Bamidele et al. *Afr. J. Clin. Exper. Microbiol.* 2022; 23 (1): 27 - 33 https://www.afrjcem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X Jan 2022; Vol.23 No.1
AJCEM/2140. https://www.ajol.info/index.php/ajcem

Review Article **Open Access**

A review of the implications of Lactic Acid Bacteria and Bifidobacteria in human and animal diseases

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Abstract:

Lactic acid bacteria (LAB) and Bifidobacteria are taxonomically distinct groups of bacteria with proven biotechnological properties such as anti-cancer, immune-stimulating, anti-microbial, maintenance of normal flora balance, probiotics, anti-inflammatory, vaccine carriers, among others. However, studies have implicated some of them, including the ones under the European Food Safety Authority (EFSA) qualified presumption of safety in fatal human and veterinary diseases. We performed online database searches of publications on Google, Google Scholar and PubMed using the criteria, "lactic acid bacteria, bifidobacteria as causative agents of human, animal diseases". Data generated showed LAB across genera and Bifidobacteria either primarily or opportunistically involved in diseases of both immuno-competent and immuno-depressed humans and animals. The members of lactobacilli such as *Lactobacillus fermentum*, *Lactobacillus paracasei*, *Lactobacillus oris*, *Lactobacillus gasseri* and *Leuconostoc mesenteroides*, were mainly implicated in nosocomial infections, endophthalmitis, neonatal meningitis, and bacteraemia while *Lactobacillus delbrueckii* and Bifidobacteria, specifically, *Bifidobacterium longum*, *Bifidobacterium breve*, and *Bifidobacterium animalis* were implicated in urinary tract infections (UTIs), necrotizing pancreatitis, fatal pulmonary infections, sepsis, and epidural abscess. The animal diseases, neonatal sepsis in foal, was caused by *Weissella confusa* while the fish pathogen, *Lactococcus garvieae* caused various zoonotic cases such as acute acalculous cholecystitis in human. In conclusion, this review showed the up-to-date reports on LAB and Bifidobacteria implicated in serious humans and animal diseases.

Keywords: Lactic acid bacteria; Bifidobacteria; Human; Animal; Diseases; Probiotics

Received Jul 25, 2021; Revised Oct 8, 2021; Accepted Oct 9, 2021; Published online Jan 18, 2022

Un examen des implications des bactéries lactiques et des bifidobactéries dans les maladies humaines et animales

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Résumé:

Les bactéries lactiques (LAB) et les bifidobactéries sont des groupes de bactéries taxonomiquement distincts avec des propriétés biotechnologiques prouvées telles que anticancéreuses, immunostimulantes, antimicrobiennes, maintien d'un équilibre normal de la flore, probiotiques, anti-inflammatoires, porteurs de vaccins, entre autres. Cependant, des études ont impliqué certains d'entre eux, y compris ceux relevant de la présomption qualifiée de sécurité de l'Autorité européenne de sécurité des aliments (EFSA) dans les maladies humaines et vétérinaires mortelles. Nous avons effectué des recherches dans des bases de données en ligne de publications sur Google, Google Scholar et PubMed en utilisant les critères «bactéries lactiques, bifidobactéries en tant qu'agents responsables de maladies humaines et animales». Les données générées ont montré des

bactéries lactiques à travers les genres et les bifidobactéries impliquées principalement ou de manière opportuniste dans les maladies des humains et des animaux immuno-compétents et immunodéprimés. Les données générées ont montré des bactéries lactiques à travers les genres et les bifidobactéries impliquées principalement ou de manière opportuniste dans les maladies des humains et des animaux immuno-compétents et immunodéprimés. Les membres des lactobacilles tels que *Lactobacillus fermentum, Lactobacillus paracasei, Lactobacillus oris, Lactobacillus gasseri* et *Leuconostoc mesenteroides* ont été principalement impliqués dans les infections nosocomiales, l'endophtalmie, la méningite néonatale et la bactériémie tandis que *Lactobacillus delbrubreifeckii* et les bifidobactéries, en particulier, *Bifidobacterium longum*, *Bifidobacterium breve* et *Bifidobacterium animalis*, ont été impliquées dans les infections des voies urinaires (IVU), la pancréatite nécrosante, les infections pulmonaires mortelles, la septicémie et l'abcès épidural. Les maladies animales, la septicémie néonatale chez le poulain, ont été causées par Weissella confusa tandis que l'agent pathogène du poisson, Lactococcus garvieae, a causé divers cas de zoonoses telles que la cholécystite acalculée aiguë chez l'homme. En conclusion, cette revue a montré les rapports à jour sur les bactéries lactiques et les bifidobactéries impliquées dans les maladies humaines et animales graves.

