



## An insight into the health-promoting effects of foods to prevent Antibiotic-associated Diarrhoea: A Review

## Sreerupa Bedi<sup>1</sup>, Manisha Maity<sup>2\*</sup>, Bidyut Bandhopadyay<sup>3</sup>, Samapti Bedi<sup>4</sup> and SatarupaGhosh<sup>5</sup>

 <sup>1</sup>Department of Food and Nutrition, School of Allied Health Sciences, Swami Vivekananda University, Barrackpore, West Bengal-700121, India, sreerupabedi8@gmail.com, 9073480465
<sup>2</sup>Department of Food and Nutrition, School of Allied Health Sciences, Swami Vivekananda University, Barrackpore, West Bengal-700121, India, manisham@svu.ac.in\*, 9434653854
<sup>3</sup>Professor, PG Department of Biotechnology and Biochemistry, Oriental Institute of Science and Technology, WestBengal, India, bidyut2006@gmail.com, 9733306660
<sup>4</sup>Department of Food and Nutrition, School of Allied Health Sciences, Swami Vivekananda University, Barrackpore, West Bengal-700121, India, samaptibedi@gmail.com, 8583036990
<sup>5</sup>Department of Food Science, Maulana Abul kalam Azad University of Technology, West Bengal, India, satarupa.ghosh8@gmail.com, 9123081103

(\*Corresponding author: manisham@svu.ac.in)

#### **ABSTRACT:**

The random use of antibiotics leads to gastrointestinal diseases with complications ranging from mild diarrhea to *Pseudomembranous colitis*, which is called antibiotic-associated diarrhea. Outbreaks of antibiotic-associated diarrhea are generally found in 10% to 30% of patients taking antibiotics, depending on the particular antibiotic used, and are caused by *Clostridium difficile* in general and *Klebsiella oxytoca, Staphylococcus aureus, Clostridium perfringens*, etc. in particular. Functional disturbances of intestinal carbohydrates, harmful effects of antibiotics on the intestinal mucosa, and allergic effects are responsible for mild antibiotic-associated diarrhea. In COVID-19, caused by SARS-CoV-2, patients treated with a variety of antibiotics have been noticed to suffer from severe antibiotic-associated diarrhea. Probiotics have been shown to play a significant role in preventing antibiotic- associated diarrhea in both COVID-19 patients and general patients. Prebiotics and dietary approaches also play a vital role in combating antibiotic-associated diarrhea. Given the increased demand for food associated with the treatment of antibiotic-associated diarrhea, the current review paper attempted to orchestrate the effect of probiotics such as yogurt, kefir, cheese, probiotic milk, and dietary foods such as ripe papaya, bananas, and other fermented foods in developing an immune system capable of effectively combating antibiotic-associated diarrhea.

Keywords: Antibiotic-associated diarrhea, Probiotics, Prebiotics, Covid-19, Antioxidants

#### INTRODUCTION

Diarrhea is the state of a patient suffering from abnormally loose or watery stools three or more times per hour. At present, the consistency and character of the stools are given prior importance to their frequency. It also appears as an adverse situation of the random intake of different antibiotics to avail the effective treatment of various infectious diseases. Lack of proper chemical investigations; over or improper intake of antibiotics; poor compliance; and the pathogenic emergence of different organisms that are resistant to antibiotics etc. lead to diarrhea. The most usual complications of the intestine arising out of antibiotic intake, which leads to destroying the microbiota present in the intestine, resulting in antibioticassociated diarrhea (AAD) (Metter et al., 2007). AAD appears as a common side antibiotic therapy. effect of The occurrence of AAD varies from five percent to twenty five percent depending on the specific antibiotic used and administered. The occurrence of more than three watery or mushy stools per day, AAD is said to be clinically significant. Pseudomembranous colitis associated with Clostridium difficile constitutes the intestinal disorders occurring in 10%-20% of all AAD (Spellberg B, Guidos et al., 2008).

## **History of AAD**

Intake of different antibiotics in the broad spectrum such as chloramphenicol and tetracycline had been started since the 1950s. AAD has become a recognized clinical concern. Little attention has been paid to its seemingly mild complications. Disease like pseudomembranous colitis (PMC), though relatively rare, was observed in ten percent of sufferers being administered with antibiotic clindamycin (Tedesco et al., 1974).

