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Review

Updating conservation metagenomics on the gut microbiome of threatened mammals

Le Wang,[1,2] Guangping Huang,[1] Guoliang Li,[1] Shibin Yuan,[2] and Fuwen Wei[1,3,*]

[1]Jiangxi Provincial Key Laboratory of Conservation Biology, College of Forestry, Jiangxi Agricultural University, Nanchang 330045, China
[2]Key Laboratory of Southwest China Wildlife Resources Conservation (Ministry of Education), China West Normal University, Nanchong 637002, China
[3]Key Laboratory of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China
*Correspondence: weifw@ioz.ac.cn
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SUMMARY

During the past two decades, much work has characterized the composition and function of the gut microbiome on diverse wildlife in the framework of conservation metagenomics. While promising for conservation, translating theory into practice remains challenging and requires progress. Here, we summarize the progress of gut microbiomes of threatened mammals from ecology and evolution to conservation practice, and propose an integrative framework for future conservation metagenomics within which multi-dimension, multi-scale, multi-technology, and multi-omics can be comprehensively considered to advance our understanding of the patterns and underpinnings of wildlife gut microbiomes. We also propose microbiome banking to archive endangered species' biological information and microbial entities. Moreover, a reference framework for cutting-edge gut metagenomics research on the giant panda is outlined, demonstrating the field's potential. Finally, while microbiome manipulation shows promise, it remains experimental—demanding stringent safety protocols, vigilant oversight, and thorough risk assessment to ensure responsible application.

INTRODUCTION

All animals are chimeric creatures colonized with complex consortia of microbes, which are collectively known as an individual's "microbiome", containing both the community of microorganisms and their "theater of activity" (structural elements, metabolites, signal molecules, and the surrounding environmental conditions).[1] The greatest diversity and magnitude of these host-associated microorganisms resides within the gastrointestinal tract, where the microbial cells are thought to outnumber host cells, referred to as the "gut microbiome".[2] Observational findings achieved during the past two decades suggest that gut microbiome plays a critical role in health, nutrition, physiology, immunity, and development of hosts across human populations or other species, and when aberrant, to the pathogenesis of various common metabolic disorders.[3,4] Thus, the mechanistic understanding of the diversity pattern and functional landscape and the relationship between the gut microbiome and host has especially captivated scientific interest.

Because of proven importance to health in both humans and non-human animals, the functional significances of gut microbiome to the adaptive potential of their hosts are considered within a conservation framework, providing important insights for the protection of wildlife.[5–12] As such, conservation metagenomics, as an emerging subdiscipline of conservation biology, aims to understand the roles of symbiotic microbiomes (including but not limited to the gut microbiome) in ecology, evolution, and conservation of wild animals (Figures 1A and 1B).[5]

Here, we systematically surveyed Web of Science for studies up to 2025 on wildlife gut microbiomes, with a focus on threatened mammal species. We first summarize the recent progress in the wildlife gut microbiome in evolution and ecology, highlighting the evidence for adaptive potential of the gut microbiome in wild species, particularly for those threatened (i.e., vulnerable, endangered, or critically endangered) and near threatened species (International Union for Conservation of Nature, IUCN, 2024). Then, we propose an integrative framework for future conservation metagenomics based on the multi-omics and functional verification combined with experimental platform from model animal to wildlife gut microbiome looking for a systems biology-based approach. Finally, we highlight the progressive achievements of the giant panda (*Ailuropoda melanoleuca*) gut microbiome, which is deposited as a research paradigm on the well-recognized flagship species for other threatened mammals.

WILDLIFE GUT MICROBIOME IN ECOLOGY AND EVOLUTION

Due to the critical importance of the gut microbiome for host functioning, driving forces that shape its assembly and composition have received increasing attention during the last 20 years. Placing the wildlife gut microbiome into its evolutionary context, all animals have developed symbiotically with a diversity of environmental microbial species, assembling and maintaining a diverse but host-specific gut microbial community (Figure 1A). Decades of research show that the gut microbiome is

