**UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL**

**FACULDADE DE ODONTOLOGIA**

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# FROM HEALTH BOUNDARIES AND GLOBAL SUSTAINABILITY TO THE DEVELOPMENT OF A HEALTHY FERMENTED BEVERAGE

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# From health boundaries and global sustainability to the development of a healthy fermented beverage

Thesis presented to the Postgraduate Program in Dentistry of the Federal University of Rio Grande do Sul as part of the fulfilments for obtaining the doctoral degree in clinical dentistry

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# SUMMARIES

## INTRODUCTION

Following a path, the present thesis begins with the translation of accumulated knowledge from the fields of environmental and planetary health to the health sciences. More specifically, in chapter one we adapt the Planetary Boundaries framework for the human body, providing an integrated perspective upon health. Through that lens, the path is continued, highlighting the power of human health as a driver of urgent necessary societal changes. In chapter two, we provide a Brazilian perspective that enters globally relevant themes, directly or indirectly referring to human health in a context given by the publication of a seminal work entitled “Earth for All”. Rather reaching a tangible checkpoint than an end, this thesis goes forth building upon the proposed paradigm of integrated processes that help to maintain human health. So, in chapter three we present the development of a product carefully elected from a myriad of possibilities for maintaining health in a sustainable and tasty way.

Each of the three above mentioned chapters ends with a scientific article, in quite different formats. The first one encompasses an extensive yet objective description of the integrated processes included in the proposed theoretical health paradigm inspired by the planetary boundaries. Summarized scientific evidences were the building elements of the panoramic scenario presented to reframe and advance the understandings of human health. The second article is a commentary, articulating key concepts presented in the first article within a broader context of global sustainability and humanitarian societal changes using Brazilian data to support our arguments.

The third and final article is a more classical research article that describes the application of a of a strategy of top-down selection of microorganisms from symbiotic microbial cultures followed by the bottom-up construction of a defined microbial consortium, comprising two bacteria and three yeasts, for the fermentation of a honey-based beverage with low acidity, low alcohol content, and no residual sugars. Strategically balancing complexity with controllability, we achieved a good consumer acceptance of the developed beverage, providing the preconditions to future evaluations of the health benefits of its consumption in relation to ultra-processed sugar-sweetened beverages.

OBJECTIVES

Chapter one aims to present a broad yet objective perspective on human health.

Chapter two aims to explore the interplay between health and sustainability.

Chapter three aims to develop a fermented healthy beverage.

# CHAPTER ONE

“To understand the nature of things,
you have to be in the nature.”
Nicole Redvers

## HUMAN MICROBIOME – A MULTITUDE SIDE-BY-SIDE

Life on earth has been studied by several generations of humans and is the only one we know. More recently, technology is advancing on the pursuit of biosignatures in other parts of the universe. But, as mundane as it may look, our human body has been explored by different life forms since early days. And we humans are only now becoming conscious about life of those who inhabit us. To be fair, it is important to cite the work of a dentist and microbiologist who elegantly postulated similar arguments more than fifty years ago in his classic book “Life on Man” (Rosebury, 1969). Dr. Theodor Rosebury was born in London in 1904 and moved with his family to the United States where he received his Doctor of Dental Surgery (DDS) degree at the University of Pennsylvania in 1928. As a researcher, among many other things, Dr. Rosebury contributed with the initial development of the anaerobic chamber, today a common apparatus used for the *in vitro* cultivation of oxygen-sensitive microorganisms (Fine, 2006). One of the main ideas of Dr. Rosebury was that “all life, including microbes, is a single community, and that it would be a good idea to stop thinking indiscriminately of our unicellular companions as repulsive”. Indeed, we live with several commensals (literally meaning to eat from the same table) and they inhabit every landscape provided by our bodies. Some may not be so tolerated nor well controlled by our immune system, but most accompany us till death doing no harm and even helping us to thrive in both good and bad times. However, it is not easy to define the difference between a commensal and a pathogen, the latter being a microorganism that cause disease. Even some of the microorganisms normally associated with diseases, such as the *Helicobacter pylori* that dwells in the harsh stomach environment, have co-evolved with the human host and, overall, might even have a positive impact on it (Falkow, 2006). Still according to Dr. Rosebury, modern humanity is facing an age of fear. Fear of germs, fear of dirt and all related things. In his own words during a radio interview: “cleanliness has become a fetish, and, of course, a very profitable one to certain people. And, so, we've become slaves to it” (WFMT, 1969). Fear of the invisible is something very present in humanity and it is undeniable that some few microorganisms deserve all the precaution and respect. Zoonotic viruses, or viruses that “jump” (during a spillover event) from a non-human animal to a human, dramatically remind us of that fear in a regular basis. Just to cite some dread episodes, the

“Spanish” Influenza pandemic hundred years ago, the Ebola, Chikungunya and Zika outbreaks in the last decade, and the 2019 novel Coronavirus pandemic latterly (Medina, 2018). The point is to give continuity to the human advances and not to remain trapped to old prejudices. In the words of the philosopher “those who cannot remember the past are condemned to repeat it” (Santayana, 1905). The development of vaccines and antimicrobial drugs were major achievements for medicine and it is essential to prioritize hygiene among other things. However, it is also very important to be aware of the presence of our microbial lifelong companions. And just knowing that we are not alone may not be enough in order to promote a good coexistence. In fact, the balance between “cleanliness” and “dirt” is just one tiny face of a very complex dilemma that is ultimately related to health and disease. According to the “Old Friends” hypothesis, our bodies need data in form of a multitude of microbial inputs, which are specially crucial in early life, in order to correctly develop and regulate its immunity (Rook et al., 2013).

## HEALTH – EQUILIBRIUM AND LIFE STYLE

Let us be clean, and so it should be clear: it is not just a matter of obsessive hygiene and cleanliness. In fact, hygiene must be adopted for the prevention of infectious diseases and should not be related to health problems. Much more important for the poor regulation of our immune systems are other lifestyle changes that modern human societies are facing. Less natural environmental exposure, rapid urbanisation, altered diet, excessive antibiotic use (misuse) are some factors that have profound impact on human microbiome and ultimately on human health (Bloomfield et al., 2016). One fascinating aspect of these lifestyle impacts, is that they are not limited to an individual nor to a society, but to entire ecosystems. In other words, the way we live affects the world just as we are affected. So, the equilibrium of several life forms, including our unicellular fellows, is what confers, in a broader sense, the equilibrium of ecosystems (Flandroy et al., 2018). Another important aspect to consider is that the interaction between the human body and the environment is not only mediated by our common known five basic senses, but also via environmental microbial signalling to the immune system (Flandroy et al., 2018). Additionally, the genes within our microbiota are capable of producing several neuroactive compounds in a way that directly affects the unconscious system regulating human behaviour (Dinan et al., 2015).