In the 1980s, researchers centered on *C. difficile* associated outbreaks (McFarland *et al.*, 1989). In the 1990s, they worked on solving the transmission of *C. difficile* disease, risk factors, and pathogenesis (Aronsson *et al.*, 1985).

A greater understanding of and attention to AAD, its risk factors, mechanisms, treatment strategies, diagnostic process, and other likely etiologies has appeared in the 21<sup>st</sup> century. AAD emerges not only as a risk for any individual bearing serious complications but also appears as a grave concern to the medical community. As the treatment regimens do not provide sufficient satisfactory achievement, AAD is supposed to be a continuing medical Uncomplicated concern. or less complicated diarrhea, PMC, or colitis also extends the domain of severity for AAD. It is true that epidemiological studies on the non C. difficile cases are limited. In health care related populations, 10- 30 out of 100 patients suffer from uncomplicated diarrhea due to C. difficile AAD, 5-10 out of 100 suffer from colitis, and PMC is rare (0.1-1 out of 100) (McFarland et al., 1998).

## **Probable Incubation Time for AAD**

The time taken from the initiation of antibiotics to the onset of diarrhea is called incubation time. Early onset occurs during treatment with antibiotics whereas delayed onset starts from 2-8 weeks after the antibiotic has been stopped. Most of the patients showed symptoms within one week of exposure to the antibiotic. Sometimes the appearance of symptoms may be delayed and exposed to 2-8 weeks after the discontinuation of antibiotics in the case of PMC patients (Berman *et al.*, 2008).

## Severe AAD

PMC generally occurred in association with *C.difficile*, and stands at the extreme end of the severity spectrum (Pepsin *et al.*, 2004). PMC is exhibited

with symptoms like fever (80%), abdominal cramping (80-90%), watery diarrhea (90-95%), leukocytes (80%) etc. (Surawicz and McFarlan *et al.*, 1999).

#### **Recurrent AAD**

A recurrent AAD may develop in about fifteen to sixty percent of sufferers with *C.difficile* AAD. Patients with this type of AAD are considered more serious in comparison to patients with early symptoms (Monagham *et al.* 2008). The more the recurrent form of AAD appears the more will be the use of antibiotics and more will be medical complications, antibiotics cost, and additional hospitalizations (McFarland *et al.*, 1998).

#### **Diagnosis of AAD**

Patients with severe symptoms like stools three or more than three times a day, watery or bloody stools, fever, leukocytosis, etc. need a diagnostic checkup with immediate effect. Specific pathogen detection is an urgent need. If it is not done, the diagnosis will have to rely on antibiotic exposure and barring another reason for diarrhea like irritable syndrome, chronic intestinal bowel disorder. inflammation. and food intolerance (Mc Donald et al., 2007).

#### **Risk factors**

In association with AAD, various types of risk factors can be grouped, such as antibiotic or medication type, host- related factors, exposure to pathogenic agents, and such process which leads to the disruption of normal microorganisms present in colon (Litao *et al.*, 2018).

#### **Direct effects of antibiotics**

*Erythromycin*: Erythromycin is said to act as an agonist for motilin receptors

(Peeters et al., 1989). The gastrointestinal peptide stimulating contraction that occurs in the area of duodenum and antrum, is called motilin. Erythromycin induces these contractions, at the same time motility inhibits peristaltic in the guineapig ileum. The effects of erythromycin are mainly found in the upper gastrointestinal tract. It also accelerates gastric emptying, which causes diarrhea.

Neomycin: Neomycin is an orally administered drug (3-12 g/day) that gives rise to different types of gastrointestinal symptoms and malabsorption. The alterations in the morphology of the mucosal cells of the intestine like epithelial crypt cell damage and reduction villi, of intestinal eosinophils, and pigment-containing macrophages occurred after 7 to 11 days of oral administration of neomycin (6gm/day) in healthy people.

*Klebsiella oxytoca*: *Klebsiella oxytoca* produces a cytotoxin. *K. oxytoca* is mainly responsible for the occurrence of amoxicillin-associated hemorrhagic colitis (Hogenauer *et al.*, 2006).

Staphyloccocus aureus: S.aureus was indicated main as agents for the occurrence of AAD. But several previous reports made a correlation between AAD and clindamycin. Generally, the intake of antibiotics like tetracycline, and neomycin, generate a positive stool for S.aureus and they are similar to recurrent AAD (Flemming et al., 2007).

