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EFFECTS OF PREBIOTIC SUPPLEMENTATION ON LACTOSE INTOLERANCE AND LACTOSE MAL-DIGESTION: A SYSTEMATIC REVIEW OF INULIN-TYPE FRUCTANS UTILIZATION BY LACTIC ACID BACTERIA AND PROMOTES GUT HEALTH

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ABSTRACT

Milk and dairy products are considering an important human diet which accelerates normal physiological growth and development in mammalian. However, the consumption of these diet not made possible to tolerate by every individual especially in adulthood. Lactose intolerance (or) lactose mal-digestion is a metabolic disorder, affects approximately 75% of the world population. In this condition, the expression of lactase in the brush border of the small intestine is reduced. Lactase is a hydrolytic enzyme which cleaves the sugar lactose found in the milk and dairy products into glucose and galactose in the small intestine. The mal-digestion of lactose results in the clinical symptoms include abdominal pain, bloating, cramps, flatulence, diarrhea, constipation, nausea, and vomiting. Several studies demonstrated that probiotics administration could alleviate in the gastrointestinal symptoms but some strains are sensitive to gastric environment and bile condition of our body and also still it is having challenges. Prebiotics are dietary fibers which shows promising results in lactose intolerance. Fructo-oligosaccharides (FOS) especially inulin-based supplements could alleviate the symptoms of lactose mal-digestion as well as they stimulate the intestinal microbial flora and encouraging their growth. This study to discuss about inulin based supplements could modify the mechanisms of microbiota and alleviate the symptoms of lactose intolerance and helps to recover from gastrointestinal disorders including lactose intolerance. Even we discuss, formulate Inulin-type Fructans, which is derived from the dandelion roots as prebiotic supplements which plays a decisive role in the stimulation and growth of beneficial gut- microbiota as well as gut health.

KEYWORDS: Lactose intolerance, Fructo-oligosaccharides, Inulin, Microbial gut flora and dairy products.

INTRODUCTION

Lactose intolerance (LI) is a metabolic disorder in which an individual is unable to digest milk or dairy products, due to the decreased expression of intestinal lactase or β- galactosidase in the brush border of the small intestinal mucosa.[1,2] Under the normal phenomenon, the enzymatic activity of the β-galactosidase or lactase which facilitates the cleavage of lactose, a disaccharide carbohydrate which composed of glucose and galactose widely distributed in mammalian milk and which are then absorbed.[3,4,5] In lactose deficiency, the disaccharide carb-ohydrate is not digested properly, which is then transported ultimately into large intestine where the bacterial microflora ferments the sugar lactose owing to their genetic capability to produce the enzyme β-galactosidase. As a result, it produces various byproduct such as lactate, short-chain fatty acids (SCFAs), H2, CO2, and CH4. These lactose metabolites are osmotic active products which causes an osmotic pressure as result large amount of water drawn into intestine which leads to develop abnormal symptoms that includes bloating, cramps, flatulence, abdominal pain, nausea and vomiting.[6] Intaking of mammalian milk or dairy products is a part of healthy diet for all age groups and it is in rich source of high quality proteins, calcium, fat, carbohydrates, minerals, vitamins, and other trace elements.[7] Physiologically, the intaking of dairy products has been associated with numerous health benefits by preventing osteoporosis, childhood obesity and type 2 diabetes, some types of cancer, and is inversely associated with hypertension, stroke, and other cardio-metabolic

diseases.[8,9,10]

LI can be primary, secondary and congenital or developmental types. Among that primary lactose intolerance is most frequent form of lactase deficiency. It is an adult-type hypolactasia which defines usually people born with enough lactase; which decreases along with age between 2 to 5 years depends upon the ethnicity.[11,12] The prevalence of primary lactose intolerance (adult-type hypolactasia), varies among different ethnic groups and geographic locations. According to NIH, across the world wide nearly 75% people are affected, out of it, 68% were adults. In East Asian heritage, it found between 70 to 100% in the general population, ranging between 75 to 90% of Americans, Black people, Asians, Mediterraneans and jewish people are affected. About 5% only Europeans have lactose intolerance. As per the report by NIH, it is estimated that about 80% people in china are being risk at LI. Followed by 36% in United States, while it accounts for approximately 61% in India.[13] In the recent years, the probiotics which are considering as living beneficial microorganisms through the oral consumption which demonstrated an enormous role in lactose intolerance.[14] Owing to their capability to modulate the intestinal microbial flora, which accelerating in lactose digestion and absorption.