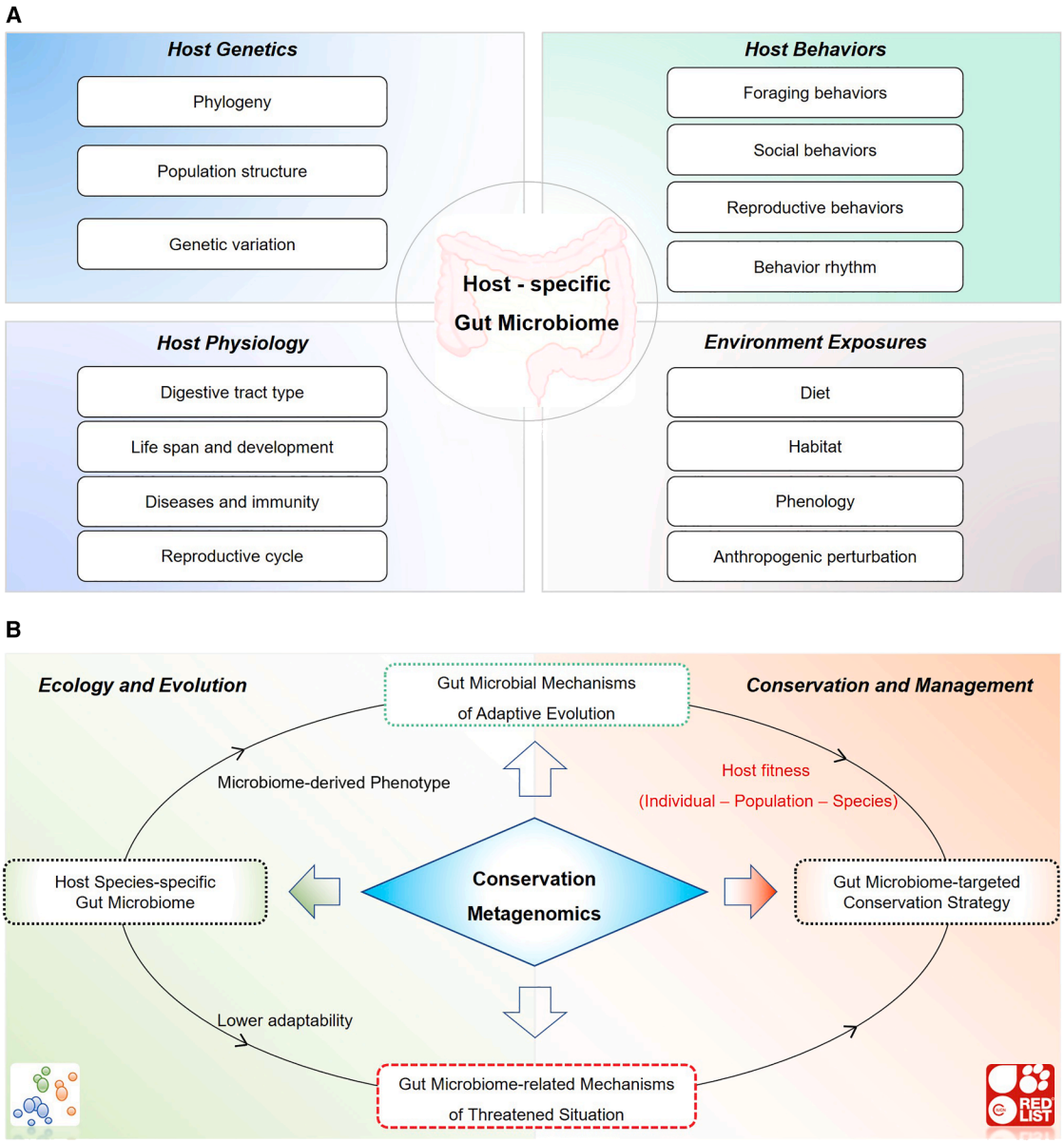

Figure 1. Determinants of wildlife gut microbiome and conservation metagenomics framework

(A) Host species-specific gut microbiome shaped by multiple factors involving both host and environment.

(B) This figure highlights the dual focus of conservation metagenomics in both understanding and preserving wildlife, by mapping the continuum from mechanistic investigations into gut microbiome ecology and evolution to translational applications for wildlife conservation.[4]

predominantly shaped by both the host (i.e., phylogeny, population structure, and genetic variation) and ecology (i.e., diet, geography, habitat, climate, etc.), generating natural selection for microbial traits that benefit the host.[2,13–27] In parallel, all animal hosts have initiated myriad symbiotic associations with microorganisms and often have maintained these symbioses for millions of years, spanning drastic changes in ecological conditions and lifestyles.[2,13–22,26] There is ample indication of inter- and intraspecific variation in wildlife gut microbiota diversity, which per se confers fitness to a certain extent with convincing examples showing that microbiota flexibility, composition, and function may well be sources of adaptive potential.[28–37]

Inter-specific variation relating to host phylogeny, diet, and geography

As the gut microbiome variability mediates short-term host fitness consequences, its persistent configuration across generations may ultimately drive macroevolutionary patterns of host adaptation and niche differentiation. To understand the coevolution of the mammals and their indigenous microbial

communities, pioneering study of Jeffrey I. Gordon group in 2008 conducted a network-based analysis of bacterial 16S ribosomal RNA (rRNA) gene sequences from the fecal microbiota of 60 species (humans and 59 other mammalian species living in zoos and in the wild) and results indicated that both host phylogeny and diet influenced bacterial diversity increases from carnivory to omnivory to herbivory.[2] And the relative contributions of these two driving factors in shaping the gut microbiome are further determined at different taxonomic scales. In general, host phylogeny strongly structures the gut microbiome across broader host taxonomic scales, a pattern known as ''phylosymbiosis'', but these gut microbiomes can be further modified by host ecology, among closely related host species.[14,15,26,38] For example, the gut microbiomes of both bamboo-eating giant pandas and red pandas (*Ailurus fulgens*) cluster with those related bears, such as the Asian black bear (*Ursus thibetanus*) and polar bear (*Ursus maritimus*), and have a carnivore-like microbiome.[2,21,39] Folivorous lemurs coexisting sympatrically in a Malagasy rainforest exhibit species-specific gut microbiomes, metagenomes, and metabolomes, each finely tuned to their distinct dietary specializations. These findings highlight the critical role of gut microbiota in facilitating niche differentiation and enabling sympatric coexistence among these primates.[28] Another two primates in Qinghai-Tibetan Plateau (QTP), rhesus macaque (*Macaca mulatta*) and Yunnan snub-nosed monkey (*Rhinopithecus bieti*), exhibited a gut microbiome composition similar to that of Tibetan people, which significantly differed from other distantly related animals in spite of the same geographical environments.[40]

Nonetheless, gut microbial convergent evolution of different species with distinct phylogenetic relatedness but similar ecological pressures (i.e., the similar diets or habitats) makes an exception.[38,39,41–43] For example, dietary bamboo specialization is one of the most extreme examples of convergent herbivory. There are four kinds of mammals feeding on high-fiber bamboos around the world, including the giant panda, red panda, bamboo rats (e.g., *Rhizomys sinensis* and *Rhizomys pruinosus*) and bamboo lemurs (e.g., *Prolemur simus*a and *Hapalemur griseus*). The giant and red pandas are distantly related members of the order Carnivora, the bamboo rats are members of the rder Rodentia, and bamboo lemurs belong to the order Primates. Comparisons of the gut microbial composition among the pandas and bamboo lemurs showed that these species shared a high number of low-abundance gut microbes.[38] Comparative metagenomics on the gut microbial function of the two pandas showed gut microbiome of both pandas possessed a high level of starch and sucrose metabolism and vitamin B12 biosynthesis.[39] For another example, the QTP is one of the most extreme high-altitude hypoxia environments setting up challenges for the survival of both human and other mammalian species. Comparative metagenomics of QTP ruminants (Yaks *Bos grunniens* and Tibetan sheep *Ovis aries*) with low-altitude relatives (cattle *Bos taurus* and ordinary sheep *Ovis aries*) showed microbial community structures and compositions contributed to convergent adaptation and convergence of microbial genes in volatile fatty acids and methane-yielding pathways.[30] The unanimous convergent evolution of high relative abundances of carbohydrate-active enzymes in the gut microbiomes of plateau-dwelling animals has been verified on QTP ungulates.[42] All these results suggest gut microbiomes co-evolve with host genomes for specific environmental adaptation.

Intra-specific variation associated with host and environmental factors

Host genetics

Within specific species, host genetics involving population structure and genetic variation have been related to the gut microbiome. For example, whole-genome sequencing revealed that there are three geographic populations of the current wild giant panda with marked recent population divergence.[44] Correspondently, the latest high-quality gut microbiome catalog of the giant panda (pandaGUT) evidenced the effects of intra-specific genetic divergence on the diversity and functional repertoire of wild giant panda gut microbiomes, indicating wildlife has hosted microbial life throughout evolutionary history.[45] However, there are some inconsistent results on other species. For two opposite examples, large-scale field surveys on the koala (*Phascolarctos cinereus*), an iconic yet endangered specialized folivore experiencing widespread decline, revealed significant correlations between gut microbial diversity distances and geographic distances, and the mismatching of gut microbiome and host population genetic patterns.[46] And the critically endangered Saiga antelope (*Saiga tatarica* ssp.) is a long-distance migratory ungulate. Its gut microbiota showed a consistent gut microbial diversity and composition across two wild populations.[47] This inconsistency among different species may be related to the history and degree of genetic differentiation of wild populations.