## ECOCENTRISM – THE MINDSET

Taken together, it seems quite obvious that human health depends on the health of the environment and that we are not completely in charge when it comes to dealing with it. These notions are intrinsic to the “ecocentric” mindset, which is an ecological reaction to the Western well-established egocentric or anthropocentric utilitarian ethics, where humans are supposed to be “masters”, above and in control of the natural world (Merchant, 2006). This discussion of ethics centred not in humans but around the whole biotic community was already proposed by the ecologist Aldo Leopold who argued that: “a thing is right when it tends to preserve the integrity, stability, and beauty of the biotic community. It is wrong when it tends otherwise” (Leopold, 1949). An important remark to update this discussion was beautifully stated by Kenneth Worthy in his book “Invisible Nature: Healing the Destructive Divide between People and the Environment” and deals with the multitude of our microbiome. In his own words: “at the most intimate level of your own body, you yourself are a community of living organisms. The boundaries of the human self are thus decidedly porous: we're all members of the larger community of life and each of us is a community of life” (Worthy, 2013). These philosophic points of view are in the background of the observation that humanity has achieved several benefits with the technological developments of the last centuries at the expense of a high portion of the natural world. And being part of the natural world, humanity has a price to pay as well. Modern society is out of balance when it comes to health. Chronic low-grade inflammation is so normal that the equilibrium must be restored with large-scale actions upon the environmental driving forces that are able to modulate the microorganisms which are essential to our physiology, which have co-evolved with us (Broussard & Devkota, 2016).

## ONE LIFE – ONE WORLD, ONE HEALTH

As proposed in the “Gaia hypothesis”, the true boundary of life is not the membrane of a cell nor the skin of an individual, but the outer space. And diversity of life is both a consequence and a driver of biosphere homeostasis (Lovelock & Margulis, 1974). Unfortunately, the evidence is crystal-clear: biodiversity loss by human activities affects current and future generations (IPBES, 2019). Already in 1992, at Rio Earth Summit, government leaders signed the Convention on

Biological Diversity (CBD) in order to promote sustainable development (CBD, 2000). And in 2010, 20 targets to be achieved at the latest by 2020, known as the Aichi Biodiversity Targets, were established by governments of the world having as vision that “by 2050, biodiversity is valued, conserved, restored and wisely used, maintaining ecosystem services, sustaining a healthy planet and delivering benefits essential for all people” (CBD, 2010). Yet, just as with climate change, most of the global common goals were not met (CBD, 2020). The post-2020 global biodiversity framework is currently under construction and will have to deal with this matter in an urgent and innovative way. Ironically, the 2020 UN Biodiversity Conference, that should take place in China, was rescheduled because of the COVID-19 and gained a virtual format. The pandemic that started in the same country reminds us that the CBD vision of living in harmony with nature by 2050 is indeed necessary. According to Sir Robert Watson, chair of the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES), this moment is “a critical milestone to see whether there is the political will to implement the transformative changes needed. The challenge is immense, but can be met if countries act individually and collectively” (Watson, 2019). There is no way to think in human health without thinking in these topics. Human and other animals are part of the environment and therefore their health is interconnected and interdependent. This is the cornerstone of the “Eco Health” and “One Health” approaches (WHO & CBD, 2015). The relation between climate change and health is also evident, where both direct impacts, such as storms, floods, droughts, heatwaves and wildfires, and indirect impacts, such as land use and ecological change, interfere with both environmental and social determinants of health. Therefore, the Paris Agreement, that clearly state the aim to hold the increase in the global average temperature to well below 2°C above pre-industrial levels and pursuit to limit the temperature increase to 1.5°C, is one of the greatest health agreements of this century (UNFCCC, 2015; WHO, 2018).

**ARTICLE 1**

**Title**:

Health Boundaries: a framework for the human holobiont

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# CHAPTER TWO

“To be a philosopher is not merely to have subtle thoughts,
..., but so to love wisdom as to live according to its dictates”
Excerpt from “Walden”
by Henry David Thoreau

## EARTH FOR ALL – AND HEALTH FOR ALL

The paradigm of human body as a planet provides plenty of space to rethink health in a broader context. But first, let us remind that who we are today comes from what we were in the past. It is undeniable that humanity has changed intensely since the beginning of the Holocene. And that we are now condemned to mitigate anthropogenic damages, exponentially amplified after the Industrial Revolution and mostly generated on a global scale with the “Great Acceleration”, after the mid-1950s. So, in the Anthropocene, we and future generations have no choice but to live within planetary boundaries (Steffen et al., 2015). Therefore, systemic changes need to take place in order to move societies away from the linear economic paradigm, focused on growth at all costs, to a well-being economy, focusing on human needs while acknowledging planetary boundaries. In this context, health might be a protagonist, driving and accelerating the turnarounds proposed by the Earth for All initiative (Dixson-Declève et al., 2022).

**ARTICLE 2**

**Title:**

Earth for All and Health – five turnarounds and their health impact: a commentary based on Brazilian data

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# CHAPTER THREE

“What seems natural to us
is probably just something familiar
in a long tradition that has forgotten
the unfamiliar source from which it arose.”
Martin Heiddeger

## DENTAL BIOFILMS – ECOLOGICAL PERSPECTIVE

Just as the environmental processes of the Earth were deeply modified by human activity, so are the processes in our bodies. At least in relation to our evolutionary history. To live within health boundaries demands a comprehensive overview of several aspects of our structure as societies and dynamics as individuals. New strategies, including those targeting oral health, arise therefrom. But first, let us define oral health. According to the World Health Organization (WHO), it is a "state of the mouth, teeth and orofacial structures that enables individuals to perform essential functions, such as eating, breathing and speaking, and encompasses psychosocial dimensions, such as self-confidence, well-being and the ability to socialize and work without pain, discomfort and embarrassment". WHO also acknowledges that it "varies over the life course from early life to old age, is integral to general health and supports individuals in participating in society and achieving their potential" (WHO, 2022). Biologically, considering the most prevalent oral diseases, most of what we understand as oral health maintenance arises from the condition of *eubiosis* between polymicrobial oral biofilms and oral tissues. In other words, the control of oral diseases related to polymicrobial biofilms usually involves mechanical plaque control associated with chemicals that have antimicrobial and/or antiplaque properties and agents that interfere with the mineral balance in the tooth/biofilm interface. In evolutionary terms, periodic biofilm disruption was a consequence of chewing raw or minimally processed foods. And evidently, eubiosis is not only related to avoiding excessive biofilm accumulation. Other health-related processes need to be considered, as explored in article 1. As the mouth has a relatively easy access in relation to other body locations, what makes it a good location for microbiome research, a lot of new evidences are allowing a better understanding of the oral cavity specificities. This should contribute for the development of nature-based solutions, which could effectively maintain or restore the host-microbial interface homeostasis. Just to exemplify the idea of homeostasis, most of us have some commensal bacteria with inhibitory activity against potentially deleterious microorganisms (Burton et al., 2013). This idea of inverse abundance between "good" and "bad" microorganisms based on interrelationships and environmental conditioning implies that commensals can promote the development of healthy biofilms (Bowen et al., 2017). Although based on an anthropocentric point of view, where

microorganisms play a dichotomic role in relation to the host, this exemplified idea of equilibrium is also well-suited in an ecological perspective.

## BIOFILM METABOLISM – AND DIET

Even with the health boundaries framework in mind, where processes are not completely independent, is difficult not to give a special room for diet in our physiology. When we focus on oral biofilms, this inclination still accurate. As expected in heterotrophic communities, biofilm metabolism depends on diet. When we talk about diet in relation to oral biofilms, it is vital to emphasize that human cells provide most of the microbial nutrition. Mainly through filtered blood present in the gingival sulcus or secreted by the salivary glands. Direct presence of foods in the oral cavity is far from irrelevant. Indeed, when we are talking about refined fermentable carbohydrates, it becomes especially relevant as a driver for *dysbiosis*. Healthy food, the other side of the coin, is not a panacea that can heal diseases as a miracle. Though having active properties that can alter the metabolism of organisms, several foods frequently only act as simply tasty tonics, sometimes enhanced by fermentation to provide nutrition in a living form. Even *functional foods*, which may be similar to conventional ones, but are designed to go beyond basic nutritional functions, are not a silver bullet against pathologies. Still, as Dr. Carlos Monteiro says: “people need nourishing food that promotes health, not the opposite” (Monteiro & Cannon, 2022).