Nowadays, numerous studies have provided the evidence that probiotics are very effective in lactose mal-digestion and eventually alleviating the abnormal symptoms in lactose intolerance.[15,16,17,18] But, there was a small study which was performed by university college London in 2014, it was concerned on the survival of the probiotics over the acidic environment of the stomach. They have subjected around 8 types of probiotics among that 2 types of probiotics were survived over the gut acidity and flourished in the intestine. Prebiotics are the functional food supplements which feeds to native gut microbiota and helps to increasing their population. The pure prebiotic Galacto- oligosaccharides (GOS) which has shown to be increased the abundance of lactose-digesting bacteria such as *Bifidobacterium*, *Faecalibacterium*, *Lactobacillus*, and *Roseburia* species.[19] GOS are conferred as short-chain galacto oligosaccharides which consisting of two to five residues of galactose terminating with an N-terminal glucose which makes the formation of lactose as a terminal disaccharide within the molecule. Generally, the prebiotics or oligosaccharides are carbohydrate fiber supplements which are not digested by human body rather it is utilized by some members of gut microbiota, notably, *lactobacilli*, *bifidobacteria* and also by other commensal gut flora of intestinal community.[20] The prebiotic inulin, a type of GOS and water soluble polysaccharide which naturally occurs in the dandelion plant root have significantly induce the abundance of good gut-microbiota through the oral food consumption. In addition, dandelion roots are fortified with higher number of phenolic acids, antioxidant properties and coumarins with anticancer, anti-inflammatory, antibacterial, and antithrombotic effects.[21]

This review paper highlights the administration of Inulin prebiotic which modifies the gut microbiota by increasing the commensal of intestinal community particularly, lactic acid bacteria. The inulin prebiotic that feeds to lactic acid bacteria, as a result that helps to alleviate the clinical symptoms from lactose intolerance by producing the enzyme β-galactosidase which breakdowns the sugar lactose into simple sugar molecules such as glucose and galactose and then are absorbed. This systemic review also expressing the potential health benefits which are corresponded with inulin prebiotic over the physiological goodness.

IMPORTANT OF LACTOSE IN HUMAN DIET

Lactose, a disaccharide carbohydrate which exhibits as white Crystalline sugar. Biochemically, it consisting of D-glucose & D-galactose which is linked by O-β-D-glucopyranosyl-(1-4)-β-glucose. Lactose is considering a main constitute and naturally occurring sugar in Mammalian milk which is synthesized by lactose synthetase system in mammary gland through the binding of D- glucose and D- galactose with a β-(1,4) glycosidic bond.[22] Since 8000 years, Milk and dairy products have been considering an important human diet as well as listed out an essential nutritional recommendations across the worldwide. Indeed, dairy products contribute about 52-65% of diet requirements as they are rich source of protein, calcium, potassium, phosphorus, Magnesium, zinc and other vital nutrients for human growth and development.[5,7] According to Randomised Controlled Trial (RCT), an intaking of dairy products have played a significant development in height, Body weight, Bone Mineral Content (BMC) especially in school girls below 10 years owing to calcium, phosphate supplements found in milk.[9] Certain substances that include dipalmitoyl, lecithin and prostaglandins in milk which promising the possible protection against mucosal damage by gastric acid. Lactose itself acts as natural prebiotic which stimulates the beneficial gut-microbiota and its indispensable functions in human gut.[10]

LACTOSE MAL-DIGESTION AND LACTOSE INTOLERANCE

For the digestion of sugar lactose our body requires a specialized enzyme, commonly known as Lactase. In the small intestine, especially the upper surface of the microvilli which possess a specialized cells called enterocytes whereas the lactase also well known as β-galactosidase are synthesized. B-galactosidase composed of two identical extracellular 160kDa polypeptide chains, as well as a short intracytoplasmic part. This enzymatic production is predominantly expressed in jejunum whereas little fermentation occurs due to the lower concentration of bacterial population. Under the normal circumstances, the milk sugar lactose disaccharides are converted into simple monosaccharides of glucose and galactose which is

facilitated by β-galactosidase. These monosaccharides are which upon actively transported into enterocytes by sodium (+)/glucose (galactose) co-transporter (SGLT1). In small intestine, hair like projections found on upper surface called microvilli uptakes all the nutrients and transport into liver for further metabolism whereas glucose utilized by living cells as energy source and galactose servers as a part of glycoproteins and glycolipids.[11,12, 13,14] In case of lactose mal-digestion, the β-galactosidase concentration is decreased which is typically begins in childhood (primary lactose intolerance). As a result of this reduction of lactase concentration, this allows the lactose disaccharides (glucose and galactose) mayenter into colon and where it is fermented by colonic microbiota and exhibits various abnormal symptoms (Fig. 1).

