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Viewpoint

Crocodile Gut Microbiome Is a Potential Source of Novel Bioactive Molecules

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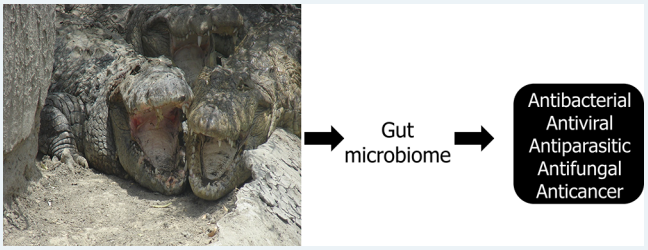
ABSTRACT: Here, it is proposed that the crocodile gut microbiome is a valuable biomaterials resource to counter threats posed by environmental and infectious hazards to the existence of *Homo sapiens*.



KEYWORDS: *gut microbiome, crocodile, health, disease, novel treatment*

Approximately 2500 years ago, Hippocrates said that "All disease begins in the gut", and now, through multiple studies, it has been revealed that the gut microbiome performs a vital role in regulating the health and behavior of the host.[1,2] The gut microbiome has also been shown to influence wisdom and loneliness.[3] Can we attribute the evolutionary success of prehistoric species of inhabiting this planet to the gut microbiome? For example, a number of species such as crocodiles have existed and successfully evolved on this planet for millions of years under conditions that would be detrimental to *Homo sapiens*. Crocodiles endure unsanitary environments; consume rotted meat; are subjected to heavy metal exposure such as cadmium, arsenic, cobalt, chromium, mercury, and nickel; and tolerate elevated levels of radiation. Crocodiles are among the very few species to have survived the catastrophic Cretaceous-Tertiary extinction event and can live up to 100 years.[4] As aging can be retarded in crocodiles, this could be of significant importance if translated to *Homo sapiens*. Logically, we speculate that crocodiles have developed mechanisms to defend themselves from noxious agents and diseased conditions, and their unique gut microbiome is most likely a contributory factor to their hardiness.[4,5]

There has been increasing research on the human gut microbiome in recent years, providing increasing evidence of the influence of the microbiome and its significant role in disease; however, little or no studies have been done in reptiles, especially regarding the gut microbiome of crocodiles and alligators, which are both remarkable and resilient species. Moreover, the understanding that long-lived and hardy species such as crocodiles and alligators might provide clues about aging and disease resistance is innovative, and recently, the sequencing of genomes has initiated new prospects to explore the molecular mechanisms involved.[6] There are two possible explanations for the hardiness of crocodiles and alligators: (i) such species have evolved a strong immune system, and/or (ii) their gut microbiome produces molecules which contribute to their hardiness. However, even though there are limited studies examining the immune system of these animals, there are very few studies on their gut microbiome. For the latter, there is a clear need to explore their microbiome to identify unique gut microbes and associated novel molecules of potential translational value for the benefit of human health. For example, it was recently shown that the crocodile gut microbiome was dominated by Firmicutes, mainly *Clostridia* and *Fusobacteria*, with the most abundant operational taxonomic unit (OTU) was represented by *Clostridium difficile*, which was indeed distinct from humans which are usually dominated by *Firmicutes* and *Bacteroidetes*.[7] This was very similar to the composition of the gut microbiome of alligators.[8,9] Other studies are currently in progress to examine the effect of the bacterial metabolites from the crocodile's gut microbiota on cellular metabolic activities as well as cellular senescence and neuroprotective effects using *in vitro* models.

A complete understanding of the crocodile and alligator gut microbiome and its associated molecules will lead to the identification of potential therapeutic leads for clinical investigations, but it is a lengthy, expensive, and laborious process. An alternative expedited approach could be the

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implantation of selected gut microbiome species of crocodiles or alligators into mammalian models of disease or aging. This could lead to the identification of potential therapeutic leads for human consumption; however, intensive research over the coming years is needed to realize these expectations. Considering the presence of a plethora of microbial species and genomes in both the crocodile and human gut microbiome, it is not far-fetched and should be explored for further investigations. In support, diet-induced obesity together with an increase in *Firmicutes* was observed recently in a mouse model.[10] Furthermore, microbiota transplantation from obese mice to leaner germ-free recipients promoted greater fat deposition than microbiota transplantation from lean mice.[10] Additionally, genetically engineered probiotics have been produced for the benefit of human health. For example, an engineered *Lactococcus lactis* has been used to treat type II diabetes.[11] Such studies could be emulated to utilize the unique microbiome of crocodiles and alligators for the benefit of *Homo sapiens* with *in vivo* work and clinical trials in the forthcoming years. Being one of the most successful and diverse animal groups in evolution, the gut microbiome of the crocodile may be a valuable resource for novel bioactive molecules of therapeutic value.