Host behaviors and physiology

Animal gut microbes depend on their host for resources and can be transmitted across the host's social network.[48–50] Mammals in nature exhibit diverse patterns of social organization, ranging from entirely solitary (such as the carnivory giant panda, primate *Nycticebus pygmaeus*) to dispersed to gregarious (such as golden snub-nosed monkey *Rhinopithecus roxellana*). These social organization and behavior contribute to microbiome assembly, with mammals and other social animals acquiring a portion of their resident microorganisms from conspecifics, either through direct physical contact and proximity among individuals or indirectly through common environmental exposures. For example, frequent social interaction promotes species richness within individual microbiomes as well as homogeneity among the gut community memberships of different chimpanzees and infants inherit gut microorganisms primarily through social transmission, generating a pan-microbiome, preserving microbial diversity across evolutionary time scales and contributing to the evolution of host species-specific gut microbial communities.[51] Importantly, the socially mediated dispersal of mutualistic gut bacteria may cf. a selective benefit to group-living and ultimately impact the evolution of animal sociality. Research on the gut microbiome of Grant's gazelle (*Nanger granti*) indicated that individuals with higher social connectivity can be rapidly recolonized with a faster increase in microbiome richness than less socially connected individuals after a perturbation event (i.e., antibiotic treatment), shaping a distinct gut microbiome to the unperturbed state.[52] Except for those social behaviors, many physiology-related behaviors (such as mating, gestation, lactation,

hibernation, etc.) have aroused interest in the role of gut microbiome in physiological adaptation. Take the case of hibernation, it is the process by which warm-blooded animals (e.g., some rodents, bears, primates, etc.) will reduce their metabolic rate and be in a state of inactivity with significant remodeling at cellular, tissue, organ, whole organism, and symbiotic microorganism levels.[53,54] Bears are fascinating creatures and one of the aspects of a bear's habits and life cycle is hibernation. Analyses on the gut microbiome of free-ranging brown bears (*Ursus arctos*) showed that microbial composition differed seasonally between hibernation and active phase. Compared to the active phase, gut microbiome in hibernation were distinct with reduced diversity, reduced levels of Firmicutes and Actinobacteria, and increased levels of Bacteroidetes, affecting blood metabolites synchronously and contributing to host energy metabolism in the hibernating brown bear.[55] Similarly, the dwarf lemurs of Madagascar (*Cheirogaleus* spp.), the only primates known to be obligate hibernators in subtropical forests,[56] exhibit seasonal reconfigurations of the gut microbiome with reduced gut microbial diversity during fattening, intermediate diversity and increased community homogenization during hibernation, and greatest diversity after emergence.[57]

Diet, season, and living environments

There are many environmental factors shaping the wildlife gut microbiome (Figure 1A). Diet, season, living environment, and anthropogenic influence are considered main factors of compelling evidence from multiple species. Taken as a whole, diet dominates over many other factors in regulating the composition of the gut microbiome. The differential diet composition related to ecological season and geographic distribution always affects the gut microbiome in a substantial manner. For example, seasonal shifts in the composition and activity of the gut microbiome provide an effective buffer against the seasonal fluctuations in energy and nutrient intake for many herbivores, such as non-human primates,[29,37,58–62] bamboo-eating pandas,[21,63–65] and ungulates.[42,66] In terms of the living environments, both the natural environmental heterogeneity and man-made disturbance shape the gut microbiome variations. For instance, altitudinal gradients drive the distinct gut microbiota structure of wild rhesus macaque populations at higher altitudes with higher alpha diversity, contributing to the energy compensation and degradation of exogenous toxins.[67]

And the artificially controlled environments arouse the greatest interest in the responses of captive wildlife gut microbiome to changing environments.[68,69] Comprehensive assessment of the relative contributions of multiple factors toward gut microbial diversity within a broad evolutionary context showed that captivity diminished the effects of host phylogeny, diet, and threatened status on the gut bacterial diversity.[68] Captive animals, compared to their wild counterparts, generally harbor distinct gut microbiome.[23,70–74] The impact of captivity on gut microbiota diversity exhibits striking interspecies variation. For example, captive Przewalski's horses (*Equus ferus przewalskii*) and Asian wild asses (*Equus hemionus*) demonstrate significant reductions in alpha diversity alongside increased abundances of potentially pathogenic bacteria, suggesting compromised host health under artificial maintenance conditions.[74] Conversely, captive spotted seals (*Phoca largha*) paradoxically exhibit greater microbial diversity compared to their wild counterparts.[72] This dichotomy highlights the species-specific nature of microbial responses to captivity, likely attributable to multiple interacting factors including natural dietary adaptations, provisioned nutritional regimes, differential microbial exposures, and cumulative environmental stressors. While standardized food provisioning, uniform healthcare protocols, and modified social structures are frequently implicated in diversity reduction, the functional implications of these microbial shifts require careful interpretation. High diversity is not necessarily "better" or "healthy" for host. Particularly for ecological specialists, elevated microbial diversity may not inherently cf. health benefits, as optimal gut community structures are evolutionarily adapted to species-specific ecological niches.

WILDLIFE GUT MICROBIOME WITHIN CONSERVATION METAGENOMICS

In the face of global biodiversity loss and mass extinction of species, resulting in the disruption of various ecosystems central to environmental functions and human health,[75] we are now firmly entrenched within a Sixth Mass Extinction event with species disappearing at an unprecedented rate.[76] More than 46,300 species worldwide are currently classified as threatened with 26 percent mammals included (IUCN, 2024). Faced with such alarming challenges, recent advances in research have indicated the potential of microbiome-based interventions a promising tool, such as gut microbiome-targeted probiotics to protect wildlife and mitigate environmental impacts, and microbiome transplants to restore ecosystems and improve their resilience within conservation biology.[75,77,78] Owing to the profound influence of gut microbiome on host performance, ecologists and conservation biologists are most often concerned with the microbiome-associated fitness, referring to an individual's ability to survive, reproductive performance and environmental adaptations responding to perturbations, and support that mapping the microbiota of wild animals could also help inform conservation assessments, monitoring, and management of wildlife in conservation efforts.[5,7,8,25,75]