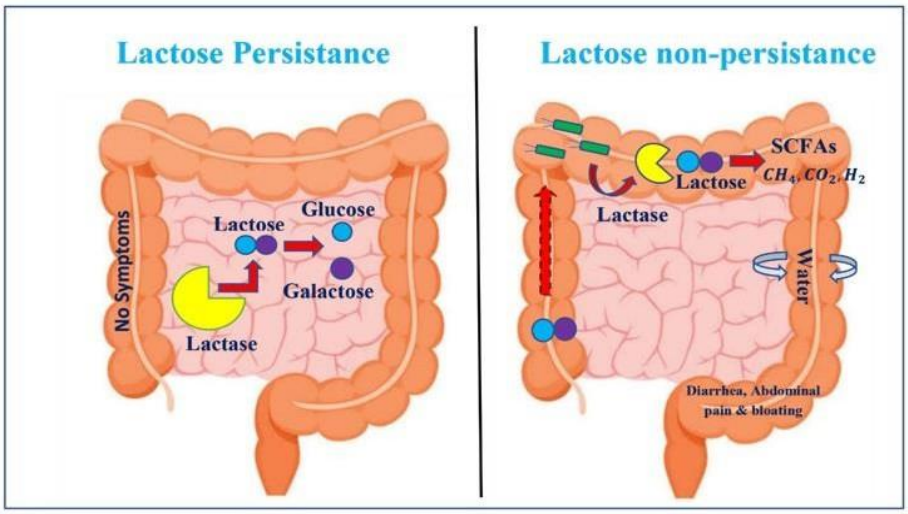

Figure. 1: Digestion and Mal-digestion of lactose in Lactose Persistance ana Lactose non-persistance

CLINICAL SYMPTOMS IN LACTOSE INTOLERANCE

In colon, wide proportion of gut-microbiota which naturally acquired the genetic capability to synthesize β-galactosidase by their own. When the undigested lactose sugar from small intestine may transported into large intestine whereas the disaccharide lactose is fermented by colonic microbiota. This colonic (anaerobic) fermentation on lactose by microbiota will results two major phenomenon. First, it increases the osmotic pressure; owing to this, large amount of water content ultimately drawn into large intestine. Secondly, the colonic fermentation of lactose sugar leading to the production of various byproducts includes lactate, short-chain fatty acids (SCFAs), H2, CO2, and CH4.[6, 23, 19] The production of these byproducts, develops abnormal symptoms such as abdominal pain, bloating, cramps, flatulence, diarrhea, borborygmi, some patients may experience,constipation, nausea, and vomiting. Typically these symptoms may appears within 1 hour or later after the consumption of lactose. Nevertheless, some toxic effects of these byproducts such as acetate and other substances may causes other extra-intestinal symptoms includes anxiety, cephalalgy mucoskeletal pain, depression, memory deterioration, hear rhythm disorders and oral mucosa ulcers.[21,24,25,26]

TYPES OF LACTOSE INTOLERANCE

Lactose mal-digestion or LI may be classified as 3 simple types; i) Primary lactose intolerance also known as lactase non-persistence, adult-type hypolactasia. Primary intolerance is regulated by genetic often it is referred as hereditary lactase deficiency. In this type, the hydrolyticcapability of β-galactosidase in small intestine obtains crest during early childhood and being continued to reduced throughout the life which usually begins at adulecenes period depending on ethnicity.[14] (adult-type hypolactasia). Comparetively with other types, adult-type hypolactasia have been observed ¼ or 1/3 across the world's population. The most common reason for occurring this phenomenon due to the variable polymorphisms occur in lactase gene particularly in the promotor region of transcription.[27] Secondary lactose in tolerance developes due to some clinical conditions such as microbial infections (rotavirus, giardiasis and cryptosporidiosis), inflammatory bowel diseases (ulcerative colitis, ulcerative colitis and celiac disease), antibiotic administrations (chemotherapeutic drugs, colchicine, kanamycin, neomycin, polymycin and tetracycline) or patients may undergo some surgical conditions (stagnant loop syndrome or short bowel syndrome) and frequent exposer into radiation. All these clinical conditions affect the microvilli found on the apex of the duodenal villus where the lactase synthesis is taking place.[28] Congenital lactose intolerance, otherwise known as a lactasia is very rare and uncommon often develops in infants. In this condition, the β-galactosidase is completely absent or unable to produce due to the inheritance of two alleles in LCT gene of brush border of the small intestine. Mostly, infants can be suffered after

