

## REVIEW ARTICLE

# The use of antimicrobials as adjuvant therapy for the treatment of obesity and insulin resistance: Effects and associated mechanisms

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**Summary**

The intestinal microbiota has come to be considered an additional risk factor for the development of metabolic diseases. Considering the potential role of antimicrobials as modulators of the intestinal microbiota, they have been investigated for use in the adjuvant treatment of obesity and insulin resistance (IR). In this regard, the present manuscript aimed to review the effect of regular use of antimicrobials on the treatment of obesity and/or IR, as well as its associated mechanisms. The regular use of antimicrobials does not seem to influence the body weight and adiposity of its consumer. Regarding IR, clinical trials did not observe positive effects, on the other hand, most of the experimental studies observed an increase in insulin sensitivity. The mechanisms used by antimicrobials that could lead to the improvement of insulin sensitivity are dependent on the modulation of the intestinal microbiota. This modulation would lead to a reduction in the stimulation of the immune system, as a consequence of improved intestinal barrier and/or the reduction of gram-negative bacteria in the microbiota. In addition, the secretion of glucagon-like peptide-1 would be modulated by metabolites produced by the intestinal microbiota, such as secondary bile acids and short-chain fatty acids. Based on the results obtained to date, more studies should be performed to elucidate the effect of these drugs on obesity and IR, as well as the mechanisms involved. In addition, the cost-benefit of the regular use of antimicrobials should be investigated, as this practice may lead to the development of antimicrobial-resistant microorganisms.

**KEYWORDS**

antibiotics, GLP-1, immune system, intestinal microbiota, metabolic disease

## 1 | INTRODUCTION

Microbiota is a term that originally refers to all commensal, symbiotic, and pathogenic microorganisms that inhabit on the body surfaces of organisms.<sup>1</sup> In this sense, the term intestinal microbiota refers to all bacteria, fungi, yeasts, archaea, viruses, and protozoa that inhabit the intestine.<sup>2</sup>

In healthy adults, the intestinal microbiota can comprise more than 100 trillion microorganisms, hosting 500 to 1000 different species, which are predominantly anaerobic bacteria.<sup>2,3</sup> This enormous

microbial diversity is essential to human health because they produce a variety of compounds and perform metabolic activities, all of which are indispensable for the maintenance of homeostasis. As a result, the intestinal microbiota can be considered an additional organ in our body.<sup>2</sup>

In this way, when there is an imbalance in the composition of the intestinal microbiota, dysbiosis occurs. Dysbiosis strongly influences host susceptibility to chronic diseases, particularly those related to chronic low-grade inflammation, such as obesity and insulin resistance (IR).<sup>1</sup>

In 2004, Bäckhed et al<sup>4</sup> proved for the first time that the intestinal microbiota is capable of increasing the risk of developing obesity and IR. In their experiment, they observed that although the food intake of conventional mice was lower (29% lower) than germ-free C57BL/6J mice, the latter's body fat mass was 42% lower. Furthermore, the conventionalization of the germ-free mice with the intestinal microbiota harvested from the conventional mice led to a 57% increase in body fat mass and IR in a span of 2 weeks, despite a 7% reduction in food intake. Ever since, attempts have been made to identify microorganisms related to the increased risk of developing obesity and IR, as well as the mechanisms used by them.<sup>5-9</sup>

Considering the high global prevalence of obesity associated with IR, its high morbidity and mortality rates, and the economic impact of its treatment,<sup>10</sup> there are a growing number of studies that focus on new adjuvant therapeutic strategies for the treatment of obesity and IR through the modulation of the intestinal microbiota. In this regard, the role of antimicrobials has been investigated because of their potential to change the composition of the intestinal microbiota in a short or long term.<sup>11</sup>

Thus, the aim of this manuscript was to review the effect of regular use of antimicrobials on the adjuvant treatment of obesity and/or IR, as well as its associated mechanisms. For this purpose, a search was performed in the PubMed/Medline database using the following descriptors: antibiotics OR antimicrobials, AND obesity OR overweight OR weight gain OR weight loss OR diabetes OR insulin resistance OR insulin sensitivity OR glucose intolerance, AND intestinal microbiota. A filter was used to select studies carried out during the last 10 years (February 2007 to February 2017). Clinical trials and experimental studies with obese individuals and/or IR individuals, of both sexes, and fully published in English were included. Studies with pregnant women, infants, children, and newborns were excluded. Similarly, studies with individuals who suffer from inflammatory bowel disease, diarrhoea, or any type of infectious disease were excluded.

