adjid, R. M. A., Saepulloh, M., Barr, J., … Field, H. (2013). Nipah Virus in the fruit bat Pteropus vampyrus in Sumatera, Indonesia. *PLoS*

ONE, *8*(7). https://doi.org/10.1371/journal.pone.0069544
Sies, H. (2015). Oxidative stress: A concept in redox biology and medicine. *Redox Biology*, *4*, 180–183. https://doi.org/10.1016/j.redox.2015.01.002
Simmons, N. B. (2000). Bat phylogeny: an evolutionary context for comparative studies. In R. A. Adams & S. C. Pedersen (Eds.), *Ontogeny, Functional Ecology, and Evolution of Bats* (pp. 9–58). New York: Cambridge University Press.
Teeling, E. C., Springer, M. S., Madsen, O., Bates, P., O'Brien, S. J., & Murphy, W. J. (2005). A molecular phylogeny for bats illuminates biogeography and the fossil record. *Science*, *307*(5709), 580–584. https://doi.org/10.1126/science.1105113
Ungvari, Z., Buffenstein, R., Austad, S. N., Podlutsky, A., Kaley, G., & Csiszar, A. (2008). Oxidative stress in vascular senescence: lessons from successfully aging species. *Frontiers in Bioscience : A Journal and Virtual Library*, *13*(March 2015), 5056–5070. https://doi.org/10.2741/3064
Wada, Y., Sasaki, M., Setiyono, A., Handharyani, E., Rahmadani, I., Taha, S., … Sawa, H. (2018). Detection of novel gammaherpesviruses from fruit bats in Indonesia. *Journal of Medical Microbiology*, *67*(3). https://doi.org/10.1099/jmm.0.000689
Wang, L. F., Walker, P. J., & Poon, L. L. M. (2011). Mass extinctions, biodiversity and mitochondrial function: Are bats "special" as reservoirs for emerging viruses? *Current Opinion in Virology*, *1*(6), 649–657. https://doi.org/10.1016/j.coviro.2011.10.013
Wilhelm Filho, D., Althoff, S. L., Dafré, A. L., & Boveris, A. (2007). Antioxidant defenses, longevity and ecophysiology of South American bats. *Comparative Biochemistry and Physiology - C Toxicology and Pharmacology*, *146*(1–2 SPEC. ISS.), 214–220. https://doi.org/10.1016/j.cbpc.2006.11.015
Wilkinson, G. S., & South, J. M. (2002). Life history, ecology and longevity in bats. *Aging Cell*, *1*, 124–131. https://doi.org/10.1046/j.1474-9718.2002.00020sm.x
Wresdiyati, T., Astawan, M., Fithriani, D., Adnyane, I. K. M., Novelina, S., & Aryani, S. (2007). the Effect of A-Tocopherol on the Profiles of Superoxide Dismutase and Malondialdehyde in the Liver of Rats Under Stress Condition. *Jurnal Veteriner*, *2*(12), 202–209.
Yin, Q., Ge, H., Liao, C. C., Liu, D., Zhang, S., & Pan, Y. H. (2016). Antioxidant defenses in the brains of bats during hibernation. *PLoS ONE*, *11*(3), 1–17. https://doi.org/10.1371/journal.pone.0152135