## DENTAL CARIES – THE BLANK PIECES

Dental caries is a biofilm-mediated, sugar-driven, multifactorial, dynamic disease characterized by progressive dental hard tissues demineralization (Pitts et al., 2017). However, there is no precise cutting point for the presence or absence of the disease since the pH fluctuations derived from biofilm metabolism lead to an ongoing physiological process of continuous mineral loss and gain at the interface between the dental biofilm fluid and the tooth surface (Manji et al., 2018). Therefore, the use new strategies to monitor and manage dental caries is very important to preserve tooth structure, rather than repair it with artificial materials (Pitts et al., 2017). The pursuit for understanding the properties of microbial communities compatible with health have driven investigations focused on biofilm metabolism. Promising therapy strategies arise from this important field. One of them is tempting to enrich the alkali production within microbial communities in

order to control the acidification of dental biofilms. The development of ecological therapies based on microorganisms is recent and encouraging. Not forgetting environmental and host-related risk factors that must be modified and included in these long-term therapeutic strategies (Hoare et al., 2017).

## PROBIOTICS – THE HIDDEN HEROES

Despite the long and inevitable tradition of eating microorganisms with fermented food, the story of probiotics is a much more recent one. In the beginning of the 20$^{th}$ century, the Nobel laureate Elie Metchnikoff, at that time director of the Pasteur Institute, postulated in his writings about human longevity that as far as the microbes living in our gut depend on the food we eat, it would be possible to replenish those that are useful to us, especially those lactic acid bacteria that could combat the harmful effects of other microorganisms in the gut. He also argued that the use of pure cultures of microbes could give a more controlled result, and that a Bulgarian yogurt made with a pure culture of lactobacilli could be consumed at a regular basis to prolongate life (Metchnikoff, 1908). The use of bacteria to resolve disturbances of the intestinal microbiota has been studied and documented over a long period. Not only bacteria are valuable in the treatment of diseases. Yeasts, such as *Saccharomyces boulardii,* can also improve the resolution of acute diarrhoea for example (Corrêa et al., 2011). This strain belongs to the species *Saccharomyces cerevisiae* and was isolated in 1923 from lychee (*Litchi chinensis*) and mangosteen (*Garcinia mangostana*) fruits in Vietnam by the French microbiologist Henri Boulard, who observed that the local population consumed a beverage made with these fruits to stop or prevent diarrhoea (McFarland & Bernasconi, 1993). In fact, the relation between medicine and plants exists since ancient times. But microorganisms provided modern medicine with plenty of new bioactive molecules, most of them also known as secondary metabolites, that can be effective therapy compounds (Traxler & Kolter, 2015). Microbial interaction can increase their biological activity, mainly through the induction and combining of metabolic pathways, resulting in increased yields of secondary metabolites (Pettit, 2009).

**ARTICLE 3**

**Title**

Development and consumer acceptance testing of a honey-based healthy beverage fermented by a defined microbial consortium

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## FINAL CONSIDERATIONS

This thesis provided theoretical basis for understanding human health by linking different scales and opening a new comprehensive path of associations between the planet and the human body. Brazilian data was used to support the role of health as a driver of the systemic societal changes pointed out by the sustainability movement. And the development and consumer acceptance testing of a healthy fermented beverage proved to be one of the countless possibilities opened by the proposed paradigm. The application of the initial insights into the oral health context, and the efficacy evaluation of the developed beverage might be further explored by future studies.

As mentioned in the introduction, this thesis has followed a unique path, probably just as every other human work does. Complex and uncontrolled factors played with current desires and needs to shape the steps of a journey that began long ago and that we hope will continue for ages. During the recent past, geopolitical instabilities, natural and anthropogenic disasters, pandemic losses and the violence of war converged to inspire different paragraphs in texts that tried to express a sound and relatively conservative interpretation of our contemporary reality to enlighten a brighter future.

In the next few ending pages, besides references exhaustively presented in the scientific articles, some background cited works are listed. Then we present an appendix with a timeline to help the chronological assessment of the dynamic path taken, as well as some documents and images to illustrate some parallel scientific production. Finally, we present a glossary with key concepts displayed in the first article to consolidate terms and intended meanings, and to avoid ambiguous misinterpretations. No conflicts of interest are to be declared other than a deep sense of gratitude for all of those who supported this work at different scales and times.

THESIS REFERENCES


Bloomfield, S. F., Rook, G. A. W., Scott, E. A., Shanahan, F., Stanwell-Smith, R., & Turner, P. (2016). Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspect Public Health*, *136*(4), 213–224-213–224. https://doi.org/10.1177/1757913916650225

Bowen, W. H., Burne, R. A., Wu, H., & Koo, H. (2017). Oral biofilms: pathogens, matrix, and polymicrobial interactions in microenvironments. *Trends Microbiol*. https://doi.org/10.1016/j.tim.2017.09.008

Broussard, J. L., & Devkota, S. (2016). The changing microbial landscape of Western society: Diet, dwellings and discordance. *Mol Metab*, *5*, 737–742-737–742. https://doi.org/10.1016/j.molmet.2016.07.007

Burton, J. P., Wescombe, P. A., Macklaim, J. M., Chai, M. H. C., Macdonald, K., Hale, J. D. F., Tagg, J., Reid, G., Gloor, G. B., & Cadieux, P. A. (2013). Persistence of the oral probiotic Streptococcus salivarius M18 is dose dependent and megaplasmid transfer can augment their bacteriocin production and adhesion characteristics. *PLoS One*, *8*, e65991-e65991. https://doi.org/10.1371/journal.pone.0065991

CBD. (2000). *Sustaining life on Earth: How the Convention on Biological Diversity promotes nature and human well-being*. Secretariat of the Convention on Biological Diversity. https://www.cbd.int/doc/publications/cbd-sustain-en.pdf

CBD. (2010). *Decision adopted by the conference of the parties to the convention on biological diversity at its tenth meeting*. https://www.cbd.int/doc/decisions/cop-10/cop-10-dec-02-en.pdf

CBD. (2020). *Global Biodiversity Outlook 5*. https://www.cbd.int/gbo5

Corrêa, N. B. O., Penna, F. J., Lima, F. M. L. S., Nicoli, J. R., & Filho, L. A. P. (2011). Treatment of acute diarrhea with Saccharomyces boulardii in infants. *J Pediatr Gastroenterol Nutr*, *53*, 497-501. https://doi.org/10.1097/MPG.0b013e31822b7ab0

Dinan, T. G., Stilling, R. M., Stanton, C., & Cryan, J. F. (2015). Collective unconscious: how gut microbes shape human behavior. *J Psychiatr Res*, *63*, 1–9-1–9. https://doi.org/10.1016/j.jpsychires.2015.02.021

Dixson-Declève, S., Gaffney, O., Ghosh, J., Randers, J., Rockström, J., & Stoknes, P. E. (2022). *Earth for All: A Survival Guide for Humanity*. New Society Publishers. https://www.earth4all.life/

Falkow, S. (2006). Is persistent bacterial infection good for your health? *Cell*, *124*, 699–702-699–702. https://doi.org/10.1016/j.cell.2006.02.004

Fine, D. H. (2006). Dr. Theodor Rosebury: grandfather of modern oral microbiology. *J Dent Res*, *85*, 990–995-990–995. https://doi.org/10.1177/154405910608501103

Flandroy, L., Poutahidis, T., Berg, G., Clarke, G., Dao, M.-C., Decaestecker, E., Furman, E., Haahtela, T., Massart, S., Plovier, H., & others. (2018). The impact of human activities and lifestyles on the interlinked microbiota and health of humans and of ecosystems. *Sci Total Environ*, *627*, 1018–1038-1018–1038. https://doi.org/10.1016/j.scitotenv.2018.01.288

Hoare, A., Marsh, P. D., & Diaz, P. I. (2017). Ecological therapeutic opportunities for oral diseases. *Microbiol Spectr*, *5*(4). https://doi.org/10.1128/microbiolspec.BAD-0006-2016

IPBES. (2019). Summary for policymakers of the global assessment report on biodiversity and ecosystem services of the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. 56. https://doi.org/10.5281/zenodo.3553579

Leopold, A. (1949). *A Sand County Almanac and Sketches here and there*. Oxford University Press.