## 2 | ANTIMICROBIALS

Antimicrobials are artificial substances synthesized in the laboratory, whose main function is to inhibit the growth of specific microorganisms. Antibiotics perform the same function as antimicrobials, but they are produced from specific fungi or bacteria species. Because of the high demand for these drugs, antimicrobials are commonly used because they are easily produced on a large scale.<sup>12</sup>

Antimicrobials are being investigated for their possible use in the treatment of chronic non-infectious diseases, such as obesity and IR because of their potential modulatory effect on the composition of the intestinal microbiota. It is expected that the regular use of antimicrobials exert a "eubiotic effect." Consequently, bacteria related to the increased risk of developing obesity and IR would be eliminated and those related to the reduced risk of these diseases could proliferate and recolonize the intestinal environment.<sup>13</sup>

Over the last years, studies have attempted to identify a specific microorganism or group (core) of those that would be responsible for the development of obesity and/or IR.<sup>14</sup> Some studies have suggested that a greater abundance of bacteria of the phylum Firmicutes

(gram positive) and a lower of Bacteroidetes (gram negatives) could be related to the increased risk of developing these diseases.<sup>5-9</sup> However, other studies have suggested otherwise.<sup>15-17</sup> Based on these findings, it is difficult to select an appropriate antimicrobial for the treatment of obesity and/or IR, since this drug acts more efficiently on bacteria of the gram-positive or gram-negative group. Thus, an antimicrobial should be selected according to a single bacteria group to be eliminated, and it is likely that within the gram-positive and gram-negative groups, there are bacteria involved in the increase and decrease of the risk for the development of obesity and IR, which makes it difficult to obtain the "eubiotic effect."

### 2.1 | Treatment of obesity and IR with antimicrobials

Regarding the effect of antimicrobial treatment on body weight and/or adiposity, most studies did not find changes in these parameters at the end of the treatment and/or in comparison with the placebo/control groups (Tables 1 and 2). To reduce body weight and/or adiposity, an energy deficit must occur; however, this does not seem to happen during the antimicrobial treatment, since some of the parameters that can influence energy metabolism were not modified, such as the quantity of energy harvested from the diet,<sup>18,30</sup> substrate utilization,<sup>31,32</sup> gastric emptying,<sup>30,32</sup> appetite,<sup>32</sup> and food consumption.<sup>18,19,23,27,29,32,33</sup>

Concerning IR, studies suggest that antimicrobial treatment affects insulin sensitivity regardless of obesity (Tables 1 and 2). The intestinal microbiota has a modulatory potential on the immune system and incretins, while those play roles in insulin sensitivity. On this manner, studies that investigated the effect of antimicrobial treatment on IR have mainly evaluated whether the microbial modulation provided by this drug influences the activity of the immune system and the intestinal secretion of incretins.<sup>34</sup>

The activation of the immune system by the intestinal microbiota can occur through the interaction of lipopolysaccharide (LPS), present in the cell wall of gram-negative bacteria, with the CD14/TLR-4 complex, located on the surface of the immune cells. This interaction can trigger a chronic low-grade inflammatory process, which can impair host metabolism, contributing to the development of IR. For the host to absorb LPS, it is necessary that its intestinal barrier be altered, a process which may occur depending on the composition of the intestinal microbiota.<sup>35</sup> Thus, to prevent the absorption of LPS, the antimicrobial can reduce the population of gram-negative bacteria in the intestinal microbiota or maintain/improve the intestinal barrier of its host (Figure 1).

