Brazilian Journal of Global Health 2024; v4 n14 Received in: 01/07/2024 Accepted in: 27/09/2024

BJGH Brazilian Journal of Global Health
Revista Brasileira de Saúde Global

Probiotics, microbiota and air pollution

Giovanna Arena Reis Santos[1], Vitoria da Paixão[1], Roberta Foster[1], Marilia Farrajota[1], Robério Pereira Pires[1], Karina Pantaleão Hilario Silva[1], Francys Helen Damian[1], André Luis Lacerda Bachi[2], Mauro Walter Vaisberg[1]

[1]Federal University of Sao Paulo, Sao Paulo – SP, Brazil.
[2]Santo Amaro University, Sao Paulo – SP, Brazil.

ABSTRACT

OBJECTIVE

The aim of this review is to focus on the effects of using probiotics as a protective factor for various organic systems, especially the respiratory tract, when exposed to air pollution.

METHODS

A narrative bibliographic review of scientific articles published between January and May 2024 in the public health databases SCIELO and PubMed, in Portuguese and English, was conducted, with the following guiding questions: What is the impact of air pollution on human health and the microbiota? What is the role of probiotics in this context? Additionally, the following descriptors were used: air pollution; microbiome; microbiota; gut microbiota; microbiota in respiratory tract; probiotics.

RESULTS

The review first introduces the reader to the main adverse effects of air pollution on human health, with a focus on the respiratory tract. Then, is provided information on the gut and respiratory microbiome and its importance in maintaining health. Finally, we review the literature demonstrating the importance of probiotics in maintaining the gut and respiratory microbiota, particularly their ability to minimize the incidence of inflammatory and infectious diseases.

CONCLUSIONS

The use of probiotics is an important tool for maintaining respiratory health in polluted environments.

DESCRIPTOR

Particulate matter, Microbiome, Microbiota, Bacteria.

Corresponding author:
Giovanna Arena Reis Santos.
Rua Pedro de Toledo, 781, 1st floor, room 03 – ORL LAB, Vila Clementino – Sao Paulo.
E-mail: giovanna.arena@unifesp.br
ORCID: https://orcid.org/0009-0000-8474-9921

DOI:

INTRODUCTION

Air pollution is now considered one of the major public health problems in both developed and developing countries. It has been exacerbated by increasing urbanization, and it is estimated that up to 70% of the population of these countries live in urban areas where anthropogenic pollutants are a major problem. Interestingly, a recent study by Gupta *et al.* (2022)[1] suggests that populations in developing countries already account for a significant number of places exposed to air pollutants[1,2].

It is estimated that millions of deaths each year are a direct result of air pollution. In addition, a significant number of diseases are associated with breathing unhealthy air, affecting virtually all organ systems, particularly the respiratory and cardiovascular systems[3].

Air pollution can be classified in different ways, such as primary if the pollutant originates from the emitting source, or secondary if it is produced by a photochemical reaction in the atmosphere[4,5]. It can also be anthropogenic if it is due to human activities, or non-anthropogenic if it is due to natural factors[4,5]. Given these different classifications, it is important to emphasize that anthropogenic emissions, which include for example the use of fossil fuels, coal, biomass and emissions from refineries, are the greatest threat to health[6].

However, the most important classification of pollutants is related to their characteristics, which can be classified as gas pollution or particulate matter (PM). PM are solid compounds suspended in the air that are small enough to be inhaled[7]. They are classified by particle size, measured in micrometers (µm), into three diameters, PM 0.1, PM 2.5 and PM 10, with the ambient concentration generally expressed in µg/m^3[7].

Human exposure to PM is associated with several respiratory diseases, including chronic obstructive pulmonary disease, asthma and interstitial lung lesions[8]. In addition, PM, especially 2,5, can not only enhance immune responses and inflammation, both locally and systemically[9], but is also considered an important factor that can alter the microbiota towards a pathogenic profile[10].

It is worth noting that while the term microbiota refers to the totality of microorganisms, the term microbiome refers to the totality of genes of these microorganisms inhabiting a given environment, including commensal, symbiotic and pathogenic bacteria that interact with each other and function as an organized community[11].