Moreover, the gut microbiota of wild animals has been proven as a largely untapped but promising resource (i.e., microorganism entities, functional genes, bioactive compounds, etc.) for the discovery of therapeutics and biotechnology applications.[14,23,79–82] For instance, metagenomics analysis on large-scale microbiomes of wild animals (more than 180 species) mapped the diversity and functional landscapes and validated the presence of genes and proteases, capable of metabolizing bacterial toxins, in the gut microbiome of a typical kind of carrion eaters (griffon vultures, *Gyps fulvus*).[14] And functional gene analyses on the gut microbiome of wildlife in captivity identify combating antimicrobial resistance genes against commonly used veterinary antibiotics, as well as resistance to vancomycin, a critical antibiotic in human medicine.[23] Mining the metagenomic data across 53 mammalian species demonstrated that polyketides and nonribosomal peptides are representative of mammals, and the microbiome-derived natural products were associated with cell-cell communication and resistance to inflammation.[80]

However, compared to the human microbiome, which has been extensively studied, the gut microbiome of wild animals has received less focus lagging far behind in either profundity or scope, most of which focusing on those famous protected species.[83]

Gut microbiome of threatened mammals responding to changing environment

Investigating factors that influence the wildlife gut microbiome experiencing rapid environmental change may improve our understanding of the role of the gut microbiota in wildlife health and conservation. Many iconic species of specific traits have been determined as sentinel species for evaluate the gut microbial plasticity in the context of environmental disturbance, such as habitat destruction and degradation, anthropogenic disturbances, and captive environments.[69,71,84–90]

For example, the polar bear (*Ursus maritimus*) is widely acknowledged as a key indicator of Arctic ecosystem health, a model species for studying the effects of climatic and other anthropogenic stressors in the Arctic, and a flagship for environmental change. Declining sea ice has led to a divide in the southern Beaufort Sea polar bear subpopulation such that an increasing proportion of individuals now inhabit onshore coastal regions during the open-water period (“onshore bears”) while others continue to exhibit their typical behavior of remaining on the ice (“offshore bears”). And gut bacterial diversity is significantly higher in onshore bears compared to offshore bears. The most enriched operational taxonomic units (OTUs) abundance in onshore bears belonged to the phylum Proteobacteria, while the most depleted OTUs abundance within onshore bears was seen in the phylum Firmicutes, evidencing that climate-driven changes in polar bear land use are associated with distinct microbial communities.[84]

The Udzungwa red colobus monkey (*Procolobus gordonorum*) is among the most threatened primate species in Africa. Primarily arboreal and highly sensitive to hunting and habitat destruction, they provide a critical model to understanding whether anthropogenic disturbance impacts gut microbiota diversity. Samples from seven social groups inhabiting two forests (disturbed vs. undisturbed) showed a marked diversification across habitats, with gut microbial diversity significantly higher in the undisturbed forest, which may be associated with food plant diversity in natural versus human-modified habitats, requiring metabolic pathways to digest xenobiotics.[85] The gut microbiome of critically endangered black-and-white ruffed lemur (*Varecia variegata editorum*) differed substantially across three classes of occupying habitats including the primary, moderately disturbed, and heavily disturbed forests showing a positive correlation between the overall dietary richness and overall gut microbiota composition.[90]

Beyond those aforementioned correlational observations, emerging causal evidence demonstrates the role of gut microbiome in the environmental adaption and application potential. For example, koalas are among the world’s fussiest eaters, consuming only the leaves of eucalyptus trees—and just a few varieties of eucalyptus at that. In some places, the koala population dwarfs the supply of eucalyptus—but even when the animals are transplanted to areas with abundant food, some die. Experiments suggest that this might be due to an incompatibility between available eucalyptus varieties and the mix of an individual koala’s gut bacteria. Thus, researchers transplanted feces from wild koalas that ate messmate into wild koalas that preferred manna gum. Within 18 days, the microbiomes of the koalas that underwent the procedure were nearly identical to those of the donor animals. A few of the animals that received transplants also seemed more willing to eat messmate. Thus, koala-to-koala fecal transplants might help to expand the types of food available to individual animals, optimize the likelihood of a microbiome-diet match and ultimately increase their chances of survival.[91]

Taken together, environmental disturbance affects the biology and health of animals globally and the gut microbiome may be an important indicator of habitat disturbance in wild mammals, which should not be ignored to conserve threatened species. In return, fecal microbiota transplantation from heterogeneous environments can effectively reshape wildlife microbiomes, offering a promising conservation strategy.

Gut microbiome of threatened species relating to host fecundity in captivity

Most threatened species are kept in man-made settings and captive animals are often healthier and longer-lived than free-living conspecifics.[92] However, for some species the opposite is true.[92] Captive animals are always susceptible to some new threats that they would not experience in their natural habitat, the most important of which is the subfertility and reproductive failure.[93] For example, most captive adult male giant pandas do not mate naturally, so that the conservation breeding program since 1960s has been dependent on artificial insemination to a certain extent.[81,94] The captive population of southern white rhinoceros (SWR, *Ceratotherium simum simum*) is not currently self-sustaining for captive-born females reproductive failure.[95] And captive black rhinos (*Diceros bicornis*) have suffered historically from low and inconsistent reproductive output caused by irregular ovarian activity and obesity.[96,97] What’s more, there are many other charismatic mammals without adequate attention are facing suboptimal natural reproductive performance in captive settings, such as the sun bear (*Helarctos malayanus*) and gray snub-nosed monkey (*Rhinopithecus brelichi*) (Figure 2A).

Significantly, there is increasing evidence demonstrating the impact of the gut microbiome on the regulation of reproductive and metabolic endocrine system in human[99] and support for an associated effect of the gut microbiome on host reproductive performance in wild animals.[98–101] Take the SWR for example, its challenge facing the species is the reproductive failure of the once robust *ex situ* assurance populations due to the reproductive failure of captive-born females (F_1), while many founders (F_0) reproduced.[95] Based on the negative relationship between diet estrogenicity and fertility of captive-born female SWR, Williams et al.[98] integrated parallel sequencing, mass spectrometry, and estrogen receptor activation assays, compared gut microbial communities, fecal phytoestrogens, and fertility of SWR to those of another rhinoceros species—the greater one-horned rhinoceros (*Rhinoceros unicornis*), which consumes a similar diet but exhibits high levels of fertility in captivity, and revealed SWR fertility varies significantly not only with respect to phytoestrogen