#### **Treatments of AAD**

Antibiotic discontinuation removes the problematic medications; however, it is frequently not suitable if the indication for such therapy was justified. Some antibiotics (quinolones, sulfonamides, metronidazole, or tetracycline) can be taken as an alternative which has much lower risk than other types of antibiotics (Barlett et al., 1992). Oral antibiotics are required in severe cases of recurrent AAD. For a 7-14-day therapy regimen, vancomycin (125mg four times a day) and metronidazole (250mg three times a day) can be utilized. Vancomycin is the least expensive option for treating C. difficile infection and is linked to developing resistance in enterococci and staphylococci.

## **Probiotic Therapy**

Several species have been utilized utilization to test the of live microorganisms for the prevention of AAD, and probiotics are commonly used for diarrhea treatment. Probiotics are living microbes that, when given in provide sufficient quantity, health advantages to the host. Altering the gut microbiota composition and metabolism, influencing solute secretion and absorption, and enhancing the intestinal barrier function and intestinal immune responses are some of the methods through which probiotics work on AAD (Mekonnen et al., 2020).

**Probiotic Yogurt:** Fermented milk and yogurt are essential sources of vitamins and minerals, as well as probiotic organisms, which may have several important uses. Yogurt made by the traditional procedure can boost digestibility and nutrient bioavailability, but they have a short shelf life after being consumed (Marteau *et al.*, 1997).

**Probiotic Cheese:** Incorporation of

probiotic bacteria into cheese can enhance the quality of probiotic products has the potential to improve the health and quality of probiotic products. Because of their higher pH and higher fat content, cheeses are a better delivery route for viable probiotics than fermentation products like yogurt because they protect the good microbes while in storage and easily pass across the GI tract (Vinderola *et al.*, 2002). Generally, probiotic bacteria such as *Bifidobacterium* and *Lactobacillus* can be obtained from cheeses. The pH of the cheese affects the cultural condition of the probiotic organism (Ross *et al.*, 2000).

## Fermented foods against GI disorder

The usage of fermented milk to cure GI disorders was first started by Pliny (Roman historian) in 76 A.D. (Ray 2016). et al., Various unfavorable situations cause disease in the gastrointestinal system. Various reports on in vitro studies observed that kefir which is a good source of compounds with bioactive properties and probiotics, was found to be beneficial to alter the composition of different microbiota by enhancing the concentration of several probiotic bacteria and increasing the numbers of Prevotella, Bacteroidetes, and Firmicutes (Jeong et al., 2017; Kim et al., 2019).

Irritable bowel syndrome may be reduced and pathobiont richness reduced by fermented milk, such as yogurt, containing Bifidobacterium animals loaded with beneficial metabolites such as SCFA. In irritable bowel syndrome patients, consumption of fermented milk reduced digestive discomfort by altering gut bacterial ecology compared to the control group (Harris and Baffy, 2017).

2023

Sauerkraut fermented with LAB has beneficial impacts on GI illnesses and gut microbiota changes, with a focus on Bowel Irritable Syndrome patients (Nielsen et al., 2018). Kimchi, a type of fermented food, aids in maintaining GI conditions and treating various disorders such as bloating, diarrhea, and functional bowel disease. With sourdough ingestion, total volume, flatulence. stomach gastrointestinal discomforts, and nausea were all significantly reduced. A ricebased fermented beverage, Haria, was thought to guard against GI problems like dysentery, diarrhea, vomiting, acidity, and amebiasis.

Prebiotics are nondigestible carbohydrates such as isomaltooligosaccharides and exopolysaccharides produced by Bifidobacterium spp during sourdough fermentation and *Lactobacillus sp* can impact on the populations of gut microbes by producing SCFA in patients with GI problems.

# Role of Banana and Papaya against diarrhea

The banana and papaya plants, as well as their numerous sections, are consumed all over the world as a nutritious and healthy fruit and are been used to treat a number of diseases. The banana and papaya plants have various pharmacological qualities, making them nutraceutical plant with a wide range of vitamins and enzymes that can be used to cure a variety of ailments, including diarrhea.

The effect of green bananas on chronic or acute diarrhea was studied, and it was discovered that a diet rich in green bananas aids in the recovery of chronic or acute diarrhea. Ripened green bananas contain a large level of amylase-resistant starch, which helps to treat diarrheal disorders by stimulating the development of colonies of short-chain fatty acids (Rabbani *et al.*,2010).