Lovelock, J. E., & Margulis, L. (1974). Atmospheric homeostasis by and for the biosphere: the gaia hypothesis. *Tellus*, *26*(1-2), 2-10. https://doi.org/10.3402/tellusa.v26i1-2.9731

Manji, F., Dahlen, G., & Fejerskov, O. (2018). Caries and periodontitis: contesting the conventional wisdom on their aetiology. *Caries Res*, *52*(6), 548-564. https://doi.org/10.1159/000488948

McFarland, L. V., & Bernasconi, P. (1993). Saccharomyces boulardii. A review of an innovative biotherapeutic agent. *Microb Ecol Health Dis*, *6*(4), 157-171. https://doi.org/10.3109/08910609309141323

Medina, R. A. (2018). 1918 influenza virus: 100 years on, are we prepared against the next influenza pandemic? *Nat Rev Microbiol*, *16*(2), 61-61. https://doi.org/10.1038/nrmicro.2017.174

Merchant, C. (2006). The scientific revolution and the death of nature. *Isis*, *97*(3), 513–533-513–533. https://doi.org/10.1086/508090

Metchnikoff, E. (1908). *The Prolongation of Life*. GP Putnam's Sons.

Monteiro, C. A., & Cannon, G. (2022). The trouble with ultra-processed foods. *BMJ*, *378*, o1972. https://doi.org/10.1136/bmj.o1972

Pettit, R. K. (2009). Mixed fermentation for natural product drug discovery. *Appl Microbiol Biotechnol*, *83*, 19-25. https://doi.org/10.1007/s00253-009-1916-9

Pitts, N. B., Zero, D. T., Marsh, P. D., Ekstrand, K., Weintraub, J. A., Ramos-Gomez, F., Tagami, J., Twetman, S., Tsakos, G., & Ismail, A. (2017). Dental caries. *Nat Rev Dis Primers*, *3*, 17030-17030. https://doi.org/10.1038/nrdp.2017.30

Rook, G. A. W., Lowry, C. A., & Raison, C. L. (2013). Microbial 'Old Friends', immunoregulation and stress resilience. *Evol Med Public Health*, *2013*(1), 46–64-46–64. https://doi.org/10.1093/emph/eot004

Rosebury, T. (1969). *Life on man*. NewYork: Viking Press.

Santayana, G. (1905). *The life of reason: Vol 1: Reason in common sense*. Dover Publications Incorporated.

Steffen, W., Richardson, K., Rockström, J., Cornell, S. E., Fetzer, I., Bennett, E. M., Biggs, R., Carpenter, S. R., de Vries, W., de Wit, C. A., Folke, C., Gerten, D., Heinke, J., Mace, G. M., Persson, L. M., Ramanathan, V., Reyers, B., & Sörlin, S. (2015). Sustainability. Planetary boundaries: guiding human development on a changing planet. *Science*, *347*(6223), 1259855. https://doi.org/10.1126/science.1259855

Traxler, M. F., & Kolter, R. (2015). Natural products in soil microbe interactions and evolution. *Nat Prod Rep*, *32*, 956-970. https://doi.org/10.1039/c5np00013k

UNFCCC. (2015). *Paris Agreement*. https://unfccc.int/process-and-meetings/the-paris-agreement/the-paris-agreement

Watson, R. (2019). *Biodiversity touches every aspect of our lives – so why has its loss been ignored?* Retrieved March 30 from

https://www.theguardian.com/environment/2019/sep/19/biodiversity-touches-every-aspect-of-our-lives-so-why-has-its-loss-been-ignored
WFMT. (1969). *Dr. Theodor Rosebury discusses his book "Life on Man"*. https://studsterkel.wfmt.com/programs/dr-theodor-rosebury-discusses-his-book-life-man
WHO. (2018). *COP24 Spetial Report - Health and Climate Change*. https://apps.who.int/iris/bitstream/handle/10665/276405/9789241514972-eng.pdf
WHO. (2022). *WHO Discussion Paper: DRAFT GLOBAL ORAL HEALTH ACTION PLAN (2023-2030)* (12 August 2022 ed.). World Health Organization. https://www.who.int/publications/m/item/who-discussion-paper-draft-global-strategy-on-oral-health
WHO, & CBD. (2015). *Connecting Global Priorities: Biodiversity and Human Health - A State of Knowledge Review*. https://www.who.int/publications-detail/connecting-global-priorities-biodiversity-and-human-health
Worthy, K. (2013). *Invisible Nature: Healing the Destructive Divide between People and the Environment*. Prometheus Books.

THESIS APPENDIX

A timeline and some attached documents and images are in this appendix to present some professional and scientific production during the doctorate period.

**TIMELINE**

01.11.2017–01.12.2017 → research project initial proposal (PPGODO UFRGS)
26.02.2018–02.03.2018 → project development (Summer School UFRGS)
08.03.2018 → doctorate admission (PPGODO UFRGS)
08.03.2018–13.12.2019 → research project improvement (PPGODO UFRGS)
18.06.2018–18.06.2019 → business pre-incubation (IECBiot UFRGS)
12.09.2018–12.12.2018 → innovation management training (NAGI-UFRGS)
01.02.2019–03.09.2019 → *Mykes* trademark development (FABICO UFRGS)
22.08.2019–25.08.2019 → sensory analysis training (Dutcosky UCS)
17.09.2019–17.11.2019 → LAB12 trademark development (UTOPIA)
21.09.2019–05.10.2019 → sensory analysis workshop (UTOPIA)
17.11.2019–24.11.2020 → trademarks registration granted (INPI)
17.07.2020–04.06.2022 → Book chapter writing (MANOLE)
28.08.2020–05.10.2020 → entrepreneurship program (SaBio-UFCSPA)
02.10.2020–25.11.2020 → international project development (PRINT UFRGS)
08.04.2021–25.07.2022 → meta-analysis on probiotics and caries (Feldmann)
01.11.2021–30.04.2022 → academic exchange (PRINT UFRGS / DKFZ)

Business pre-incubation

INCUBADORA EMPRESARIAL DO CENTRO DE BIOTECNOLOGIA

Porto Alegre, 18 de junho de 2018.