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Author Contributions

R.S. and N.A.K. conceptualized the work amid critical discussions with N.C.S. R.S. conducted literature review and prepared the first draft of the manuscript. N.A.K. corrected the manuscript. All authors contributed to the manuscript and will act as guarantors.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Fasano, A. (2020) All disease begins in the (leaky) gut: Role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F1000Research 9*, 69.

(2) Shreiner, A. B., Kao, J. Y., and Young, V. B. (2015) The gut microbiome in health and in disease. *Curr. Opin. Gastroenterol. 31*, 69−75.

(3) Nguyen, T. T., Zhang, X., Wu, T. C., Liu, J., Le, C., Tu, X. M., Knight, R., and Jeste, D. V. (2021) Association of Loneliness and Wisdom with Gut Microbial Diversity and Composition: An Exploratory Study. *Front. Psychiat. 12*, 648475.

(4) Siddiqui, R., Jeyamogan, S., Ali, S. M., Abbas, F., Sagathevan, K. A., and Khan, N. A. (2017) Crocodiles and alligators: Antiamoebic and antitumor compounds of crocodiles. *Exp. Parasitol. 183*, 194−200.

(5) Jeyamogan, S., Khan, N. A., Sagathevan, K., and Siddiqui, R. (2020) *Crocodylus porosus*: a potential source of anticancer molecules. *BMJ. Open Sci. 4*, e100040.

(6) Green, R. E., Braun, E. L., Armstrong, J., Earl, D., Nguyen, N., Hickey, G., Vandewege, M. W., St. John, J. A., Capella-Gutierrez, S., Castoe, T. A., Kern, C., Fujita, M. K., Opazo, J. C., Jurka, J., Kojima, K. K., Caballero, J., Hubley, R. M., Smit, A. F., Platt, R. N., Lavoie, C. A., Ramakodi, M. P., Finger, J. W., Suh, A., Isberg, S. R., Miles, L., Chong, A. Y., Jaratlerdsiri, W., Gongora, J., Moran, C., Iriarte, A., McCormack, J., Burgess, S. C., Edwards, S. V., Lyons, E., Williams, C., Breen, M., Howard, J. T., Gresham, C. R., Peterson, D. G., Schmitz, J., Pollock, D. D., Haussler, D., Triplett, E. W., Zhang, G., Irie, N., Jarvis, E. D., Brochu, C. A., Schmidt, C. J., McCarthy, F. M., Faircloth, B. C., Hoffmann, F. G., Glenn, T. C., Gabaldon, T., Paten, B., and Ray, D. A. (2014) Three crocodilian genomes reveal ancestral patterns of evolution among archosaurs. *Science 346* (6215), e1254449.

(7) Lin, M., Zeng, C., Li, Z., Ma, Y., and Jia, X. (2019) Comparative analysis of the composition and function of fecal-gut bacteria in captive juvenile *Crocodylus siamensis* between healthy and anorexic individuals. *MicrobiologyOpen 8*, e929.

(8) Willson, N. L., Van, T. T., Lever, J., Moore, R. J., and Stanley, D. (2019) Characterisation of the intestinal microbiota of commercially farmed saltwater crocodiles, *Crocodylus porosus*. *Appl. Microbiol. Biotechnol. 103*, 8977−8985.

(9) Keenan, S. W., Engel, A. S., and Elsey, R. M. (2013) The alligator gut microbiome and implications for archosaur symbioses. *Sci. Rep. 3*, e2877.

(10) Turnbaugh, P. J., Bäckhed, F., Fulton, L., and Gordon, J. I. (2008) Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe 3*, 213−223.

(11) Callewaert, C., Knödlseder, N., Karoglan, A., Güell, M., and Paetzold, B. (2021) Skin microbiome transplantation and manipulation: Current state of the art. *Comput. Struct. Biotechnol. J. 19*, 624−631.