Mots-clés: Bactéries lactiques; Bifidobactéries; Humain; Animale; Maladies; Probiotiques

Introduction:

Lactic acid bacteria (LAB) are composed of thirteen genera of Gram-positive bacteria that include *Carnobacterium*, *Lactobacillus*, *Lactosphaera*, *Leuconostoc Oenococcus*, *Enterococcus*, *Lactococcus*, *Pediococcus*, *Paralactobacillus*, *Streptococcus Tetragenococcus*, *Vaginococcus* and *Weissella* (1). They are divided into two groups based on their metabolic end products from glucose or other hexose sugars. Those that produce solely lactic acid as major product are known as homofermenters while those producing equal molar amounts of lactate, CO_2 and ethanol are designated heterofermenters (1). The genus *Bifidobacterium* on the other hand, has the ability to produce both lactic acid and short chain fatty acids. It is not grouped directly under LAB because they are strict anaerobes, do not produce gas during growth and have GC content of about 55-67 mol% (2).

Over the years, LAB and indeed Bifidobacteria have been proven to be safe for human and animal consumption through various experiments and scientific procedures hence, they have assumed the 'Generally Regarded As Safe' (GRAS) status (3). To this end therefore, many studies have demonstrated the beneficial roles played by these set of bacteria such as; lactose digestion, immune stimulating, diarrhoea treatment and prevention (4), production of useful industrial and medical products (5,6), probiotics and growth promoters in livestock, substituting for antibiotics (7,8), anti-inflammatory (9), anti-cancers (10), and as vaccine carriers (11,12). In spite of these track records, LAB and Bifidobacteria have been implicated in many human and animal diseases. In this study, we reviewed various published articles reporting the involvement of selected genera of LAB and Bifidobacteria that have been regarded to be safe, in human and animal diseases.

Methodology:

Online literature searches were conducted on Google search engine, PubMed and Google Scholar using the following words as criteria; "lactic acid bacteria, bifidobacteria as causative agents of human and animal diseases" to generate results for a traditional narrative review. These criteria were further refined to "diseases caused by probiotic lactic acid bacteria or bifidobacteria" to remove unwanted publications. Due to paucity of publications in the literature, the searches were not specified to cover particular periods.

A total of 85 published articles were retrieved from the database searches and evaluated based on credibility of sources, key concepts, and theories. Twenty-one publications were excluded after they were deemed to be irrelevant, leaving a total of 64 articles for the review.

Results:

The summary of Lactic acid bacteria and Bifidobacteria implicated in human and animal diseases is shown in Table 1.

Leuconostoc

These are Gram positive, facultative anaerobic coccobacilli which may be misidentified as *Enterococcus* or *Streptococcus* by routine biochemical testing (13). They have been reported as emerging pathogens in nosocomial outbreaks, immunosuppression and vancomycin resistance (14–19). Singh et al., (20) reported a case of acute endophthalmitis caused by *Leuconostoc* spp. after intravitreal bevacizumab injection in an 86-years old immunocompetent female. Damasceno et al., (21) also reported isolation of *Leuconostoc mesenteroides* in the blood and vitreous cultures of a patient who presented 48 hours after uncomplicated intravitreal injection of ranibizumab. Two other sets of researchers (22,23) have previously reported *Leuconostoc* associated endophthalmitis in

Table 1. Summary of Lactic acid bacteria and Bifidobacteria implicated in human and animal diseases

LAB/Bifidobacteria	Disease	Reference
Lc. mesenteroides, *L. rhamnosus*, *L. fermentum*, *L. paracasei*, *Lc. oris*, *L. gasseri*, *L. iners*, *L. salivarius*	Nosocomial infections	(14-19,27)
Lc. mesenteroides	Endophthalmitis	(20)
L. rhamnosus, *P. acidilactici*, *B. longum*, *B. breve*, *B. animalis*	Neonatal meningitis, Bacteraemia, Necrotizing pancreatitis, Sepsis, Epidural abscess, Fatal pulmonary infections	(28-30,55,71,75-79)
L. delbrueckii, *L. jensenii*, *Bifidobacterium* spp.	Urinary tract infections	(37,38,74)
Weissella confusa	Systemic infections Neonatal sepsis in foal Pneumonitis	(49) (50) (60)
Lactococcus garvieae	Endocarditis Acute acalculous cholecystitis Post-operative osteomyelitis abscess Infected prosthetic joint	(53,64-66) (56) (57) (58)

Lc = Leuconostoc; L = Lactobacillus; LAB = Lactic acid bacteria; B = Bifidobacterium; P = Pediococcus

immuno-competent patients following uncomplicated phacoemulsification surgery.