In this way, it has been observed that the antimicrobial treatment can reduce the serum concentration of LPS,<sup>11,18,22,26,28,29</sup> as well as pro-inflammatory cytokines.<sup>11,18,24,26-29</sup> This result may be a consequence of the reduction in intestinal permeability caused by the treatment.<sup>22,28,31</sup> Regarding the gram-negative bacteria, it is observed that when an antimicrobial with spectrum of action against these bacteria is used, its populations is reduced; however, when an antimicrobial with spectrum of action against gram-positive bacteria is used, the population of gram-negative increases, especially those belonging to the phylum Proteobacteria (Table 3). However, the treatment with an antimicrobial with spectrum of action against gram-positive

**TABLE 1** Main results of the experimental studies that evaluated the effect of antimicrobial treatment on obesity and insulin resistance

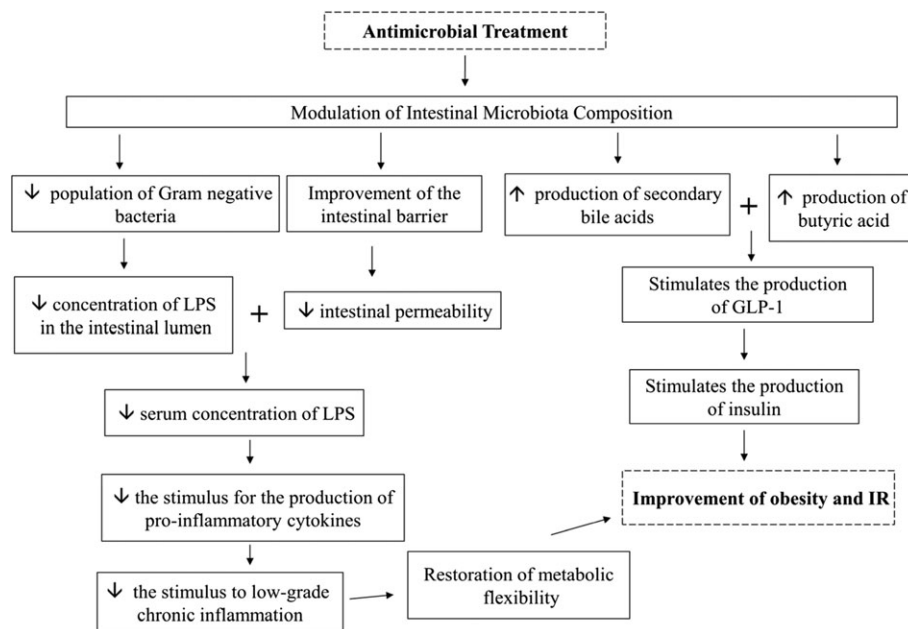
Reference	Animal Model	Experimental Diet	Intervention (Antimicrobial, Dose, and Duration)	Main Results (Intervention vs Control Group)
Di Luccia et al <sup>18</sup>	Male Sprague-Dawley rats with 14 wk old	Diet rich in fructose (20.4%)	Ampicillin (1 g /L) and neomycin (0.5 g/L) In the drinking water 8 wk	Did not alter body weight ↑ insulin sensitivity and glucose tolerance
Hwang et al <sup>19</sup>	C57BL/6J male mice with 8 wk old	High-fat diet with 60% fat	Vancomycin (0.5 g/L) and bacitracin (1 g/L) In the drinking water 4 wk	Did not alter body weight and body fat mass ↓ insulinemia ↑ insulin sensitivity and glucose tolerance
Rajpal et al <sup>20</sup>	C57BL/6 male mice with 14 wk old	High-fat diet with 45% fat	Ceftazidime (50, 150, or 500 mg/kg) or vancomycin (50, 150, or 500 mg/kg) Mixed in the diet 2 wk	<i>Ceftazidime</i> : ↓ body weight and body fat mass (150 or 500 mg/kg); glycaemia and insulinemia (500 mg/kg) <i>Vancomycin</i> : ↓ body weight (150 mg/kg)
Rajpal et al <sup>20</sup>	Mice Zucker (ZDF-Lepr <sup>fa</sup> /CrI) males with 7 wk old	Standard diet with 17% fat	Ceftazidime (500 mg/kg) Via gavage 2 wk	↓ HbA1c, fasting glycaemia, and insulinemia ↑ body weight
Del Fiol et al <sup>21</sup>	Male Wistar rats	Standard diet	Amoxicillin (150 mg/kg) Via gavage 2 wk	Did not alter body weight and body composition
Ghosh et al <sup>22</sup>	Male LDLR <sup>-/-</sup> mice with 10 wk old	Diet with 21% fat and 0.15% of cholesterol	Neomycin (100 mg/d) polymyxin B (10 mg/d) In the drinking water 16 wk	Did not alter body weight and fasting glycaemia ↑ glucose tolerance