**EDITAL 01 IECBiot/ 2017-2018 – PROCESSO SELETIVO 2018/01**
**RESULTADO FINAL**

A comissão de seleção da Incubadora Empresarial do Centro de Biotecnologia da Universidade Federal do Rio Grande do Sul (IECBiot/UFRGS), no uso de suas atribuições, homologa o resultado final do Edital IECBiot/2017-2018 – processo seletivo 2018/01, com os dois empreendimentos aprovados para a pré-incubação.

| EMPREENDEDOR | NOTA |
|---|---|
| Camila Corrêa Vargas | 9,67 |
| Gustavo Eidt | 8,17 |

Atenciosamente,

Prof. Dr. **Giancarlo pasquali**
Diretor da IECBiot
Prof. Dr. Giancarlo Pasquali
Diretor da Incubadora Empresarial
do Centro de Biotecnologia
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# CERTIFICADO

Certificamos que

***Probiotika***

Participou do Programa Rota da Inovação, do Núcleo de Apoio à Gestão da Inovação da Universidade Federal do Rio Grande do Sul (NAGI-UFRGS), no período de setembro a dezembro de 2018.

Porto Alegre/RS, 12 de dezembro de 2018.

Marcelo Lubaszewski

Diretor do Zenit – Parque Científico e Tecnológico da UFRGS

Realização

Apoio

Sensory analysis workshop

# 05.10.2019

**ENDEREÇO – Utopia Biergarten**

Rua Emílio Michel, 719, Venâncio Aires, RS

**PROGRAMAÇÃO**

13:00 – Recepção

13:30 – Teoria (Introdução)

15:00 – Prática (Teste de identificação)

15:30 – Coffee-break

16:00 – Teoria (Métodos)

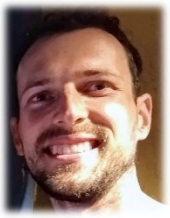
17:00 – Prática (Teste triangular)

18:00 - Encerramento

# ANÁLISE SENSORIAL

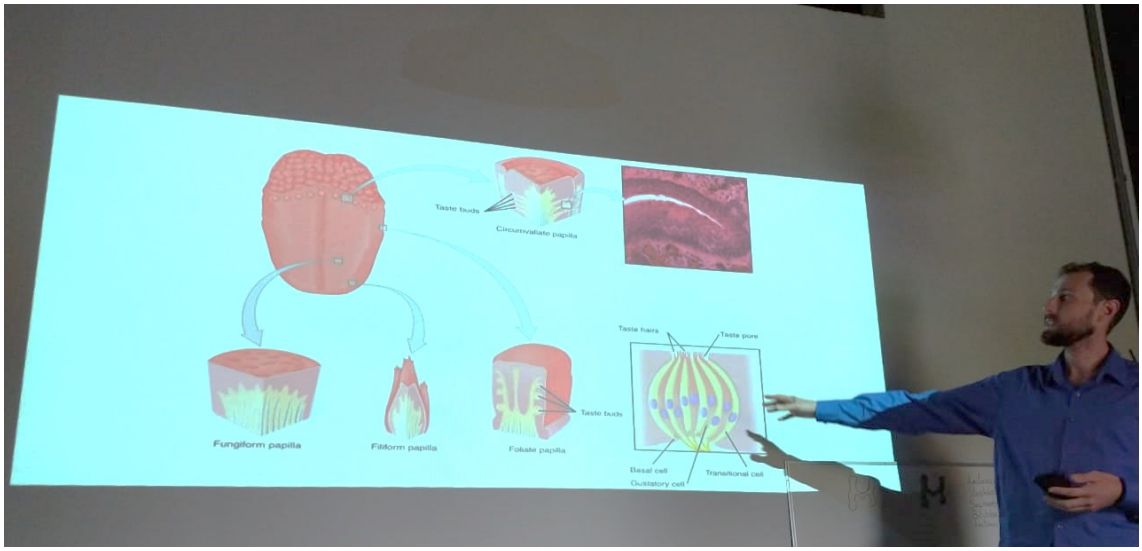
## O ESSENCIAL PARA PRODUTORES DE BEBIDAS ARTESANAIS

**PALESTRANTE:**



**Gustavo Eidt**

dentista, doutorando em clínica odontológica pela ufrgs, produtor e desenvolvedor de bebidas fermentadas artesanais



# Trademarks registration granted

Nº do Processo: **918681340**

Marca: LAB12

Situação: Registro de marca em vigor

Apresentação: Mista

Natureza: Produtos e/ou Serviço

| Classificação de Produtos / Serviços | | |
|---|---|---|
| Classe de Nice | Situação da Classe | Especificação |
| NCL(11) 32 | Vide Situação do Processo | Bebida fermentada não alcoólica;Bebidas não alcoólicas à bas... |

| Classificação Internacional de Viena | | |
|---|---|---|
| Edição | Código | Descrição |
| 4 | 26.3.1 | Um triângulo |
| 4 | 27.5.22 | Monogramas formados por letras enlaçadas, sobrepostas ou combinadas de outra maneira |
| 4 | 29.1.3 | Verde |
| 4 | 29.1.8 | Preto |

| Titulares | |
|---|---|
| | Nome |
| Titular(1): | GUSTAVO EIDT |

Nº do Processo: **919427391**

Marca: Mykes

Situação: Registro de marca em vigor

Apresentação: Mista

Natureza: Produtos e/ou Serviço

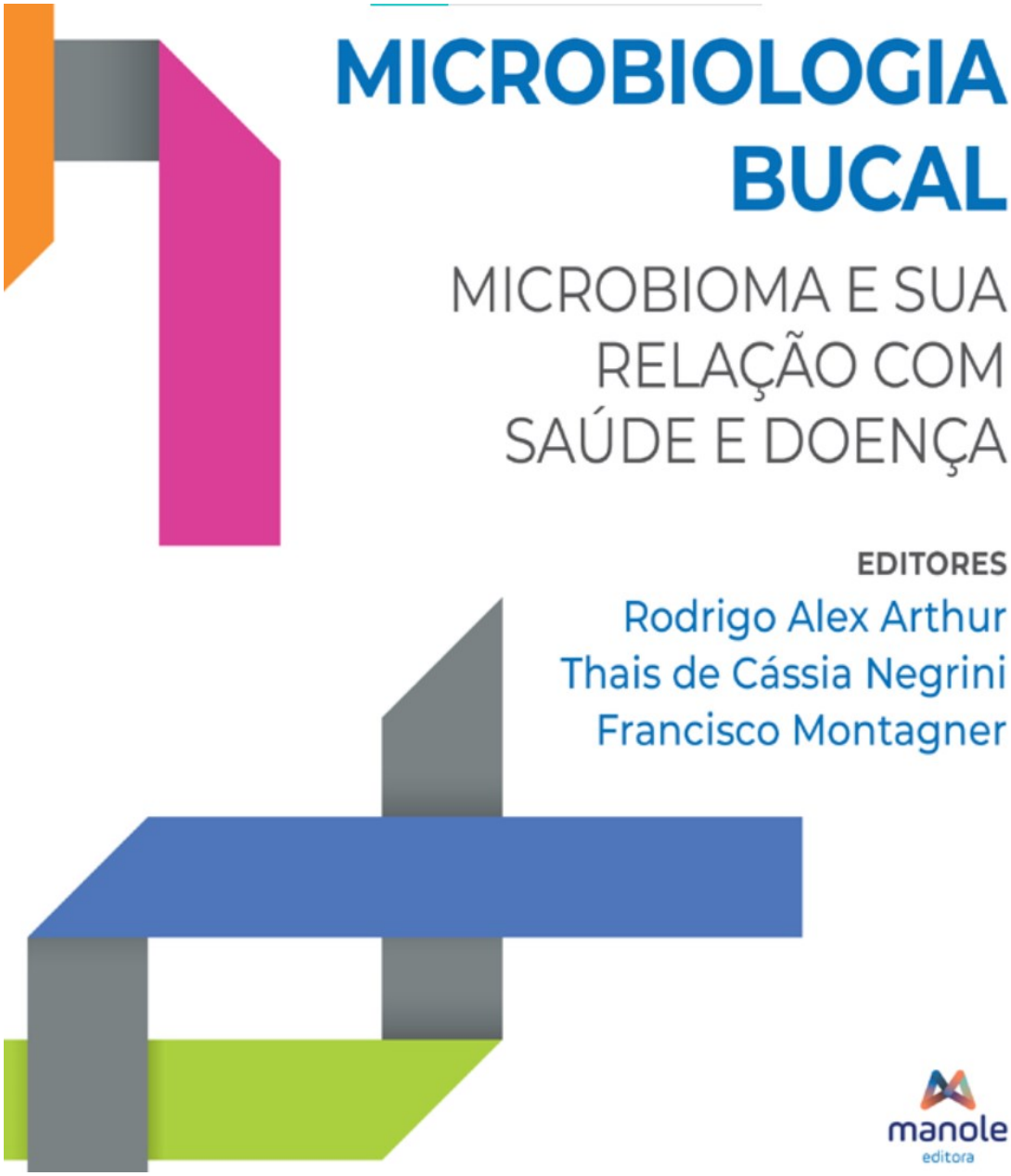
| Classificação de Produtos / Serviços | | |
|---|---|---|
| Classe de Nice | Situação da Classe | Especificação |
| NCL(11) 30 | Vide Situação do Processo | Fermento [lêvedo];Levedura * |