Lactobacillus

These are non-spore forming, aerotolerant LAB comprising of more than 237 species and sub-species (www.bacterio.net/lactobacillus.htm). Lactobacilli are rarely associated with diseases in immunocompetent people except in the presence of risk factors and underlying conditions such as diabetes mellitus, pre-existing structural heart defects, cancer, and antibiotic therapy (23,24) where they cause endocarditis, bacteraemia, neonatal meningitis, liver abscess, pulmonary infections, pyelonephritis, meningitis, postpartum endometritis and chorioamnionitis (25,26). In a reported case of bacteraemia in Argentina between 2012 and 2017 by Roca et al., (27), *Lactobacillus rhamnosus* was most commonly isolated followed by *L. fermentum*, *L. paracasei*, *L. oris*, *L. gasseri*, *L. iners* and *L. salivarius*.

In premature infants, cases of infections caused by probiotic *L. rhamnosus* have been reported such as late onset sepsis (LoS) following a laparotomy and bacteraemia after tube feeding with the bacterium (28-30). It seems the potential for probiotics to cause sepsis is greater in immuno-deficient neonates and this was recently supported by a report of sepsis in humans (31). In adults, endocarditis caused by *Lactobacillus* spp is not uncommon and this occurred in patients who had dental extractions or gingival bleeding after toothbrushing (32), after colonoscopy (33) and in haemorrhagic telangiectasia (34). Also associated with Lactobacilli is bacteraemia especially when probiotics are consumed by patients undergoing haematopoietic stem cell transplantation and HIV-infection (31,35).

Other cases such as meningitis where *Lactobacillus* spp was isolated from blood and CSF in a neonate, and in a 10-year-old neutropaenic child with acute leukaemia, were suspected to be from the mothers' genital tracts. Meningoencephalitis in a 63-year-old man with metastatic planoepithelial lung cancer have been hypothesized to be due to direct bacterial (*Lactobacillus*) dissemination from the gastrointestinal tract (36). *Lactobacillus delbrueckii* and *L. jensenii* have been reported to cause urinary tract infections (chronic pyuria and pyelonephritis) in women (37,38).

Studies on virulence of *Lactobacillus* spp have implicated *L. rhamnosus* and *L. paracasei*, which are widely used as probiotics, to be virulent, for instance, some strains can aggregate human platelets (39, 40). *Lactobacillus rhamnosus* has been linked more frequently with infections than other lactobacilli (41,42). Apart from their propensities to cause infections, *Lactobacillus* have been demonstrated as reservoirs of antibiotic resistance genes and possess ability to transfer them. For instance, resistance to tetracycline, erythromycin, clindamycin and chloramphenicol have been acquired by foodborne lactobacilli (43, 44). Also, in *L. ingluviei*, *L. amylophilus* and *L. amylotrophicus*, resistance genes on mobile genetic elements with potential for horizontal transfer, have been reported by Campedelli et al., (45).

Weissella

Although the bacteria under this genus have several strains used for biotechnological and probiotic purposes, some have been reported to possess inherent abilities as pathogens. Abriouel et al., (46) found several virulence determinants such as collagen adhesins, aggregation substances, mucus binding proteins and haemolysin, including several antibiotic resistance encoding genes in some species in an *in-silico* analyses of their whole genome sequences. The species of *Weissella* include, *W. ceti, W. cibaria, W. confusa, W. halotolerans, W. hellenica, W. koreensis, W. oryzae, W. paramesenteroides* and *W. thallandensis*. Of all *Weissella*, only *W. confusa, W. cibaria* and *W. viridescens* have been isolated from human clinical specimens (47,48) while *W. confusa* has been documented as a cause of systemic infection in healthy primates (49) and neonatal sepsis in a foal (50). In humans, most isolated *W. confusa* infections were from immunocompromised patients (51,52), which may be occasioned by organ transplant, long term use of steroids, chronic renal insufficiency, and diabetes mellitus (53,54). The common human infections caused by *W. confusa* are bacteraemia (55), endocarditis (53), post-operative osteomyelitis (56), abscess (57), and prosthetic joint infections (58).

Pediococcus

These bacteria have been infrequently isolated from the human respiratory tract, stool, urine and blood of immunocompromised patients, and in patients with malignancy, cardiovascular, lung diseases, and diabetes mellitus (13,59), while *Pediococcus acidilactici* specifically has been implicated in pneumonitis and bacteraemia in a pregnant woman, and septicaemia caused by vancomycin resistant strain (60). In a fatal case of necrotizing cellulitis of the abdominal wall secondary to the rupture of a retroperitoneal stromal tumor in a 60-years old Caucasian male patient, *Pediococcus pentosaceus* strain resistant to vancomycin, teicoplanin, trimethoprim and kanamycin was isolated from blood, subcutaneous, and peritoneal specimens (61).