The nutritional and medicinal properties of papaya are intimately linked. When compared to other foods, papaya is considered a nutrient-dense food since it provides many more nutrients per calorie. The mineral and chemical makeup, as well as vitamins. The consumption of papaya after a meal can improve digestion, prevent bloating and chronic indigestion, as well as help in preventing nausea and vomiting.

Antibacterial activity against Staphylococcus aureus, Bacillus cereus, Bacillus subtilis. Salmonella typhi, Proteus vulgaris. Pseudomonas aeruginosa, Escherichia coli. and Shigella flexneri has been documented in both ripe and unripe fruits reported antibacterial action against trophozoites of Trichomonas vaginalis Latex proteins are thought to have antifungal properties. These help to prevent diarrhea (Chen et al., 2007).

## Gastrointestinal Manifestations of Covid – 19

Coronavirus disease 2019 (Covid-19) is a respiratory ailment occurred by coronavirus 2 that produced severe respiratory problems. The World Health Organization categorized it as a pandemic in March 2020, making it a public health emergency. Although it is largely a respiratory condition, its impact can be seen in the digestive system and manifests as diarrhea, anorexia, and vomiting (Ungaro et al., 2020). Our body's largest immune organ is known as the GI tract and places millions of microorganisms. Reports of GI symptoms including diarrhea in covid- 19 patients establish the relationship between the GI tract and the disease. These GI symptoms of covid-19 make it difficult to feed patients and meet their nutritional goals. During the Covid-19 situation, gut organisms were also suggested as it found to be beneficial for different other diseases with the same kind of complications. It's crucial to note that various drugs for Covid-19, like antivirals and antibiotics, may affect the gut bacteria, opening up new prophylaxis for which they might use. Probiotics can affect host immunological networks by activating numerous immune systems. The use of probiotics to enhance the immune system is suggested in the Covid-19 guidelines.

## CONCLUSION

Antibiotic-associated diarrhea (AAD) is a typical side effect of antibiotic therapy that can be mild or severe. AAD is becoming more common as broadspectrum antibiotics become more widely available, the population ages, and health issues grow more prevalent. Studies frequently reported diverse etiologies or do not properly diagnose them; have a range of incubation period definitions; follow patients for varying amounts of time; and use diagnostic methods. Specific etiologic diarrhea requires treatment. Functional foods, such as probiotics, are beneficial to one's health. Fermented foods contain live microbes and their secondary metabolites, which are responsible for a variety of healthpromoting characteristics and

antimicrobial properties. Nutritional care was offered for many GI symptoms and treatments of people with Covid 19.

**Conflict of Interest:** Authors have declared that no competing interests exist.

Author contributions: Paper writing was carried out by Sreerupa Bedi and Manisha Maity. The information collection was done by Samapti Bedi and Satarupa Ghosh. The main conceptualization of the study was done by Bidyut Bandhopadyay.

## ACKNOWLEDGEMENT

The authors acknowledge the support given by the School of Allied Health Sciences, Swami Vivekananda University, India forthis study.

## REFERENCES

- Aronsson, B., Mollby, R. and Nord, C. E. (1985). Antimicrobial agents and Clostridium difficile in acute enteric disease: epidemiological data from Sweden, 1980–1982. Journal of Infectious Diseases, 151(3), 476-481.
- Bartlett, J. G. (1992). Antibioticassociated diarrhea. *Clinical Infectious Diseases*, 15(4), 573-581.
- Berman, L., Carling, T., Fitzgerald, T. N., Bell, R. L., Duffy, A. J., Longo, W. E. and Roberts, K. E. (2008). Defining surgical therapy for pseudomembranous colitis with toxic megacolon. *Journal of clinical gastroenterology*, 42(5), 476-480.
- Brown, E., Talbot, G. H., Axelrod, P., Provencher, M. and Hoegg, C. (1990). Risk factors for Clostridium difficile toxin- associated diarrhea. *Infection Control & Hospital Epidemiology*, 11(6), 283-290.
- 5. Chen, Y. T., Hsu, L. H., Huang, I. P.,

Tsai, T. C., Lee, G. C. and Shaw, J. F. (2007). Gene cloning and characterization of a novel recombinant antifungal chitinase from papaya (Carica papaya). *Journal of agricultural and food chemistry*, 55(3), 714-722.