| Classificação Internacional de Viena | | |
|---|---|---|
| Edição | Código | Descrição |
| 4 | 29.1.3 | Verde |
| 4 | 27.5.8 | Letras ligadas a um elemento figurativo |
| 4 | 27.5.1 | Letras apresentando um grafismo especial |

| Titulares | |
|---|---|
| | Nome |
| Titular(1): | GUSTAVO EIDT |

Book chapter writing

ISBN 978 6 55 576206 8




**CAPÍTULO 18**

Uso de prebióticos e probióticos na Odontologia


- Gustavo Eidt
- Heitor Sales de Barros Santos
- Maria Eduarda Lisboa Pagnussatti
- Rodrigo Alex Arthur

Número da ação: 42811

# ATESTADO

O Zenit - Parque Científico e Tecnológico da UFRGS confere a

Gustavo Eidt

o presente certificado pela participação no SaBio Empreendedor, ocorrido de 28/08/2020 a 05/10/2020, com carga horária de 22 horas.

Coordenador(a) do NITE-UFCSPA

Coordenador do Projeto de Extensão UFRGS

Diretor(a) do ZENIT- UFRGS

SaBio Empreendedor

UFRGS UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

UFCSPA

ZENIT PARQUE UFRGS

IECBiot Incubadora Empresarial do Centro de Biotecnologia UFRGS

ESCOLA DE ADMINISTRAÇÃO

ESCOLA DE ENGENHARIA UFRGS

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IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

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Heidelberg, 07/06/2022

**Regarding: Advisor´s reference for Gustavo Eidt on the work developed in the Radiooncology/ Radiobiology Division, DKFZ, Germany 11/2021 – 04/2022**

Gustavo Eidt came to Heidelberg in November 2021 to work on his research project entitled: "Dental caries, periodontal diseases and oral cancer: microbiome interrelations". Due to Covid19 pandemic restrictions, the patient influx was compromised. Therefore, sample acquisition was hampered. Gustavo went to the Universitätsklinikum Düsseldorf (UKD) to personally follow the planned workflow of sample acquisition and meet the personal to discuss some practical details of the research. With the help of the research fellow Dr. Renan Cavalheiro Langie, clinical samples from two patients were taken. However, in order to meet the sample size requirement during the already extended research schedule, we are currently making a research partnership with the Hals-Nasen-Ohrenheilkunde (HNO) at UKD and a Grant submission at Deutsche Krebshilfe (DKH).

In order to exploit his academic stay in Heidelberg, Gustavo also took part in the research project entitled: "The role of SOX2 and SOX9 as regulatory genes of the head and neck squamous cell carcinoma microenvironment", working together with PhD student Silvia Barbosa and the team of the Radiooncology / Radiobiology division (E220) of DKFZ, especially with the lab technician Mahnaz Bonrouhi. In practical terms, Gustavo became familiar with the *in vitro* cultivation of epithelial cancer cells already in November and December 2021. Gustavo also worked in optimizing the doxycycline-inducible SOX9 silencing protocol, exposing (for 24, 48 or 72 hours) genetically modified cell lines (HNO223 shSOX9), as well as the Wild Type (HNO223), to culture medium with two different concentrations of doxycycline (1mg/mL and 500µg/mL) and also to culture medium without doxycycline (control). To analyse the results of these experiments (performed in triplicate), Gustavo quickly learned how to perform the Western Blot technique. Based on the identification and

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quantification of proteins, the concentration of 1mg/mL doxycycline for 72 hours was defined as the protocol for the next experiments.

In addition, Gustavo could learn how to analyse the efficacy of the gene silencing induction through confocal microscopy, once the genetic modification did also incorporate a sequence for Green Fluorescence Protein (GFP), that is expressed after doxycycline induction. This know-how was also important for other subsequent experiments, such as the growth evaluation after exposure of these cell to radiation (either in a 10Gy single dose or a 5 times 2Gy fractionated scheme). In this context, Gustavo could also learn how to fix and stain the cell colonies in a Clonogenic Assay to evaluate the impact of SOX9 silencing on the radiosensitivity of these cells.

Finally, Gustavo participated on immunohistochemical staining of epithelial tissue samples using SOX9 markers and on the RNA extraction of the cultivated HNO223 cells for RT-PCR analysis of gene expression after gene silencing and exposure to radiation. All these laboratorial activities were performed during the winter semester of 2021 / 2022, more specifically, from the beginning of November 2021 to the end of April 2022. During this period, Gustavo also participated in the weekly lab meetings, presenting two seminars. The first was entitled "Microbiome in cancer treatement" and was presented on February 8, 2022. The second was on the 22nd of March and was about the main Western Blot results.

Gustavo could also improve his professional skills through the participation in a biostatistics discipline with Prof. Dr. Annette Kopp-Schneider from April 8 to April 26, 2022. And in a career development course entitled "Toolkit1 for PostDocs" with Dr. Alexander Schiller and Dr. Daniel Mertens from March 16 to March 18, 2022. Gustavo participated on the 2nd of February in a seminar about Intellectual Property and on March 29 in the 73rd Heidelberg Grand Round about Inflammation and Cancer.

In conclusion, Gustavo had and used that great opportunity to learn new research techniques while actively contributing with my group. Despite not being able to finish the research on the microbiome interrelations between oral cancer and common oral diseases, such as dental caries and periodontitis, Gustavo continues taking part in project-related meetings to improve the influx of patients in the cohort between UKD and DKFZ. In a near future, Gustavo hopefully will be able to further collaborate with this important research.

Sincerely

Ina Kurth

## GLOSSARY

Terms are ordered by appearance in article 1.

*Holobiont* – an evolutionary ecological unit, comprising microbial species on a eukaryotic host.

*Homeostasis* – a stable state of equilibrium of a system that is dynamically maintained by self-regulating mechanisms in face of external inconstant conditions. Homeostasis is normally associated with, but not restricted to healthy states.