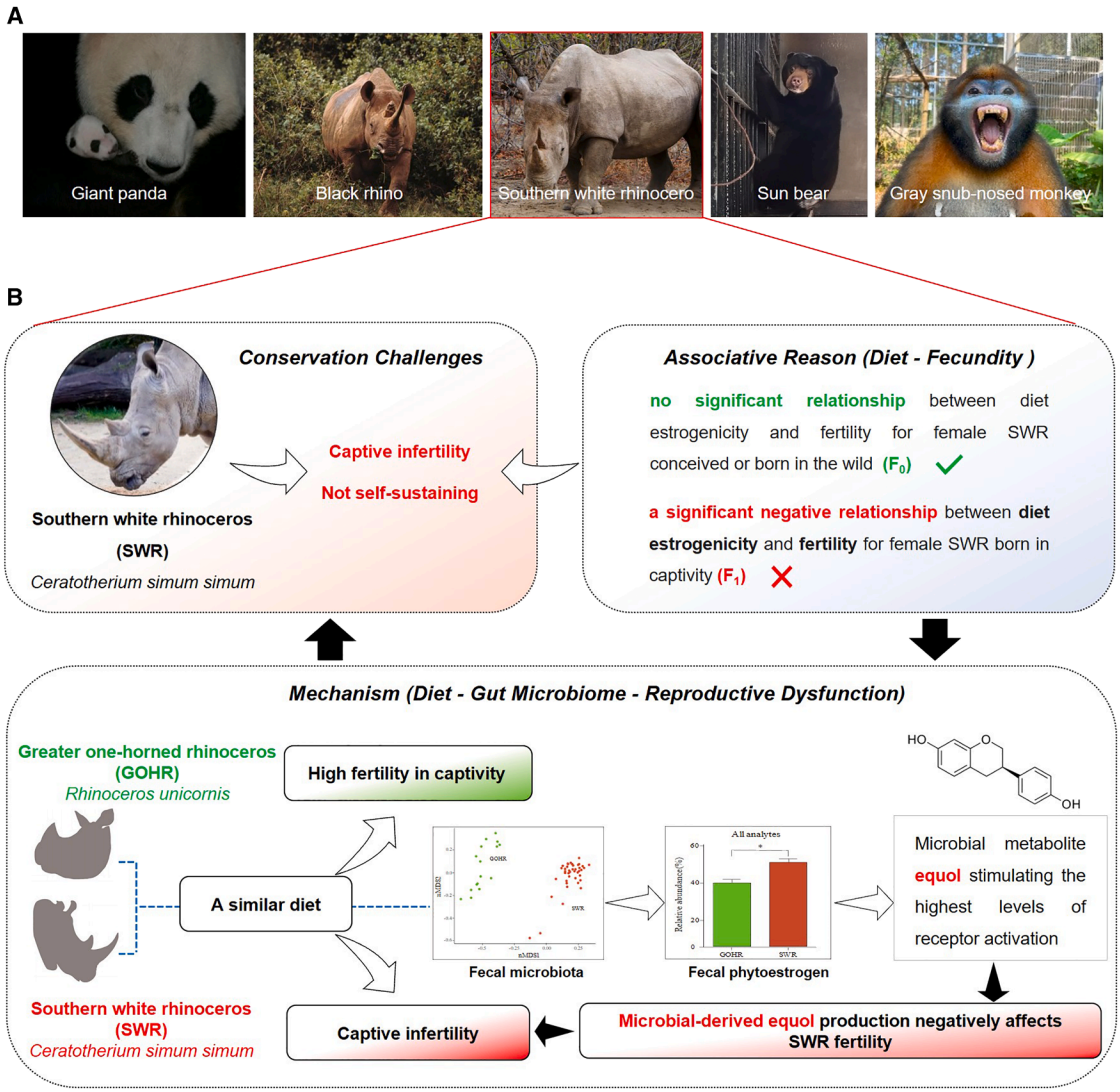

Figure 2. Instances of threatened mammals with poor natural reproductive performance in captivity and a typical case of gut microbiome-related reproductive difficulty

(A) Five instances of threatened mammals with some reproductive disturbances in captivity, including the giant panda (*Ailuropoda melanoleuca*), black rhino (*Diceros bicornis*), southern white rhino (SWR, *Ceratotherium simum simum*), sun bear (*Helarctos malayanus*), and gray snub-nosed monkey (*Rhinopithecus brelichi*), respectively.

(B) A case study of conservation metagenomics on the gut microbiome of a large threatened mammal, which revealed the causal relationship between gut microbial metabolism of dietary phytoestrogen and infertility of captive-born SWR.[98]

profile but also with respect to the abundance of several bacterial taxa and microbially derived phytoestrogen metabolites, suggesting that in addition to species differences in estrogen receptor sensitivity to phytoestrogens, reproductive outcomes may be driven by the gut microbiota's transformation of dietary phytoestrogens in captive SWR females (Figure 2B).

Similarly, the wild black rhino is under considerable threat due to poaching for their horns, with approximately 5,000 individuals remaining in the wild across a highly fragmented landscape (critically endangered), including only 900 of the eastern black rhino (*D. b. michaeli*) subspecies. Examining the relationship between the gut microbiome in wild versus captive populations showed that wild rhinos have significantly different functional bacterial communities compared to their captive counterparts.[102] Research on the relationships between gut microbiota and hormone production of eastern black rhino indicated that many members of the gut microbiome are associated with hormone production and breeding success, and some members of rare microbiota appear to be particularly important, of which four genera (i.e., Aerococcaceae, Atopostipes, Carnobacteriaceae, and Solobacterium) were associated with multiple indicators of reproductive output.[101] Although the directionality of the relationship is unclear, the variation in gut microbiome communities represents a potential biomarker of reproductive health

indicating these could be candidate probiotics to improve the breeding success of black rhino in zoo-based conservation breeding programmes.

Given these cases providing insight into the host-microbe relationship with fertility, advancing our sparse knowledge of the gut microbiome and reproductive physiology is essential for the effective conservation of threatened mammals. The gut microbiome has become an indispensable target that needs to be considered to improve captive animal reproductive health. Further work is required to understand the efficacy and feasibility of this, either directly through microbial augmentation (i.e., probiotics) or indirectly via dietary manipulation or prebiotics.

UNDERSTANDING WILDLIFE GUT MICROBIOME REQUIRES INTEGRATIVE STRATEGIES

Our knowledge of the gut microbiome began with visualization of life forms colonizing the host, advanced to microbial cultivation, and gradually culture-independent approaches.[103–105] It is worth pointing out that advances in DNA sequencing technologies have enabled extensive profiling of composition and function of microbial community. In addition to the sequencing techniques and accompanying analysis tools at the genome level (metagenomics), the rapid development of other omics (such as transcriptomics, proteomics, and metabolomics) and laboratory techniques (such as fecal microbiota transplantation and germ-free mouse model) have convincingly promoted research moving from descriptive microbiota census analyses to cause-and-effect studies in human and model animals.