- 6. Flemming, K. and Ackermann, G. (2007). Prevalence of enterotoxin producing *Staphylococcus aureus* in stools of patients with nosocomial diarrhea. *Infection*, 35, 356-358.
- Harris, L. A. and Baffy, N. (2017). Modulation of the gut microbiota: a focus on treatments for irritable bowel syndrome.
- 8. *Postgraduate medicine*, 129(8), 872-888.
- Högenauer, C., Langner, C., Beubler, E., Lippe, I. T., Schicho, R., Gorkiewicz, G., ... & Hinterleitner, T. A. (2006). Klebsiella oxytoca as a causative organism of antibioticassociated hemorrhagic colitis. *New England Journal of Medicine*, 355(23), 2418-2426.
- 10. Jeong, D., Kim, D. H., Kang, I. B., Kim, H., Song, K. Y., Kim, H. S. and Seo, K. H. (2017). Modulation of gut microbiota and increase in fecal water content in mice induced bv of administration Lactobacillus DN1. kefiranofaciens Food Å function, 8(2), 680-686.
- 11. Litao, G., Jingjing, S., Yu, L., Lei, Z., Xiaona, H., & Zhijing, Z. (2018). Risk antibiotic-associated factors for diarrhea in critically ill patients. *Medical* science monitor: international medical journal of experimental and clinical research, 24, 5000.
- 12. Marteau, P. M., Minekus, M., Havenaar, R. and Huis, J. H. J. (1997).

Survival of lactic acid bacteria in a dynamic model of the stomach and small intestine: validation and the effects of bile. *Journal of dairy science*, 80(6), 1031-1037.

- McDonald, L. C., Coignard, B., Dubberke, E., Song, X., Horan, T., Kutty, P. K. and Ad Hoc Clostridium difficile Surveillance Working Group. (2007). Recommendations for surveillance of Clostridium difficile– associated disease. *Infection Control & Hospital Epidemiology*, 28(2), 140-145.
- McFarland, L. V. (1998). Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. *Digestive Diseases*, 16(5), 292-307.
- Т., 15. Monaghan, Boswell, T. and Mahida, Y. R. (2009).Recent advances in Clostridium difficileassociated disease. *Postgraduate* medical journal, 85(1001), 152-162.
- 16. Nielsen, E. S., Garnås, E., Jensen, K. J., Hansen, L. H., Olsen, P. S., Ritz, C. and Nielsen, D. S. (2018). Lactofermented sauerkraut improves symptoms in IBS patients independent of product pasteurization–a pilot study. *Food & function*, 9(10), 5323-5335.
- 17. Peeters, T., Matthijs, G., Depoortere, I., Cachet, T., Hoogmartens, J. and Vantrappen, G. (1989). Erythromycin is a motilin receptor agonist. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 257(3), G470-G474.
- 18. Pépin, J., Valiquette, L., Alary, M. E., Villemure, P., Pelletier, A., Forget, K. and Chouinard, D. (2004). *Clostridium* difficile- associated diarrhea in a region of Quebec from

1991 to 2003: a changing pattern of disease severity. *Cmaj*, 171(5), 466-472.

- 19. Ray, M., Ghosh, K., Singh, S. and Mondal, K. C. (2016). Folk to functional: an explorative overview of rice-based fermented foods and beverages in India. *Journal of Ethnic Foods*, 3(1), 5-18.
- Ross, R. P., Stanton, C., Hill, C., Fitzgerald, G. F. and Coffey, A. (2000). Novel cultures for cheese improvement. *Trends in Food Science* & *Technology*, 11(3), 96-104.
- 21. Spellberg, B., Guidos, R., Gilbert, D., Bradley, J., Boucher, H. W., Scheld, W. M. and Infectious Diseases Society of America. (2008). The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clinical infectious diseases*, 46(2), 155-164.
- 22. Surawicz, C. and McFarland, L. (1999). Pseudomembranous colitis: causes and cures. *Digestion*, 60(2), 91-100.
- 23. Tedesco, F. J., Barton, R. W. and ALPERS, D. H. (1974). Clindamycinassociated colitis: a prospective study. *Annals of internal medicine*, 81(4), 429-433.
- 24. Ungaro, R. C., Sullivan, T., Colombel, J. F. and Patel, G. (2020). What should gastroenterologists and patients know about COVID-19?. *Clinical Gastroenterology and Hepatology*, 18(7), 1409-1411.
- 25. Vinderola, C. G., Mocchiutti, P. and Reinheimer, J. A. (2002). Interactions among lactic acid starter and probiotic bacteria used for fermented dairy products. *Journal of Dairy science*, 85(4), 721-729.