being fed with breast milk or consumption of milk and dairy formulations. The clinical syndromes include renal tubular acidosis, alkalosis, aminoaciduria, dehydration, and hyper calcemia.[29] Also, we discussed about the various types of LI in Table 1.

Table. 1: Glossary with definitions related to lactose intolerance or lactose mal-digestion.

Glossary	Acronym	Definition
Lactose Persistence	LP	People can efficiently digest lactose due to intestine produce sufficient lactose.
Lactose non-persistence	LNP	An individual has reduced lactase activity in the brush border of Small intestine.
Lactose Mal-digestion	LM	Due to lactase deficiency, an individual doesn't digest lactose.
Lactose Mal-absorption	LM	Inability of an individual body doesn't absorb lactose due to lactase deficiency.
Lactase Deficiency	LD	The decreased or inability synthesis of lactase in the brush border of small intestine.
Primary lactose intolerance	PLI	The synthesis of lactase in the peak at birth meanwhile reduced during adolescence.
Secondary lactose intolerance	SLI	Insufficient lactase production due to severe infection, inflammatory bowl disease or patient may undergoes surgery.
Congenital lactose intolerance	CLI	Reduced lactase activity due to genetic factors.

EPIDEMIOLOGY

The prevalence of lactose non-persistance (LNP) or LI firmly depends on ethnic groups. Since the prevalence of LNP are widely distributed in Northen European population as compared to Southern European Population. Establishment of some Epidemiological studies revealed that between 2/3 and ¾ of human poplation were affected and ¼ and 1/3 of world population retain the ability to digest the lactose.[27] According to NIH, across the world wide nearly 75% people are affected, out of it, 68% were adults. In East Asian heritage, it found between 70 to 100% in the general population, ranging between 75 to 90% of Americans, Black people, Asians, Mediterraneans and jewish people are affected. About 5% only Europeans have lactose intolerance. As per the report by NIH, it is estimated that about 80% people in china are being risk at LI. Followed by 36% in United States, while it accounts for approximately 61% in India.

EVALUATION AND THE CONCEPTUAL MODEL OF PREBIOTICS

In 1995, the conceptual model of prebiotics was first developed by Glenn Gibson and Marcel Roberfroid.[30] In general, prebiotics are referred as non-digestible fibers mostly belonging to oligosaccharides which cannot be digested by human body. In 2004, Gibson et al were coined a term called "bifidogenic factors" non-digestible food ingredients which are resist to gastric acid and not breakdown by mammalian enzymes rather it plays a beneficial role by stimulating the growth of selectively good gut-microbiota (*bifidobacteria, lactobacillus*) and limiting the number of colonic microbiota, thus improves the gut health.[31] In 2008, an International Scientific Association of Probiotics and Prebiotics (ISAPP) used a term "dietary prebiotics" are fermented oligosaccharides which selectively modifies the intestinal gut-microbioa thus, promotes host health.[32] Prebiotics are promising the health benefits through various factors in host by producing SCFA's, acetate, butyrate and propionate, anti-inflammatory properties, decreases the toxic productions in colon, enhances Th1/Th2 ratio, formation of leukocytes and stimulates IgA secretion in intestine.[33]

The prebiotic substance should posess the following characteristics in order to obtain the host to be benefited; it should be resist to acidic pH of stomach, it cannot be digested by mammalian enzymes rather utilized by gut-microbiota and it should selectively enhances the growth of good gut-microbiota.[34] An additionally different function of prebiotics are described in Table 2.