However, working with wildlife, particularly those threatened and near threatened species, presents its common challenges and species own unique bottlenecks. Firstly, it is almost impossible to collect fresh biological samples for most threatened species in the wild, specifically for those large obligatory carnivorans (e.g., Siberian tiger, *Panthera tigris*), solitary species (e.g., giant pandas), and species living in aquatic environments (e.g., the Yangtze finless porpoise, *Neophocaena asiaeorientalis asiaeorientalis*[106]). Secondly, there are so many kinds of hosts across the animal kingdom, most of which we have a poor understanding of their basic biological properties. The last but the most important, hosts and their microbiomes are complex ecological systems. The role of wildlife gut microbiome in host fitness is a collective effort that makes it exceedingly difficult to reconstruct the driving effects of organism-associated gut microbial communities in lab. Despite these challenges, however, research on the wildlife gut microbiome over the past decade seems to be making headway, providing important insights for the protection of threatened species.[5,75,77] Based on the current progress of conservation metagenomics on wildlife gut microbiome, we propose an integrative strategy with respect to different scales and multiple dimensions, combining with progressive laboratorial methods and top-down multi-omics (Figure 3).

Firstly, the gut microbiome is an intricate ecosystem with extensive interactions between hosts and microorganisms in an ever-changing environment. As discussed previously, the gut microbiome is shaped by both the intrinsic factors of host and extrinsic factors of environment (Figure 1A). Therefore, understanding gut microbiomes of diverse wildlife requires a multi-dimensional perspective with simultaneous consideration of host, gut microbiome, and environment.

Secondly, the gut microbiome is a dynamic system with time and space of different scales. Most research in wild mammals have provided evidence for the temporal changes of gut microbiome composition, as linked with changes in the cycle of natural seasons and associated dietary switching, and demonstrated by an age-related development over a lifetime. Correspondingly, spatial variation of gut microbiome always comes with geographic separation of host populations or habitual migration. One step further, flexible and stable adaptation of gut microbiome only has value in a comparative ecological context. The gut microbiome-host coevolution is accompanied by spatiotemporal trends, which is responsible for fundamental aspects of mammalian biology on the evolutionary scale. Thus, we conceive of the gut microbiome as being in a constant state of change that only has value in a comparative context of temporal, spatial and evolutionary scales.

Thirdly, it is highly recommended that measuring functional composition of the gut microbiome from non-invasive samples, such as feces, which could provide a useful and practical tool for determining conservation priorities as proxies for the distal colon microbiome. On this basis, high-throughput sequencing technologies, such as the next and long-read sequencing techniques and single-cell genomics and RNA sequencing,[107–109] would facilitate the characterization of the gut microbiome with exceptional resolution. Besides, other technologies independent of living wildlife *in vivo*, such as microbial culture *in vitro* (particularly high-throughput culturomics),[110–112] fecal microbiota transplantation, and germ-free animal model,[55,113] have been applied to functional verification of gut microbial community. All these technologies are of great essentiality for dissecting the causal relationship between the gut microbiome and host phenotype with their own advantages.

Finally, the analysis of various omics data, including metagenomics, metatranscriptomics, metaproteomics, and metabolomics, holds great potential for revealing information about microbial composition, functional genes, proteins, and metabolites, enhancing our understanding of the functional outcomes of gut microorganisms and how they interact with the host. Joint analyses of high-throughput multi-omics data, such as fecal metagenomics and fecal metabolomics data, together with host metabolome, measures of host physiology, and mechanistic experiments in animal models, hold potential as initial steps in the identification of potential molecular mechanisms behind reported associations.

Together, we aim to highlight the future intersection of multi-dimension, multi-scale, multi-technologies, and multi-omics in advancing our understanding of the wildlife gut microbiome, which holds promise for improving gut microbiome-targeted conservation in the era of omics, as we unravel the intricate interactions between the gut microbiome and host. Building on this foundation, we recommend developing microbiome banking systems that systematically archive and integrate multi-dimensional biological data (including genomic sequences, transcriptomic profiles, metabolomic signatures, and microbial isolates) from threatened species, thereby creating an essential platform for sustainable conservation science.

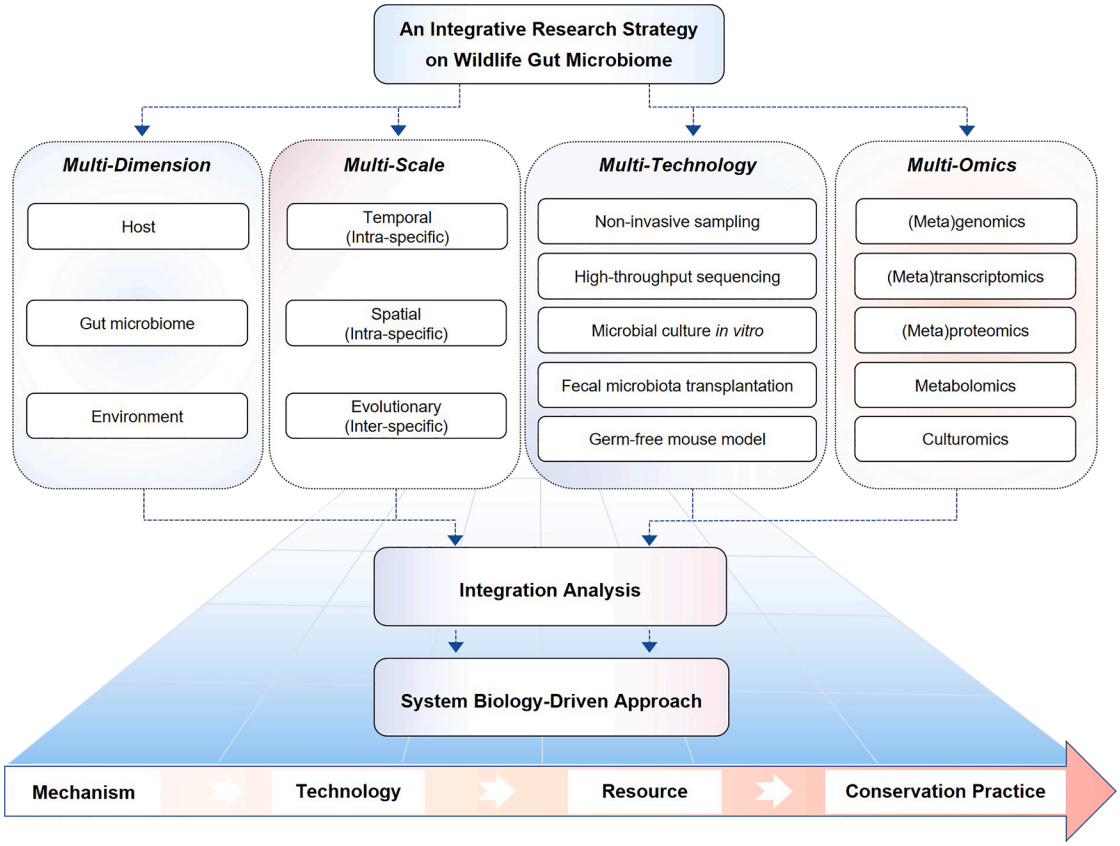

Figure 3. An integrative research strategy illustrating the roadmap for future conservation metagenomics