*Resilience* – the amount of disturbance an ecosystem can experience while undergoing change before losing its characteristic functions and structure. While building resilience is crucial to persist healthy, the resilience of disease-associated stable states impairs reversal to healthy states during treatment.

*Anthropocene* – a geological epoch in which the major forces shaping the Earth system are human-driven.

*Holocene* – the geological epoch that started more than 10,000 years ago, after the last ice age, and ended with the Anthropocene. During the Holocene, all human civilizations developed under short-ranged fluctuations of biochemical and atmospheric conditions.

*Syndemics* – aggregated sequential diseases with social/environmental factors that amplify disease burden of each separate disease.

*Global Syndemic* – the syndemic of climate change, obesity and undernutrition on a global level.

*One Health* – an approach that recognizes the health interconnections between humans, non-human animals, and our shared environment.

*Planetary Health* – an approach that recognizes that our civilization depends on a wise stewardship of the planetary natural resources because human health and the health of our planet are deeply linked.

*Planetary Boundaries* – a framework with nine integrated global processes whose boundaries define a safe operating space for humanity to prosper and remain in a Holocene-like state.

*Health Boundaries* – an adaptation of the Planetary Boundaries framework with nine integrated processes at the holobiont level whose boundaries define a safe operating zone for human health.

*Processes* – biophysical subsystems or functions whose continuing changes sustain a bigger system. In the context of Planetary Health, the Earth system is sustained by nine processes: climate change; biosphere integrity; land-system change; novel entities; biogeochemical flows; ocean acidification; atmospheric aerosol loading; stratospheric ozone depletion; and freshwater change. In the context of Human Health, the Holobiont system is sustained by nine processes: diet; biointegrity; nature exposure; physical activities; psychological well-being; social environment; hygiene; pollution; and novel entities.

*Tipping points* – thresholds or critical points from which gradual changes are followed by abrupt, often irreversible changes.

*Catastrophic transition* – the abrupt, often irreversible transition of an ecosystem.

*Ecological shift* – the shift between alternative ecological states.

*Control variables* – variables used to quantify the integrated systemic processes.

*Boundary transgression* – the transgression from the safe operating space into the zone of uncertainty, where progression to high-risk zone implies greater risk of crossing tipping points and reaching catastrophic transitions.

*Empty calories* – caloric energy with little else of nutritional value, coming primarily from foods and beverages rich in refined oils or sugars.

*Planetary Health Diet* – a reference plant-based diet, designed by the EAT-Lancet Commission on Food, Planet and Health, that provides objective targets considering environmental sustainability and human health.

*Great Food Transformation* – the global food systems transformation to benefit the health of the people and of the planet by increasing the consumption of some dietary components, such as fruits, legumes, and nuts, while decreasing the consumption of other dietary components, such as meat and sweeteners.

*Non-communicable diseases* (NCDs) – diseases that are often chronic and not caused by an acute infection.

*Metabolic syndrome* – a state of immune-metabolic alterations, often characterized by abdominal obesity, insulin resistance, hyperglycaemia, dyslipidaemia, and hypertension.

*Metaflammation* – a low-grade chronic inflammation in multiple organs often associated with pathological states.

*Plant-based diet* – a diet based on plant components, such as whole grains, legumes, nuts, tubers, seeds, fruits and vegetables. Plant-based diets might be vegetarian or flexitarian, as the Mediterranean diet, which is a traditional plant-based diet that includes a small amount of animal products.

*Epigenetics* – reversible but often heritable functional genetic changes without altering the DNA sequence. Epigenetic gene expression modulation is crucial for the holobiont adaptability.

*Short-chain fatty acids* (SCFA) – microbial metabolites from the consumption of dietary fibres and starch-resistant food. Acetate, propionate and butyrate are the main SCFAs, and they exert important physiological effects on the holobiont.

*Gut-brain axis* – *a* bidirectional communication axis between the central nervous system and the enteric nervous system, involving the vagus nerve and other components.

*Microbiome integrity* – a malleable functional state of high microbial diversity.

*Symbiotic microbial communities* – communities of microorganisms with a major abundance of commensals that need to be assembled by the holobiont during early life due to their important role in the immune system development.

*α-diversity* – the microbial genetic diversity within the holobiont at a specific location.

*β-diversity* – the microbial genetic diversity between individuals, or between locations. It is a measure of taxonomic dissimilarity.

*Immunosenescence* – the weakening of the immune system related to the aging process and associated with several diseases.

*Site-dependent* – a characteristic of being dependent to a location, due to the activity of specific community members.

*Biogeography* – the geographical distribution of microorganisms over the set of habitats of the host.

*Functional microbiome* – the complex set of interkingdom microbial interactions responsible for the function of the microbiome in the holobiont.

*Ecosystem services* – the direct and indirect services of an ecosystem that contribute to human health and well-being.

*Biodiversity hypothesis* – a hypothesis stating that proper human development depends on the global biodiversity. Therefore, the observed decline of biodiversity might particularly affect the microbial component of the holobiont, increasing disease susceptibility.

*Regenerative systems* – mostly agricultural systems that produce food and other goods while actively restoring and regenerating nature and the involved actors. Regenerative systems are intrinsically ecocentric and nature-based, and they have been employed by indigenous people for thousands of years.

*Health equity* – a public health concept where everyone has conditions to attain integral health, without any avoidable and unfair disparities.

*Biophilia hypothesis* – a hypothesis on which humans have an innate emotional affiliation to other living organisms. Therefore, environmental stewardship and human well-being depend on an intrinsic connection with the natural living world.

*Anthromes* – anthropogenic biomes, or landscape patterns resulting from direct and indirect sustained interactions between humans and ecosystems.

*Zoonotic diseases* – diseases caused by microorganisms that are transmitted from domestic or wild animals to humans. They are also known as zoonoses.

*Green Exercise* – outdoor physical activities in urban green spaces or in natural environments.

*Ultraviolet radiation* (UVR) – electromagnetic radiation of higher energy than light visible to the human eye. The spectrum of UVR ranges from the violet end of visible light (wavelength of 400nm) to the beginning of the X-ray region (wavelength of 100nm). Most of UVR reaching the Earth is emitted by the sun and is absorbed by the stratospheric ozone layer.

*Sedentarism* – minimal levels of physical activities artificially afforded by human exploitation and technological development.

*Metabolic equivalent* (MET) – the resting energy cost, measured as volume of oxygen uptake per body weight per time. One MET is assumed to be 3.5

mL O2/kg/min, and the energetic cost of physical activities can be expressed as MET. For instance, during a vigorous-intensity physical activity of 10 MET, the expected energetic consumption is ten times the energetic cost of rest.

*Physical activity paradox* – a paradox on which leisure-time physical activities might reduce the risk of disease development, while excessive occupational physical activities might actually increase the risk of disease development.

*Body-mass index* – the weight in kilograms divided by the square of the height in meters ($kg/m^2$) of a person. This index can be employed for the categorization of an adult, for instance as underweight (<18.5 $kg/m^2$) or obese (≥30 $kg/m^2$).

*Hypothalamic-pituitary-adrenal axis* – a complex axis involving the hypothalamus, pituitary, and adrenal glands, their respective secreted hormones (corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol), and the hormone receptors. It is a major neuroendocrine stress related system that regulates several physiological and pathological processes of the body.

*Global Burden of Disease* (GBD) – an online open tool to quantify health loss (mortality and disability) from more than 350 diseases, injuries, and risk factors, across locations (195 countries) and over time (1990-present).