In this context of interaction between bacteria and the organisms in which they live, a probiotic is defined by the consensus of the International Scientific Association of Probiotics and Prebiotics as "a product containing bacteria that are alive and viable at the time of administration to the host, in the quantity required to effectively benefit those using the product "[12].

There is growing evidence that probiotics have immunomodulatory, metabolic and other health-promoting properties[13].

Although it is clear that air pollution is an important contributor to human health and can even lead to changes in the microbiota, the role of probiotics in this context has been little studied. For this reason, this review focuses on the key findings of this triad - air pollution X microbiota X probiotics - on human health.

METHODS

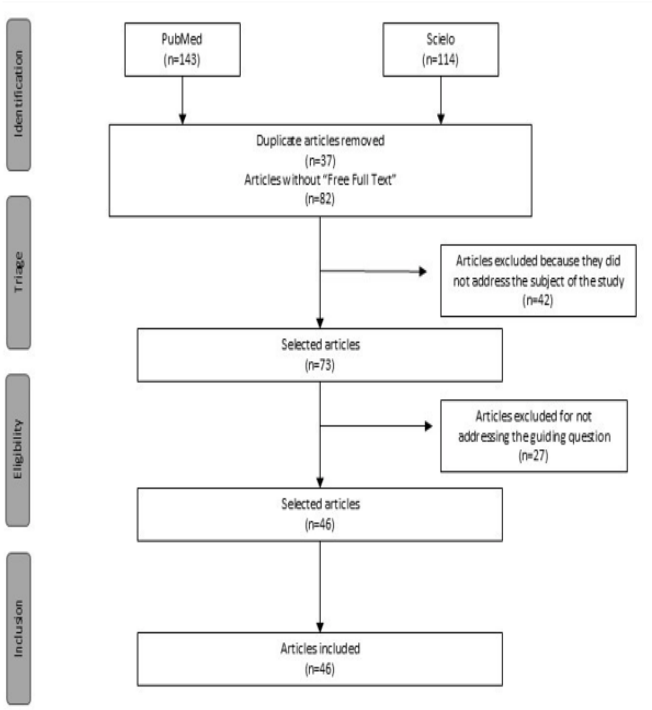
This study is structured as a narrative literature review that provides a critical analysis of the current scientific evidence on the proposed main topic. It will also provide information that will contribute to evidence-based healthcare practice. Five steps were recommended to conduct this study: 1) definition of the topic and the main objective of the study, 2) definition of the inclusion criteria for the studies, 3) definition of the selected studies, 4) methodological assessment of the included studies and 5) interpretation of the main results.

After these steps, and after defining the topic and the main objective of the study, the following guiding questions were formulated: What is the impact of air pollution on human health and the microbiota? What role do probiotics play in this context? On this basis, the following descriptors were used in the study: Air pollution, microbiome, microbiota, gut microbiota, microbiota in respiratory tract, and probiotics. It should be clarified that not only the Boolean operator "AND" was used to combine the descriptors and thus limit the search to articles that dealt with these specified terms, such as "air pollution 'AND' microbiota 'AND' probiotics", but also the Boolean operator "OR" was used to extend the search to include articles that contained any of the specified terms, such as "air pollution 'OR' microbiota 'OR' probiotics".

As this is a narrative review, a bibliographic review was conducted through an online search for scientific articles in the public health databases SCIELO (Scientific Electronic Library Online) and PubMed (National Institutes of Health of the US National Library of Medicine) published between 2004 and 2024. This included original articles as well as systematic reviews and meta-analyses in Portuguese and English in the above-mentioned databases from 2004 to 2024. All data analyses were conducted between January and May 2024.

After searching for articles, 257 articles that met the inclusion criteria were initially selected. However, the following were excluded: 37 articles because they were duplicates, 82 articles without "*free full text*", 42 articles because they did not address the topic of the study and a further 27 studies because they did not answer the guiding questions. Thus, 46 articles were used that fully met the inclusion criteria recommended for this narrative review article according to the flowchart shown in Figure 1.

Figure 1: Flowchart of the article selection process.



Source: Authors (2024).