INULIN; A POTENTIAL PREBIOTIC

Inulin is considering as one of the good sources of prebiotics, which are water soluble polysaccharide belongs to fructan type carbohydrate. They are polymers (fructans) consisting of two chains; longer chain is inulin which has DP- 2 to 60 and shorter chain is fructo-oligosaccharides contains DP- 2 to 8 and linked by terminal α-linked glucose by β-2,1 bond.[33,35] The dietary fibers of inulin makes the mammalian enzymes to digest very difficult due to the presence of β- D- frutosyl fructose bonds otherwise it is possible for colonic bacteria.[36] (Illippangama 2022). These inulin-type fructans are non-digestible carbohydrate whose DP is <10%, low in calories and most commonly utilized by food industries. Nowadays the necessity of inulin in food industries become wide as they are having the property of replacing fat and sugar in various food preparations andenhancing the flavor of food as well.[37,38]

Table 2: Sources, structure and functions of various prebiotics.

Types of Prebiotics	Sources	Chemical structure	Functions
Galactooligosaccharides (GOS)	Human's milk and Cow milk.	Galactose and Glucose bound by β (1? 3) and β (1? 4) linkages	Increases bifidobacterium activity.
Fructooligosaccharides (FOS)	Asparagus, Sugar beet, Garlic, Chicory root, Onion, Banana etc.	Glucose and Fructose units linked by β (2? 1) glycosidic linkages	Enhances miniral absorption, immunity, prevents diabetes, cancer and inhibits pathogenic microorganisms.
Fructans	Chicory root, Jerusalem artichoke, Onion, Garlic, Wheat, Barley etc.	fructose with β (2? 1) linkage	Modulate the gut-microbiota.
Xylooligosaccharides (XOS)	Bamboo shoots, Fruits, Vegetables, Milk, Honey and Wheat bran.	xylose units linked through β (1? 4) bonds	Non-digestible and carcinogenic, promotes gut health.
Soybean oligosaccharides (SOS)	Soybean	galactose α-(1-6) linked to glucose (Raffinose)galactose α-(1-6) linked to terminal galactose (Stachyose)	Improve immunity especially IgG level.
Pectinoligosaccharides (POS)	Fruits and Vegetables.	(1-4)-α-D-GalA (galacturonic acid) - (1,2)-α-L-Rha	Anti-inflammatory properties.
Isomaltooligosaccharides (IMO)	Honey and Sugarcane juice.	Glucose bonds by α (1? 4) type	Improve Gut-microbiota population.
Guar gum	Cyamopsis tetragonoloba.	β-D-mannopyranosyl (1-4) linked with α-D-	Improve cholesterol, glycemia.

THE CHARACTERIZATION AND DIVERSITY OF GUT MICROBIOME

The diversity and distribution of human gut-microbiota obtains several taxa which includes bacteria, viruses, protozoa, and fungi. Approximately 100 trillion microorganisms harbour in human gut is estimated; they includes *Actinobacteria, Bacteroidetes, Fusobacteria, Firmicutes, Proteobacteria and Verrucomicrobia*. Among that, *Bacteroidetes* and *Firmicutes* are primarly colonized as a part of human gut (90%) whereas *Actinobacteria, Proteobacteria,* and *Verrucomicrobia* are harboured lesser amount.[39,40] According to the distribution, colonization and functions of these probiotics are classified into 3 major groups; *Lactobacilli, Bifidobacteria* and others. Among all these probiotics, Lactobacilli are promising various beneficial aspects in human at present.[41] Nowadays, the microbial sequencing includes 16srRNA sequencing and whole genome sequencing includes metabolomics, metagenomics, metaproteomics and metatranscriptomics are the possible insights for the eco-system and metabolic activities of gut-microbiota.[42] The function of intestinal gut microbiota discussed in Table 3.

Table. 3: Functions of various intestinal gut-microbiota.

LAB Strains	Functions
Bifidobacterium longum	Antioxidant, Anticancer, Antibacterial, immunological activities, inhibiting linoleic acid peroxidation.
Bifidobacterium adolescentis	Reduces the inflammation occurs in spleen and brain. Modulating the microbiota of cecum and colon. Increases the TNF-α Production.
Lactobacillus casei	Prevents the intestine from diseases. Induce apoptosis.
Lactobacillus acidophilus	Anti-cancer activity, induces apoptosis, increases immune cells such as T-cells, NK-cells etc. Lower cholesterol level and relieve from diarrhea.
Lactobacillus rhamnosus	It has anti-bacterial, anti-fungal activity. Preventing UTI infections in women.
Lactobacillus lactis	Breakdowns amino acids into volatile flavor substances and enhancing the texture and flavor of fermented products.
Streptococcus thermophilus	It releases ROS protective factors.
Pediococcus pentosaceus	Binds with colonic cancer cells and produce SCFAs.