Jena et al <sup>23</sup>	Male Wistar rats with 8 to 10 wk old	Diet with 65% of fructose	Cefdinir Via gavage 4 wk	↓ body weight and fat mass, and glycaemia ↑ glucose tolerance
Rune et al <sup>24</sup>	Male C57BL/6NTac mice with 0 d old	High-fat diet with 60% fat	Ampicillin (1 g/L) In the drinking water 5 wk	Did not alter body weight and insulinemia ↓ HbA1c ↑ glucose tolerance
Bech-Nielsen et al <sup>25</sup>	C57BL/6 female mice with 3 wk old	Standard diet with 12.6% fat	Ampicillin (1 g/L) or erythromycin (1 g/L) In the drinking water 5 wk	Did not alter body weight ↓ fasting glycaemia ↑ glucose tolerance
Carvalho et al <sup>26</sup>	Male Swiss rats with 6 wk old	High-fat diet with 55% fat	Ampicillin (1 g/L), neomycin (1 g/L), and metronidazole (1 g/L) In the drinking water 8 wk	Did not alter the size of adipocytes ↓ body weight ↑ glucose tolerance and insulin sensitivity
Murphy et al <sup>27</sup>	C57BL/6J male mice with 7 wk of age	High-fat diet with 45% fat	Vancomycin (2 mg/d) Via gavage 8 wk	Did not alter insulinemia ↓ body weight
Cani et al <sup>28</sup>	Male C57BL/6J mice with 12 wk old	High-fat diet with 72% fat	Ampicillin (1 g/L) and neomycin (0.5 g/L) In the drinking water 4 wk	↓ body weight, adipocyte size, insulinemia, and fasting glycaemia ↑ glucose tolerance
Cani et al <sup>28</sup>	Male <i>ob/ob</i> mice with 6 wk old	Standard diet	Ampicillin (1 g/L) and neomycin (0.5 g/L) In the drinking water 4 wk	↓ body weight, adipocyte size, insulinemia, and fasting glycaemia
Chou et al <sup>29</sup>	Male <i>ob/ob</i> mice	Standard diet	Norfloxacin (1 g/L) and ampicillin (1 g/L) In the drinking water 2 wk	Did not alter body weight ↓ fasting glycaemia and insulinemia ↑ glucose tolerance and insulin sensitivity
Chou et al <sup>29</sup>	Male C57BL/6J mice	Standard diet	Polymyxin B (0.5 g/L) and neomycin (1 g/L) In the drinking water 2 wk	Did not alter body weight and fasting glycaemia
Membrez et al <sup>11</sup>	Male <i>ob/ob</i> mice with 8 to 10 wk old	Standard diet	Norfloxacin (1 g/L) and ampicillin (1 g/L) In the drinking water 17 d	Did not alter body weight ↓ fasting glycaemia and insulinemia ↑ glucose tolerance
Membrez et al <sup>11</sup>	Male C57BL/6J mice 6 to 7 wk old	High-fat diet with 60% fat	Norfloxacin (1 g/L) and ampicillin (1 g/L) In the drinking water 17 d	Did not alter body weight ↓ fasting glycaemia and glucose tolerance