This figure emphasizes the systematic approach needed for future research. Developing universal principles of host-microorganism interactions depends on a thorough analysis of their eco-evolutionary relationships within defined environments. Elucidating host-microbiome interactions requires innovative technologies: non-invasive sampling, high-throughput sequencing (especially single-cell genomic and RNA sequencing), and metagenome-guided culturomics, etc. Certainly, advanced multi-omics technologies will significantly enhance our ability to decipher the systemic top-down functional architecture.

RESEARCH PARADIGMS BASED ON GIANT PANDAS

In spite of the surge of researches in the wildlife-associated gut microbiome, which play a critical role in influencing a diverse suite of whole-organism functions, there is limited literature on wild animals compared to the large body of research on model species and humans, particularly in the threatened species. The giant panda is the most famous bamboo specialist on earth that evolved from carnivores. It is once threatened by environmental and anthropogenic pressure. But latest data show that the wild population has grown from around 1,100 in the 1980s to nearly 1,900. The global captive population now stands at 757 (https://www.forestry.gov.cn/lyj/1/lcdt/20240126/543787.html). Based on the systematic assessment of population parameters and compared to standardized criteria used by IUCN to determine the status of all species, the IUCN has downgraded the giant panda's status from endangered to vulnerable.[114] Thus, it is irrefutably a conservation success story in the making as the world's most widely recognized conservation icon.[114] Most noteworthy, it is well-known for both its biological uniqueness and conservation plight. These remarkable achievements rely on rapidly advancing conservation science, including the conservation genomics and conservation metagenomics focusing on both the giant panda (its own genome) and its symbiotic microorganisms (the second genome).[115–118]

Looking back at the conservation metagenomics on the giant panda gut microbiome, multiple rapid techniques drive the progressive advancement, along with which research depth spans from descriptive gut microbiota census analysis, to correlation analyses, and to cause-and-effect relationship analyses (Figure 4). As the most famous bamboo specialist within the mammalian order Carnivora, the giant panda possesses a gastrointestinal tract typical of carnivores. This dietary oddity makes it an ideal model to determine the coadaptation of gut microbiota for dietary shift. What's more, it is the comprehensive foundation of behavioral and ecological research on the wild population, precise management of the captive population, and reintroduction attempt of captive giant pandas into the wild, that provide us with opportunities to decipher the compositional pattern, functional mechanism and conservation application potential of the gut microbiome by non-invasive fecal sampling (Figure 4).

Earlier studies on the giant panda gut microbiome rely on the traditional isolation and culture.[119,120] And then, bacterial 16S

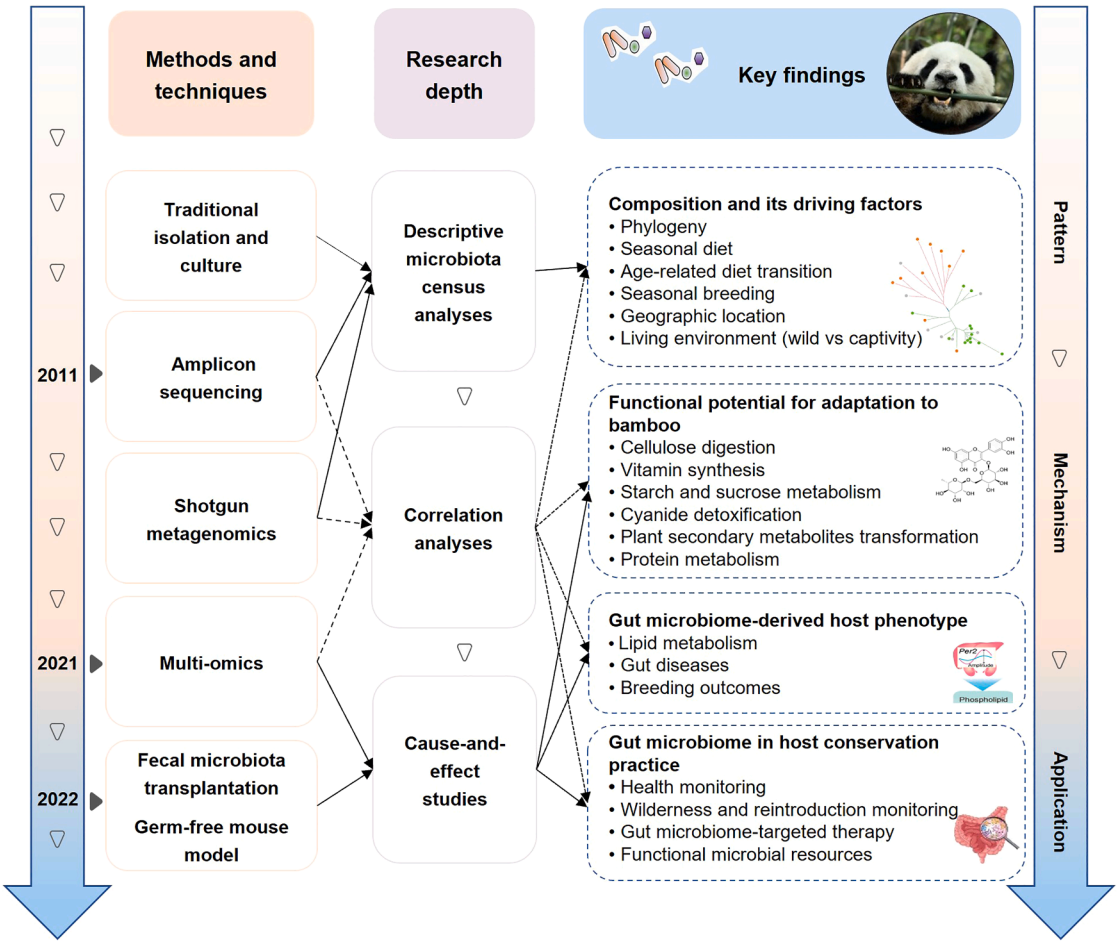

Figure 4. Research paradigms based on the giant panda

This figure traces two decades of progress in conservation metagenomics for the giant panda gut microbiome. It is the integration of multiple advanced techniques that has driven the progressive transformation from basic research to conservation applications.

rRNA sequencing technique is used to sketch the compositional outline of gut bacteria in multiple studies providing taxonomy-related insights, and all these studies revealed the carnivore-like gut microbiota, which is marked different from that of herbivores.[21,121,122] As with all other wildlife, the composition of giant panda gut microbiome is drove by seasonal diet change,[21,63] age-related lifestyle conversion,[123–125] geographic location,[45,124,126] captive living environment[122,126] and so on.