IMPACT OF FOS ON GUT MICROBIOME AND HOW DOES INULIN MODIFIES GUT MICROBIOME?

Inulin are non-digestible dietary fibers which play a tremendous role in response to regulating the gut-microbiota. More recently, International Scientific Association of Pro- and Prebiotics (ISAPP-2017) defined prebiotics as "substrates which selective fermented ingredients which is adopted and metabolized by gut-microbiota thus, improving the human intestinal health.[34] GOS which predominantly increases *Bifidobacterium, Faecalibacterium, Lactobacillus,* and *Roseburia* species.[43, 44] Moreover, Inulin-type fructans are selectively promotes the abundance of *bifidobacterium* and *Lactobacilli* which are currently accelerating its potential in more research studies at present (Fig. 2). It is estimated that prebiotics might boosting up gut health by maintaining the integrity of mucosal protection through increasing the beneficial and commensal bacteria.[45] The administration of inulin dietary fibers not only promotes the growth of gut-microbiota but also develop protective barrier of mucosal layer of intestine which defeat the colonization and growth of opportunistic pathobionts (enterobacteriacae).[46,47]

In addition, for modifying the abundance of *bifibacterium* and *lactobacilli*, the potential use of inulin dietary fibers have been shown promising aspects in recent times. The inulin-type fructans, primarily accelerating immune response, reducing inflammation, improving bowl functions and representing as blood markers such as glucose, lipids and inulin.[48,49,50,51] For instance, inulin dietary fibers naturally found in chicory root and Jerusalem artichokes large amount.[52] Several animal studies have demonstrated that bacterial fermentation of inulin may results in acidification of gut environment, intensify the calcium, magnesium absorption and bone mineralization.[53] The intermediate metabolites are formed by the inulin fermentation by bacteria, produces short-chain fatty acids (SCFA) and lipopolysaccharides which are reported has to be modified gut-microbiota. These Short Chain Fatty Acids (SCFA's)released into bloodstream thus interacting with various immune cells and regulates Apoptosis, differentiation, gene expression, proliferation to enhance immune function and butyrate are utilized by intestinal colonic epithelial cells.[54]