Abbreviations: HbA1c, glycated haemoglobin; ↑, increased; ↓, decreased.

**TABLE 2** Main results of the clinical trials that evaluated the effect of antimicrobial treatment on obesity and insulin resistance

Reference	Study Participants	Study Design	Intervention (Antimicrobial, Dose, and Duration)	Main Results (Intervention vs Placebo Group)
Mathur et al <sup>30</sup>	11 adult subjects, obese, pre-diabetic, and with methane-positive breath	Transversal	Rifaximin (1650 mg/d) and neomycin (1000 mg/d) 10 d	Did not alter body weight ↓ fasting glucose and insulinemia
Reijnders et al <sup>31</sup>	57 adult Caucasian men, overweight or obese, glucose intolerant and insulin resistant	Randomized, double-blind, placebo controlled	Amoxicillin or vancomycin 1500 mg/d 7 d	Did not alter body weight, size and number of adipocytes, fasting glycaemia, insulinemia, HOMA index, and the sensitivity of adipose tissue and liver to insulin.
Mikkelsen et al <sup>32</sup>	12 adult male, Caucasian, healthy and eutrophic	Prospective with reassessment 180 d after the intervention	Vancomycin (500 mg/d), gentamicin (40 mg/d) and meropenem (500 mg/d) 4 d	Did not alter body weight, fasting glycaemia, insulinemia, HOMA index, and serum concentrations of C peptide and HbA1c.
Vrieze et al <sup>33</sup>	20 Caucasian men with metabolic syndrome	Randomized, single blind, placebo controlled	Amoxicillin or vancomycin 1500 mg/d 7 d	Did not alter body weight, insulinemia and fasting glucose.

Abbreviations: HbA1c, glycated haemoglobin; HOMA, homeostatic model assessment; ↓, decreased.



**FIGURE 1** The potential mechanisms used by antimicrobials to improve obesity and insulin resistance (IR). The effects produced by antimicrobial treatment would be a consequence of the modulation of the composition of the intestinal microbiota. This modulation may lead to a reduction in the population of gram-negative bacteria, which contain lipopolysaccharide (LPS) in their cell walls. Additionally, such modulation would improve the intestinal barrier and consequently reduce intestinal permeability. All of these would culminate in reducing the stimulation of the immune system by LPS, decreasing the stimulus for low-grade chronic inflammation, that characterizes these diseases and helping restore metabolic flexibility. Another mechanism is related to the increase in glucagon-like peptide-1 (GLP-1) production, which would be a consequence of the activity of the metabolites produced by the microbiota, such as secondary bile acids and short-chain fatty acids. The increase in the serum concentration of GLP-1 stimulates the pancreatic production of insulin

bacteria is also capable of improving the intestinal permeability of its consumers.<sup>19</sup> Thus, these antimicrobials can be used in the adjuvant treatment of IR as long as they do not increase intestinal permeability.

The incretin, glucagon-like peptide-1 (GLP-1), can regulate carbohydrate metabolism through the stimulation of insulin production by the pancreas in the postprandial state. Glucagon-like peptide-1 is produced by the enteroendocrine L cells, mainly located in the ileum and colon.<sup>36</sup> It has been suggested that the intestinal microbiota is capable of regulating the production of this incretin, through the activity of

some metabolites it produces,<sup>32</sup> such as the secondary bile salts and short-chain fatty acids (SCFA) (Figure 1). In this way, it is possible that changes in the composition of the microbiota caused by antimicrobial treatment could interfere in the production of GLP-1 and consequently IR.

Secondary bile salts are produced by some specific microorganisms found in the intestinal microbiota through the deconjugation, oxidation, and dehydroxylation of primary bile salts. These secondary bile salts could bind to G-protein receptors, specifically TGR5, present in