RESULTS AND DISCUSSION

In a systematic review and meta-analysis, Bont *et al.* (2022)[14] presented evidence of an association between air pollution and various diseases, with PM 2.5 in particular being strongly associated with an increased risk of atherosclerosis, hypertension and stroke[14].

When inhaled, larger diameter PM (>10) are restricted to the upper respiratory tract, while smaller particles (<2.5) can reach the alveoli. PM 2.5 can also penetrate the endothelium of the airways, enter the capillaries and accumulate in the systemic circulation[15]. From the blood, this PM can in turn cross the endothelium and reach various extrapulmonary organs[16].

However, the lungs are still considered to be the organ most affected by pollution and are better characterized in terms of the effects of exposure to PM. In this sense, it has been described that every 10 μg/m³ increase in PM 10 in the air is associated with a 0.58% increase in respiratory mortality, while the same increase in PM 2.5 is associated with a 2.07% increase in hospital admissions for respiratory diseases[17,18].

In mice, exposure to PM 2.5 reduced mitochondrial density, increased expression of NADPH oxidase 2, significantly reduced total lung capacity, inspiratory capacity and lung compliance[19].

It is also important to note that PM 2.5 has a large enough surface area to transport biological material such as viruses and bacteria, as well as chemical substances and metallic compounds that accumulate in the lungs and promote inflammation with potential functional impairment[20].

Therefore, PM, especially PM 2.5, is considered a major environmental stressor and significant threat to public health, as shown by Gupta *et al.*(2024)[20] where a 1 μg/m³ increase in PM 2.5 concentration was associated with a 13.5% increase in serum levels of tumor necrosis factor-alpha (TNF-alpha).

Indeed, it has been reported that PM 2. 5 can enhance immune responses and inflammation by apparently recruiting leukocytes, secreting immunoglobulin E (IgE) and histamine, activating Toll-like receptors (TLRs) 2 and 4, and promoting increases in interleukins (IL) IL-4, IL-5, IL-13 and IL-17, chemokines such as IL-8, ROS, and the production of pro-inflammatory cytokines, IL-4, IL-5, IL-13 and IL-17, chemokines such as IL-8, reactive oxygen species (ROS), lipid peroxidation and the production of pro-inflammatory cytokines, in contrast to the inhibition of cytokines such as interferons (IFNs) and transforming growth factor beta (TGF-beta)[9,21].

In addition to this information highlighting the impact of air pollution on human health, the involvement of the microbiota and probiotics in the same context was also the subject of this review.

Although the exact role of the microbiota and its importance in the process of chronic disease development is still unclear, it is clear that disruption of indigenous microbial populations leads to a proliferation of pathogens and increased susceptibility to infection, which has been demonstrated in both the gastrointestinal tract and the respiratory tract[22].

With regard to the microbiota of the respiratory tract, it should be noted that it depends on factors such as the intrinsic characteristics of the individual, diet and environmental factors. The importance of the microbiota lies mainly in the fact that the loss of its integrity is associated with the proliferation of pathogenic bacteria that cause respiratory diseases with high morbidity and mortality, especially in young adults and children[10].

The nasal cavity is the site of the initial airway defense against inhaled pollutants, and the nasal microbiota also acts as a defense against noxious stimuli, both through the stimulation and mechanical action of the cilia and as a protection against certain pathogens, such as *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis*. In this way, the mechanisms of the immune response at this site serve not only to eliminate microorganisms but also to adapt to the environment[23]. However, although the physiological barriers of the nose are very efficient, many pollutants are not eliminated by the mucociliary barrier or by mechanisms mediated by macrophages, among others, and can be taken up by epithelial cells and translocated to other organs, both via the bloodstream and the lymphatic system[24].

In a literature review, Xue *et al.* (2020)[10] showed that increasing environmental pollution led to a decrease in corynebacteria and an increase in pathogenic bacteria, including *Haemophilus influenzae* and *Streptococcus pneumoniae*.

Several studies in the literature indicate that both the gut and respiratory microbiota play an important role in lung homeostasis[1,25,26], suggesting that the gut microbiota is fundamental to the regulation of human physiology, including respiratory health.