Lactococcus

Lactococcus species are mainly associated with infective endocarditis, hepatic abscess and hip prosthetic infections (62,63). In particular, *L. garvieae* which is reputed to be a fish pathogen has been implicated in zoonosis following consumption of raw fish by humans, causing diseases such as acute acalculous cholecystitis, endocarditis (64-66), and knee periprosthetic infection in a 79 years old male with multiple comorbidities, who had a habit of eating perch fish (67). *Lactococcus lactis* subsp *lactis* was isolated from samples of facial cellulitis and apical periodontitis. This bacterium was resistant to multiple antibiotics. Eiji et al., (68) reported virulence genes in *L. garvieae* from different sources using comparative genomic analysis and recently, this bacterium isolated from diseased rainbow trout was reported to have carried important virulence genes such as haemolysins 1,2,3, NADH oxidase, phosphoglucomutase, adhesins, superoxide dismutase, enolase, among others (69,70).

Bifidobacteria

These are strictly anaerobic commensals that colonize the oro-gastrointestinal tract and are said to rarely cause invasive infections. However, they have been demonstrated to be implicated in fatal bacteraemic infections especially *B. longum, B. breve* and *B. animalis* in both immunocompromised and immunocompetent hosts, and in patients with gastrointestinal tract related conditions (71). Also, they have been estimated to constitute 0.5-3.0% of anaerobic blood culture isolates (31,72), and until 2015, only 15 adult cases were reported in the literature (73). Bifidobacteria have been implicated in cases of necrotizing pancreatitis, sepsis, epidural abscess, fatal pulmonary infection, dental caries and urinary tract infections (74-79).

Esaiassen et al., (71) reported 98 putative virulence genes among 15 *Bifido bacterium* isolates, such as iron and magnesium transport, adhesin, toxin secretion, immune invasive, stress proteins, among others. Also reported is the ability of Bifidobacteria to harbour antibiotic resistance genes including those on mobile genetic elements. These genes, found mainly in *B. animalis* were confirmed by high resolution molecular analysis, to have been acquired through horizontal gene transfer (80,81) with heavier presence of Bifidobacteria in guts of antibiotic treated adults and children when compared to non-antibiotic treated persons.

Discussion:

This review was necessitated by the historic accolade of "Generally Regarded As Safe' (GRAS) status given to LAB and Bifidobacteria, which has placed them as probiotics or "good" bacteria and alternative therapeutics without side effects. Their biotechnological properties have been demonstrated and reported in various literatures. Although, there exist quite a few published data on the subject of LAB and disease causation, this review calls for continuous surveillance of these bacteria as regards their implications in human and veterinary diseases.

In this review, it was revealed that

the common denominator is that these bacteria are always involved in opportunistic infections especially in immuno-compromised patients or in patients on long hospitalization with underlying conditions such as diabetes mellitus, cancers, or with use of steroids and antibiotic therapy (14-19,23,24,27), and the commonest LAB are of *Lactobacillus* species, while Bifidobacteria are sparsely reported as pathogenic (37,38,74). The ability of Lactobacilli and Bifidobacteria to acquire and disseminate antibiotic resistance through mobile genetic elements should be taken seriously especially in this era of global problems of antimicrobial resistance (AMR). Also, Lactobacilli are resident flora of human gastrointestinal tract (GIT), and with their consumption as adjuncts in fermented food products, they can be means through which the AMR genes are transferred to GIT commensals. Surveillance efforts should be geared up in fermented foods and products supplemented with LAB and Bifidobacteria probiotics, and such surveillance should include annotation of all functional genes in the genome of these bacteria.

The animal diseases were reported more commonly in fish and this was caused mainly by *Lactococcus* species especially *L. garvieae* and as a matter of fact, this LAB is reputed for fish disease (64-66), although with few exceptions in humans who have direct contact with fish and certain marine animals.

Conclusion:

Although Lactic acid bacteria from different niches are generally regarded as safe by the Food and Agricultural Organization (FAO) and the World Health Organization (WHO), they may play either primary or opportunistic pathogenic roles, as reported by different studies over time in causality of serious diseases of human and in veterinary setting, irrespective of the host immune status, and they can additionally carry transferrable antibiotic resistance genes.

Acknowledgements:

The provision of internet access by the Nigerian Institute of Medical Research to gather articles for this review is appreciated and the invaluable mentorship of the Director of Research, Clinical Sciences Department of the Institute, Professor Ezechi Oliver, helped in classifying this type of review.

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