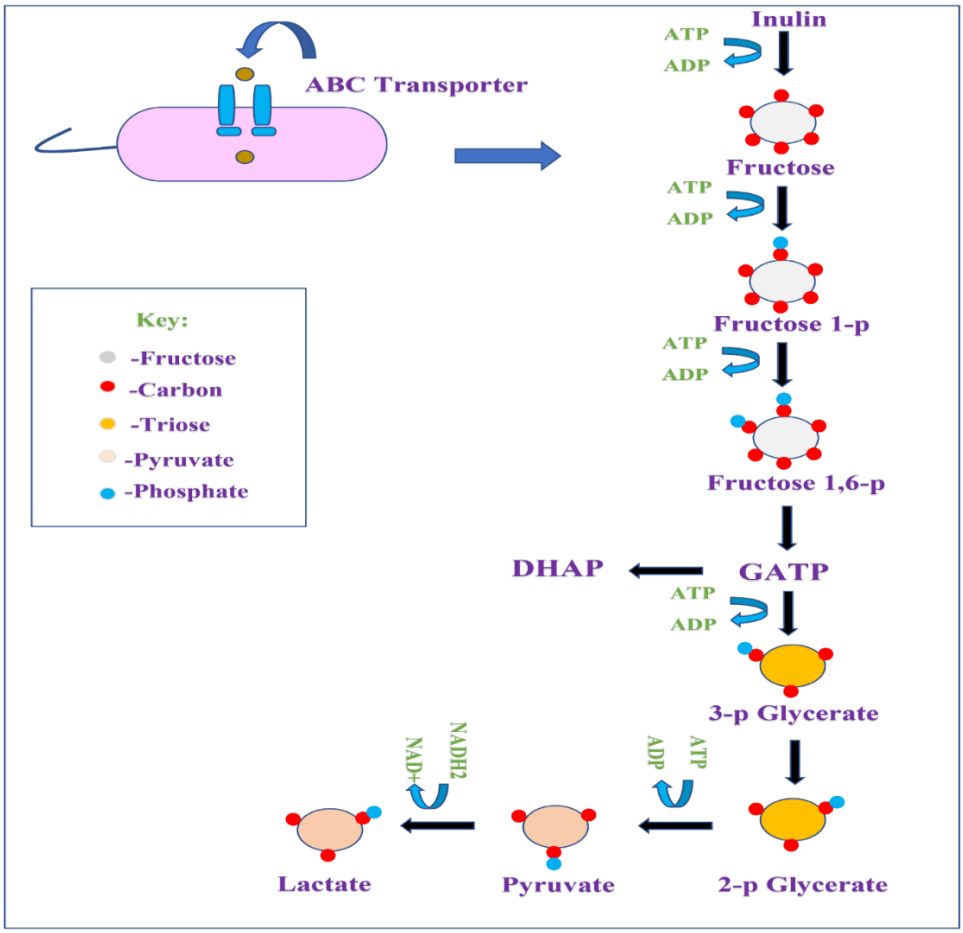

Figure 3: Inulin utilization by lactic acid bacteria.

EFFICACY OF LAB TO ALLEVIATE SYMPTOMS IN LI

Lactic Acid Bacteria, *lactobacilli* and *bifidobacterium* have been estimated the great intensively producers of β-galactosidase. Several studies were revealed that lactic acid bacteria containing fermented dairy products includes yogurt and fermented milk foods efficiently hydrolyse the lactose disaccharide hence, reduces the LI symptoms.[55] (Fig 3, 4). After the four-week consumption of fermented dairy products such as yogurt which contains *Lactobacillus casei, Lactobacillus shirota* and *Bifidobacterium breve* eventually reduces the Hydrogen production and symptoms in LI patients.[56] A recent systematic review of several treatments has anticipated the administration of probiotics such as *Bifidobacterium animalis, Bifidobacterium longum.*

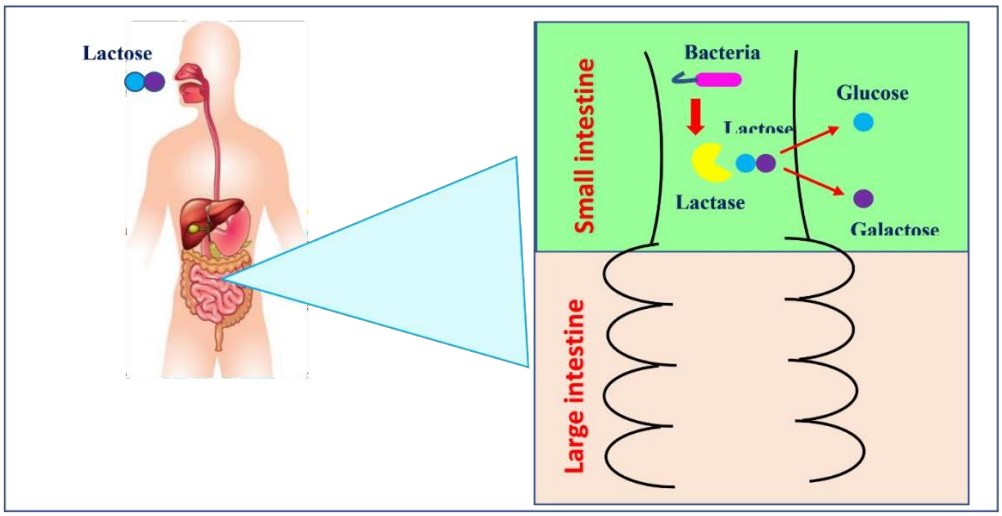

Figure 3: Lactose metabolism by lactic acid bacteria which results in no clinical symptoms.