It is important to clarify that the composition of the gut microbiota can be altered by air pollutants, particularly PM 2.5, a factor that has been associated with the development of lung disease due to disruption of the gut-lung axis[27] . In this context, it has been suggested that the gut microbiota can modulate airway homeostasis through the production of molecules known as PAMPs (Pathogens-Associated Molecular Patterns), which migrate from the gut to the lungs and modulate airway immune functions. However, it is worth noting that pollution in itself is a factor that alters the airway microbiota, which in turn leads to changes in the composition and proliferation of pathogenic bacteria[10,28].

Therefore, pollutants that come into contact with the upper respiratory tract, such as pathogens and pollutants from different parts of the body, alter homeostasis by activating the innate immune response and inducing an inflammatory response[29].

Similar to the gut, the upper respiratory tract harbors a very diverse microbiota, including pathogenic, symbiotic and commensal microorganisms, and each environment may have one or more different types of microbiota[29-31].

It is also worth noting that the most abundant 'phylum' in the upper respiratory tract is Proteobacteria, Firmicutes and Bacteroids[31] and this composition can vary according to individual factors such as genetics, diet and advancing age[32].

With this in mind, it is clear that the intake of probiotics not only modulates the composition of the microbiota, but can also provide significant health benefits, particularly through their immunomodulatory and metabolic properties[13].

According to the literature, the effect of probiotics is based on a complex network of signaling pathways that enable an exchange of information between the cells of the immune system and commensal bacteria. Specifically at the gut level, this close communication between the cells themselves and the microbiota favors and maintains the balance between immunological tolerance and immunogenicity, leading to immune homeostasis[33].

It is widely recognized that the immunomodulatory functions of the gut microbiota influence not only the local and systemic immune system, but also the nervous and respiratory systems, thus describing the gut-brain and gut-lung axis. Changes in the microbiota can therefore lead to significant changes in the immune functions of these systems[33].

In addition to these aspects, it is known that colonization of the gut by beneficial commensal microbiota in response to ingestion of probiotics is also able to induce luminal production of secretory immunoglobulin A (IgA), thus enhancing local protection[34,35] and to increase the expression of TLR-2 and the mannose receptor CD206 on the surface of dendritic cells (DC) and macrophages, favoring the stimulation of the adaptive immune response[36].

In the case of pattern recognition receptors such as TLRs, once identified, probiotic agents promote the regulation of key signaling pathways, leading to the release of the transcription factor NF-κB and mitogen-activated protein kinases (MAPKs), resulting in the secretion of cytokines by T cells and the feedback of the innate immune response[36].

Probiotics such as *Lactobacillus helveticus* IMAU70129, *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* KLSD and *Lactobacillus casei* IMAU60214, can stimulate innate immunity, by increasing the phagocytic and bactericidal activities of human monocyte-derived macrophages and reactive oxygen species levels, and enhancing nuclear translocation of the transcription factor NF-κB pp65 and TLR2-dependent signaling[37].

In addition, probiotics can modulate the inflammatory response of non-specific innate immunity[38] by not only stimulating the production of ILs, IFNs, TNF-alpha and growth factors by dendritic cells, lymphocytes, macrophages, mast cells, granulocytes or intestinal epithelial cells[39,40,41] but also by stimulating the production of IL-10 and regulatory T cells (Tregs)[42].

According to the systematic review and meta-analysis by Ebrahimpour-Koujan *et al.* (2020)[43] *Lactobacilus casei* Shirota, both fermentum and rhamnosus, can influence the release of cytokines in saliva and reduce inflammation in the face of environmental pollution[44]. In particular, the study by Aghamohammad *et al.* (2022)[45] showed a decrease in IL-6 production.

It is important to note that it has been reported that PM 2.5-induced lung inflammation can be modulated by probiotics through the gut microbiota, which in turn promotes the action of various protective mechanisms, such as direct neutralization of PM, blocking of oxidative stress and induction of cellular defense mechanisms[20,46].

CONCLUSIONS

It is well known that the study of the microbiota has expanded from the gut to other systems, and in this sense, the respiratory tract as a whole also harbors diverse microbiota, the maintenance of which is important for the respiratory health of individuals. Although environmental pollution is one of the factors associated with microbiota dysfunction in this area of the body, the use of probiotics has been shown to protect the respiratory tract from the development of infectious and inflammatory diseases.

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