At the functional level, Zhu et al.[122] took the lead in the application of metagenomic approach based on next-generation *de novo* sequencing to identify functional attributes encoded in the gut microbiome. The results uncovered the dominant presence of Firmicutes, a phylum of bacteria with putative genes coding for cellulose and hemicellulose digesting enzymes (i.e., cellulase, beta-glucosidase, xylan 1,4-b-xylosidase), which supplemented the lack of the enzyme homologs needed for cellulose digestion in host genome.[122] In addition to the cellulose degradation, the gut microbiome has also been proven to be of great potential in the detoxification of toxic cyanide compounds (i.e., linamarin, lotaustralin),[127] and extensive biotransformation and enhanced utilization of beneficial secondary metabolites (i.e., bamboo flavonoids) in a recent research by integrating multi-omic approaches and *in vitro* culture experiment.[64] Furthermore, animal model systems circumventing the limitations of invasive work, such as fecal microbiota transplantation with germ-free mice, have been considered essential and useful to study the giant panda gut microbiome.[113,128] Germ-free mice receiving giant panda fecal microbiota of different seasons exhibited seasonal marked differences in gut microbiota assemblage and host body mass phenotype similar to those of the giant panda, synchronizing host peripheral circadian rhythm for physiological adaptation to a low-fat diet in the giant panda.[113] Significantly, with advances in long- and short-read sequencing technologies and algorithms to build metagenomic assembled genomes, a large-scale study established a high-quality gut microbiome catalog of the giant panda (pandaGUT), captured the bacterial diversity, function, and resistome landscapes, and provided largely untapped resources for biochemical and biotechnological applications as well as potential intervention avenues for conservation management of wildlife.[45]

More usefully, to protect giant pandas, the *ex situ* conservation breeding program for giant pandas has been implemented since the 1960s. Benefited from the breakthroughs in breeding and raising methods, a self-sustaining captive population has been achieved. However, the conservation management is confronted with new challenges with respect to captivity-associated health problems, of which the abnormal expression of natural mating behavior particularly the subject of growing concern.[81] A latest research showed significant differences in the composition of gut microbiota between two groups of captive male pandas capable and incapable of natural mating, and the capable group had significantly higher abundance of *Clostridium sensu stricto* 1, providing a theoretical and practical basis for further understanding the microbial-associated behavioral degradation mechanisms of giant pandas.[129] In addition, to restore the wild populations, Chinese government runs a giant panda reintroduction program working on releasing captive-born individuals into the wild. After more than 10 years of efforts, reintroduction shows a bright future with new cubs birthed and new genetic material introduced into the local population.[130] With intensive metagenomic monitoring over 10 years of captive giant pandas reintroduced to the wild, the gut microbiome is confirmed as a key monitoring indicator for reintroductions of captive animals with successive ecological adaption.[126]

Finally, the giant panda gut microbiota has been considered as an important microbial resource. Multiple studies have identified some microbial entities from giant panda feces with clear biological functions.[131–137] For example, the giant panda gut harbors a high diversity of lactic acid bacteria.[133,137] The panda-derived *Lactobacillus plantarum* G201683 could alleviate the inflammatory response in dextran sulfate sodium (DSS)-induced panda microbiota-associated mice.[134] Besides, several strains of *Bacillus subtilis* can survive in and adapt well to a high-fiber environment with good cellulose decomposition ability.[132] The *Klebsiella oxytoca* HKOPL1 can degrade cellulose within 72 h[131] and *Clostridium butyricum* 14 administration can attenuate DSS-induced colitis in mice, helping regulate the balance of the intestinal microecology by suppressing immune pathways and enhancing barrier-protective proteins.[136] Concurrently, there are many species of antimicrobial resistance, including *Escherichia coli*, *Enterobacter* spp., *Klebsiella pneumoniae*, and *Enterococcus* spp. isolated from the feces of giant panda.[135,138,139]

Given that so much ground has been gained during the past two decades, it is instructive to bring together a synthesis of significant findings on the conservation metagenomics of giant panda gut microbiome (Figure 4). In this sense, these systematic research and solid achievements have made this flagship of biodiversity conservation as a benchmark species (pacesetter) in the field of conservation metagenomics, providing a scientific paradigm for other threatened mammals.

PROSPECT

The well-being of gut microbiomes of wild animals in their natural habitats has significant implications beyond individual animals to encompass broader consequences for ecosystem health, biodiversity, and the potential transmission of zoonotic diseases to humans.[25,77,140] Therefore, a holobiont-based approach to health and disease evaluation can significantly improve wildlife health management. This systemic perspective also profoundly influences animal husbandry, wildlife conservation, and ecological balance. Gut microbial communities maintain dynamic equilibrium through metabolic interactions, shaping the health of humans, animals, and ecosystems. Such insights can drive innovative techniques, policies, and international collaborations to advance One Health strategies for biodiversity conservation.[140] With the growing knowledge of host-microbiome interactions, the gut microbiome offers a promising opportunity to gain insights into the well-being of animals and has emerged as a novel avenue for conservation effort of threatened wildlife.[6,77] However, as discussed previously, more than 90% of the current studies have only focused on the gut microbiome composition and its driving factors from host and environment. Given the current challenges to manipulate gut microbiomes for better conservation practice of threatened mammals, it is of more necessity to uncover the regulatory mechanisms and potential application for wildlife conservation. Here, we have argued that much more information and functional studies are needed into the direction of conservation metagenomics by using the aforementioned research strategy and referring to the paradigm on the giant panda.

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AUTHOR CONTRIBUTIONS

F.W. and L.W, conceptualization, writing - original draft, and writing - review and editing; G.H., G.L., and S.Y, writing - review and editing.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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