**TABLE 3** Effect of the antimicrobial treatment on intestinal microbiota composition

Reference	Sample	Method	Antimicrobial	Main Results (Antimicrobial vs Placebo)
Mathur et al <sup>30</sup>	Faeces	q-PCR	Rifaximin and neomycin	... ↓ <i>Methanobrevibacter smithii</i> species
Reijnders et al <sup>31</sup>	Faeces	Microarray ( <i>human intestinal tract chip analysis</i> )	Vancomycin	↑ Phylum Proteobacteria, members of the cluster of <i>Clostridium</i> IX, genus <i>Enterococcus</i> and species <i>Lactobacillus plantarum</i> ↓ Phylum Firmiutes, members of the cluster of <i>Clostridium</i> IV and XIV as the species <i>Coprococcus eutactus</i> , <i>Faecalibacterium prausnitzii</i> , <i>Anaerostipes caccae</i> and <i>Clostridium leptum</i>
Di Luccia et al <sup>18</sup>	Cecal content	Pyrosequencing	Ampicillin and neomycin	↑ Phyla Proteobacteria and Bacteroidetes, and the class Bacteroidia ↓ Class Bacilli, and genera <i>Coprococcus</i> and <i>Ruminococcus</i> .
Hwang et al <sup>19</sup>	Cecal content	Pyrosequencing	Vancomycin and bacitracin	↑ Phylum Proteobacteria and the specie <i>Escherichia coli</i> ↓ Phylum Firmicutes, mainly the family Lachnospiraceae; and the phylum Bacteroidetes, mainly the family Porphyromonadaceae
Mikkelsen et al <sup>32</sup>	Faeces	Plating in specific media	Vancomycin, gentamicin and meropenem	... ↓ Total anaerobes, coliforms, and the genera <i>Enterococci</i> and <i>Bifidobacterium</i>
Rajpal et al <sup>20</sup>	Faeces	Sequencing of metagenomic DNA	Vancomycin	↑ Phylum Proteobacteria ...
Rajpal et al <sup>20</sup>	Faeces	Sequencing of metagenomic DNA	Ceftazidime	↑ Phylum Firmicutes, mainly the genus <i>Lactobacillus</i> ↓ Phylum Bacteroidetes and the class clostridia
Vrieze et al <sup>33</sup>	Faeces	Microarray ( <i>Human Intestinal Tract Chip phylogenetic</i> ).	Vancomycin	↑ Phylum Proteobacteria, mainly the genera <i>Haemophilus</i> and <i>Serratia</i> , and the species <i>E. coli</i> and <i>L. plantarum</i> ↓ Phylum Firmicutes, mainly the clusters of <i>Clostridium</i> IV and XIVa, and the species <i>F. prausnitzii</i> and <i>Eubacterium hallii</i>
Jena et al <sup>23</sup>	Cecal content	Plating in specific media	Cefdinir	... ↓ Family Enterobacteriaceae
Carvalho et al <sup>26</sup>	Faeces	Metagenomic analyses (BLASTX)	Ampicillin, neomycin and metronidazole	↑ Phylum Proteobacteria ↓ Phyla Bacteroidetes, Verrucomicrobia and Firmicutes
Murphy et al <sup>27</sup>	Feses	Pyrosequencing	Vancomycin	↑ Phylum Proteobacteria; families Enterobacteriaceae, Streptococcaceae, Desulfovibrionaceae, and Alcaligenaceae; genera <i>Lactococcus</i> , <i>Sutterella</i> , and <i>Desulfovibrio</i> ↓ Phylum Firmicutes and Bacteroidetes; families Clostridiaceae, Bacteroidaceae, Porphyromonadaceae and Deferribacteres; and the genera <i>Bacteroides</i> , <i>Clostridium</i> , and <i>Odoribacter</i>
Cani et al <sup>28</sup>	Cecal content of the <i>ob/ob</i> mice	DGGE	Ampicillin and neomycin	... ↓ Genera <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Bacteroides</i> , and <i>Prevotella</i>
Cani et al <sup>28</sup>	Cecal content of the mice feed with the high-fat diet	DGGE	Ampicillin and neomycin	↑ Genera <i>Lactobacillus</i> , <i>Bacteroides</i> , and <i>Prevotella</i> ↓ Genera <i>Bifidobacterium</i>
Chou et al <sup>29</sup>	Faeces	Plating in specific media	Norfloxacin	... ↓ Family Enterobacteriaceae
Chou et al <sup>29</sup>	Faeces	Plating in specific media	Ampicillin	... ↓ Genus <i>Bacteroides</i>
Membrez et al <sup>11</sup>	Cecal content	Plating in specific media	Norfloxacin	... ↓ Family Enterobacteriaceae
Membrez et al <sup>11</sup>	Cecal content	Plating in specific media	Ampicillin	... ↓ Genus <i>Bacteroides</i>

Abbreviations: DGGE, gel electrophoresis with denaturing gradient; q-PCR, quantitative polymerase chain reaction; ↑, increased; ↓, decreased.

the L cell membrane, stimulating the production of GLP-1.<sup>37,38</sup> In this regard, Reijnders et al<sup>31</sup> and Vrieze et al<sup>33</sup> observed that the treatment with vancomycin (1500 mg/d for 7 d) reduced faecal excretion of secondary bile salts and increased primary bile salts, while amoxicillin

(1500 mg/d for 7 d) did not alter bile salt homeostasis in comparison with placebo. As a consequence of these effects, no differences were observed in fasting and postprandial serum GLP-1 concentrations, as well as IR-related parameters.