*Major Depressive Disorder* (MDD) – a common mental disorder, also known as clinical depression, medically diagnosed through a combination of persisting symptoms.

*Feedback loops* – self-regulation mechanisms that might accelerate a changing process (positive feedback loops) or slow down changes to sustain a stable state (negative feedback loops). In the context of human diseases, feedback loops might accelerate disease progression or impair treatment by sustaining a diseased state. Otherwise, feedback loops might regulate physiological development and health maintenance.

*Social Determinants of Health* (SDoH) – the conditions in which people live that influence health outcomes apart from health care or lifestyle choices. Income, education, housing, social norms, and political systems, are examples of factors and forces that constitute the SDoH.

*Health inequities* – the avoidable and unfair systematic health differences within and between countries or social groups.

*Commercial Determinants of Health* (CDoH) – corporate activities and omissions that positively or negatively impact human health.

*Agency* – actions and capacities of individuals or organizations that might modify the environment of the agent to achieve self-determined goals.

*Structural influences* – the social structures that influence individual and collective action. Structural influences might arrive from patterned power arrangements in economic and political institutions, or from social norms and values.

*Health in All Policies* (HiAP) – intersectoral collaboration in the decision-making process that systematically considers to improve health while generating co-benefits for non-health sectors. HiAP recognizes the interdependency of economic, environmental, and social development.

*Sustainable Development Goals* (SDGs) – 17 interlinked global goals adopted by the United Nations in 2015.

*2030 Agenda* – articulation and call to action to achieve most SDGs targets by 2030.

*Earth for All* – an initiative based on computer-modelling that proposes five extraordinary turnarounds to steer humanity away from social and ecological collapse while delivering the most good for the majority of people. Ending poverty, reducing inequalities, empowering women, and transforming the food and energy systems are the turnarounds enabled by shifting the economic system, from the linear infinite growth illusion to well-being economies that prioritize human basic needs over profits at all costs.

*Universal Declaration of Human Rights* – a milestone document published in 1948 by the United Nations General Assembly that consists of 30 articles recognizing the rights and freedoms of all human beings.

*Universal Health Coverage* (UHC) – the coverage of essential services, from health promotion to health care over the life course, for all people with good quality and without financial hardship.

*Socioeconomic status* (SES) – the status or position of an individual or a group on a socioeconomic scale, based on a combination of factors such as income, educational level, occupation, residence location, and in some societies, ethnics and religion.

*Social capital* – the resources or potential value generated with the support from cohesive social networks. Usually based on cooperation and mutual benefits.

*Social mobility* – the mobility of an individual or a group through a socioeconomic scale or social stratification throughout life course.

*Human Development Index* (HDI) – a summary measure of three dimensions of human development. The value is the geometric mean of normalized indices for life expectancy at birth, mean years of schooling for adults (≥ 25 years), expected years of schooling for children, and the logarithm of gross national income per capita. HDI does not measure inequalities.

*Gini coefficient* – a measure of dispersion that represents economic inequalities within a country or social group. Developed by Corrado Gini, the Gini coefficient is a value ranging from of 0, or theoretical absence of economic inequalities, to 1, or maximal theoretical inequality.

*Safe drinking water, safe sanitation facilities, and hygiene practices* (WASH) – recognized by the World Health Organization and by the United Nations as a human right, universal access to safely managed WASH services is essential to human health, welfare and development.

*Social vulnerability* – the vulnerability or susceptibility of an individual or a social group within an unequal society. The higher the social vulnerability, higher are the disproportional risks and adverse impacts of natural hazards, diseases, and injuries.

*Menstrual health* – a multidimensional concept that recognizes the special needs of girls, women, and all those who experience a menstrual cycle. Menstrual health encompasses access to menstrual management material, hygiene services, and changing privative facilities. As well as basic understanding of the menstrual cycle without discrimination or stigmatization.

*Low-income and middle-income countries* (LMICs) – all countries that are not considered by the World Bank to be high-income countries. As of July 1, 2021, high-income countries were those with annual gross national income of more than USD 12,695 per capita.

*Household air pollution* – air pollution in and around the home, mostly generated by the use of inefficient and polluting fuels and technologies for cooking, space heating and lighting.

*Ambient air pollution* – outdoor air pollution that is well beyond individual control.

*Particulate matter* (PM) – a proxy indicator for air pollution.

*Greenhouse gases* (GHG) – atmospheric gases that contribute to the greenhouse effect.

*Black coal* – part of fine particulate matter emitted when fossil fuels or biomass fuels are burned. Also known as soot, black coal does not last long in the atmosphere.

*Short-lived climate pollutants* (SLCPs) – powerful climate pollutants that remain in the atmosphere for a much shorter period than carbon dioxide. Black coal, methane, hydrofluorocarbons, and tropospheric ozone are important SLCPs.

*Paris Agreement* – international treaty on climate change adopted by 196 Parties near Paris, France in 2015, at the Conference of the Parties (COP21) of the United Nations Framework Convention on Climate Change (UNFCCC). Its goal is to limit global warming to well below 2 °C, preferably to 1.5 °C, compared to pre-industrial levels.

*Plastic pollution* – accumulation of plastics in the environment affecting the biosphere.

*Pollutome* – all forms of pollution combined.

*Drugs* – chemicals that affect the central nervous system, often changing behaviour and causing addiction.

*Overdose epidemic* – increasing cases of drug overdose, often associated with death events and social impacts on communities.

*Summary exposure value* (SEV) – a relative measure of exposure to some risk factor ranging from 0 %, when the entire population is exposed to minimum risk, to 100 %, when everyone is at maximum risk.

*Communicable diseases* – diseases caused by microbial agents that can be transmitted between persons by vectors, contaminated air, water, body fluids, or other means. Also known as infectious or transmissible diseases.

*Heavy episodic drinking* – drinking more than 60 g of pure alcohol, or approximately 6 standard alcoholic drinks, on a single occasion. Also known as binge drinking.

*Artificial intelligence* (AI) – the ability of machines or any artificial device to perform activities that would require animal intelligence, such as learning and thinking.

*Digital ecosystem* – integration of digital data and technology resources into human daily lives, creating an interconnected ecosystem that transcends the digital space.

*Telemedicine* – health care provided remotely. Telemedicine encompasses remote monitoring and remote consultation using electronic devices.

*Cybersecurity* – security or protection of a digital information, system, or device, against unauthorized access or digital attack.

*Computer vision syndrome* – vision-related symptoms associated with prolonged screen time, such as eye strain, blurred vision, and eye dryness.

*Health literacy* – the degree to which individuals or organizations can obtain and understand health information to guide healthy decisions.

*Precision medicine* – an approach that considers individual specificities or disease subtyping to deliver tailored care maximizing benefits and minimizing risks. Also known as personalized medicine.

*Panarchy* – the overall hierarchical organization and structure of complex systems across space and time. Panarchy admits both top-down as well as bottom-up influences across scales over time.

*Interactome* – network of functional molecular interactions within a cell, a tissue, a holobiont, or ultimately, within the biosphere.

*Lifestyle medicine* – a medical specialty whose therapeutics are holistic lifestyle interventions.

*Embodiment* – is the biological incorporation, over the life course, of the material and social world in which we live.

*Purchasing power parity* (PPP) – is an indicator of price level differences across countries, being the theoretical exchange rate that allows to buy the same amount of goods and services with another currency.

*Disability-Adjusted Life Years* (DALYs) – are a measure of total disease burden, being the sum of the years of life lost due to premature mortality and the years lived with disability. One DALY represents the loss of the equivalent of one year of full health.