Considering that vancomycin acts mainly against gram-positive bacteria, which are the primarily responsible for initiating the production of secondary bile salts,<sup>39</sup> it is then probable that the changes in the intestinal microbiota composition associated with vancomycin treatment would have compromise the production of secondary bile salts (Table 3). Corroborating with this hypothesis, treatment with amoxicillin was unable to influence bile salt homeostasis, since the composition of the intestinal microbiota of the treated individuals remained similar to the placebo group (Table 3).

The modulation of the intestinal microbiota with the aim to increase the production of secondary bile acids should be carried with caution, since high concentrations of these bile acids may increase the risk of developing colorectal cancer because they increase local production of free radicals, stimulate the synthesis of prostaglandin E2, activate the  $\beta$ -catenin/Wnt signalling pathway and alter the intestinal barrier. Furthermore, secondary bile acids can prevent the repair of damaged DNA and favours the resistance of cancer cells to apoptosis.<sup>40,41</sup>

Another metabolite capable of influencing the production of GLP-1 is butyric acid. This SCFA could interact with the G-protein receptors, stimulating the expression of the transcription factor cdx-2, which would act on the proglucagon gene promoter region increasing the expression of GLP-1.<sup>42</sup> The primary bacteria that produce butyric acid belong to the Firmicutes phylum, mainly the Clostridia IV and XIVa groups, being the main producing species *Faecalibacterium prausnitzii*, *Coprococcus eutactus*, and *Eubacterium rectale*.<sup>43</sup>

Regarding the effect of antimicrobial treatment on the production of butyric acid, Reijnders et al<sup>31</sup> observed that treatment with vancomycin (1500 mg/d for 7 d) reduced the faecal concentration of total SCFA and butyric acid. This result could be a consequence of the decrease in the bacteria population that produces butyric acid in the intestinal microbiota as a consequence of the vancomycin treatment (Table 3). Further, the authors observed that treatment with amoxicillin (1500 mg/d, for 7 d) did not alter the faecal concentration of this SCFA as well as the composition of the intestinal microbiota of the treated individuals compared with placebo.

The production of SCFA depends on the composition of the microbiota and the availability of substrate, mainly indigestible carbohydrates.<sup>43</sup> Obese and/or IR individuals tend to consume low amounts of fibre; thus, even if there is an increase in the population of SCFA-producing bacteria as a consequence of the antimicrobial treatment, it does not necessarily guarantee an increase in the production of SCFA.

To date, it has not been possible to determine a specific antimicrobial for the adjuvant treatment of obesity and/or IR that would provide positive results. It is likely that the findings so far were influenced by the different experimental designs (type, dose, and duration of treatments), the population investigated, and the animal models used. Furthermore, the pharmacokinetics, pharmacodynamics, path of administration, and spectrum of action may influence the modulatory effect of an antimicrobial. Moreover, inherent consumer characteristics such as age, composition of the initial intestinal microbiota and lifestyle would also influence the modulatory effect of antimicrobials.<sup>13</sup>

Obesity is a complex disease, which requires a multiprofessional intervention for its treatment. Since antimicrobial treatment only acts on one casual factor, an investigation into the outcome of the treatment when associated with dietary re-education and the practice of regular physical activity is of great interest. In some cases, the antimicrobial treatment was capable of restoring the metabolic flexibility of the liver, muscle, and adipose tissue,<sup>11,20,23,26,29</sup> which could contribute to weight loss if the treatment period is extended; however, prolonged antimicrobial treatment is not recommended.

In general, studies suggest that, partially, the effect of antimicrobial treatment on IR could be attributed to reduced interaction of LPS with the immune system. Regarding the production of GLP-1, the influence of antimicrobials appears to be limited. However, it is worth mentioning that the increase in GLP-1 production does not necessarily imply an improvement in IR, since some alterations in the insulin receptor could compromise the adequate binding of the insulin produced as a consequence of GLP-1 stimulation.

Thus, more studies are necessary for the mechanisms used by the antimicrobials that would lead to this improvement in obesity, and IR can be better understood and afterwards amplified so that better results can be obtained.

### 3 | MAIN LIMITATIONS OF THE STUDIES

Most of the experimental studies included in this review administered the antimicrobial by diluting a given amount of the drug in the drinking water of the animal model (Table 1). Although 3 of these studies<sup>11,18,19</sup> quantified the amount of water consumed by the animals, it is difficult to define the actual amount of antimicrobial consumed. Such information is essential for conducting further studies as well as justifying results. Thus, an alternative solution to this limitation would be the administration of the antimicrobial via gavage, ensuring that the pre-established dose is consumed.

The clinical trials, included in this review, did not evaluate the composition of the diets consumed by the participants. Diet exerts a great modulatory effect on the composition of the intestinal microbiota<sup>3</sup> and influences the modulatory potential of antimicrobials,<sup>28</sup> being therefore essential to verify if there were changes in diet during the treatment period, mainly in the consumption of macronutrients and fibres.

Another limitation concerns the use of absorbable antimicrobials such as norfloxacin, amoxicillin, and ampicillin, which have limited effect on TGI levels but could interfere with insulin sensitivity through its systemic activity.<sup>11</sup> Thus, it is suggested that studies aiming to investigate the effect of antimicrobials on obesity and IR through the modulation of the intestinal microbiota should use only antimicrobials that act locally on TGI (non-absorbable).

### 4 | FUTURE PERSPECTIVES

The indiscriminate use of antimicrobials can lead to the development of antimicrobial-resistant microorganisms, which is a cause of great concern because of the risk of spreading infectious diseases.<sup>44</sup> Therefore, the choice of the type of antimicrobial as well as dose and



duration of treatment should take into account the possibility of antimicrobial resistance, especially in clinical trials. Moreover, it should be investigated whether antimicrobial treatment provides better results than the regular consumption of probiotic, prebiotic, or symbiotic foods. Since these foods can modulate the composition of the intestinal microbiota without contributing to the development of antimicrobial-resistant microorganisms.<sup>45</sup>

The modulatory effect of antimicrobials on the composition of the intestinal microbiota should be investigated in the long term, since their regular use may increase the proliferation of microorganisms that contribute to the development of other diseases.<sup>13</sup> Some studies observed that treatment with antimicrobials resulted in the increase of the Enterobacteriaceae family (Table 3), which comprises some species related to the increased risk of developing colorectal cancer.<sup>46,47</sup>

As discussed earlier, the metabolites produced by the microbiota exert considerable influence on host metabolism.<sup>34</sup> In this sense, future studies on microbial treatment should make an effort not to only identify changes in the composition of microorganisms but also the metabolites produced by them.

In the future, it is necessary to investigate the minimum age at which antimicrobial treatment of chronic non-infectious diseases can be realized, since it has been suggested that the intake of antimicrobials during infancy may contribute to the development of obesity.<sup>48</sup> Another aspect to be investigated is the duration of the effectiveness of antimicrobial treatment after its discontinuation. It is possible that if there are no lifestyle changes, the composition of the intestinal microbiota could return to its initial state, accompanied with metabolic changes that lead to the development of obesity and IR.<sup>32</sup>

## 5 | CONCLUSIONS

Regarding obesity, the effects of antimicrobial treatment appear to be limited. For IR, so far, positive results have been reported only in experimental studies, whereas in clinical trials, no changes were observed. Regarding the mechanisms used, it was proposed that antimicrobial treatment would interfere in the activation of the immune system by LPS and modulate the production of incretins; however, the results are still inconclusive.

In this light, further studies are needed in order to better understand the effect of antimicrobial on obesity and IR. In addition, the risks associated with the regular use of this drug should be investigated, as well as comparing its effect with other potential modulators of the composition of the intestinal microbiota.

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