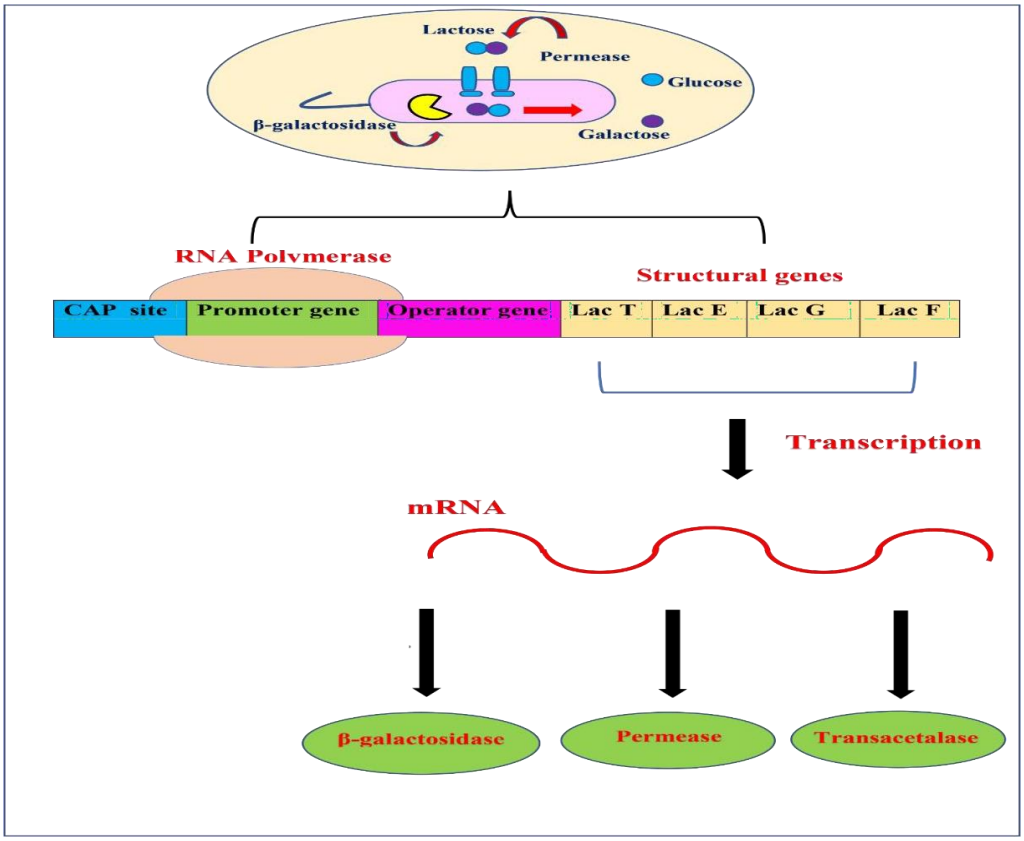

Fig. 4: Gene expression of *lactobacillus sp.*, in Lac Operon model.

Lactobacillus spp., are actively produces lactase in small intestine.[57] In general, some beneficial gut-microbiota includes *Streptococcus thermophiles*, *Lactobacillus delbrueckii spp. Bulgaricus* are effective against the LI patients due to their intensive hydrolyze of lactose by synthesizing β-galactosidase.[50] It is observed that the aboundance of bacterial fermentation primarly taking place in small intestine hence, there could not be any colonic fermentation will occur on lactose which dominates the formation of clinical symptoms.[58] Recent research suggested the GOS and Inulin-type fructans are brokendown by β-galactosidase secreted by *Bifidobacterium, Faecalibacterium, Lactobacillus*, and *Roseburia* and promotes the growth of lactose-fermenting gut-microbiota such *as Bifidobacterium breve, B. longum, B. infantis, L. acidophilus, L. casei, L. rhamnosus* and *S. thermophilus* thus reduces the abnormal symptoms in LI patients.[59,44]

CONCLUSION

This paper mainly highlights that prebiotics administration, especially inulin-based fructans are non-digestible dietary fibers which are not utilized by human body rather it is metabolized by gut-microbiome as a result the increased growth of gut-microbiome particularly Lactic Acid Bacteria. These lactic acid bacteria are capable of producing β-galactosidase enzyme which hydrolysis the lactose disaccharide sugar into simple monosaccharide namely glucose and galactose. This enzymatic phenomenon of lactic acid bacteria thus, results in reducing the abnormal gastro-intestinal symptoms such as bloating, vomiting, nausea, diarrhea, abdominal pain and flatulence etc. Further research into the mechanism of lactic acid bacteria with regards to reduction of clinical symptoms of lactose intolerance are necessary. This review paper also emphasizing a promising outcomes to formulate a prebiotic supplements namely FOS from the source of root dandelion. These prebiotics selectively stimulates the microbiota and consequently results in the improvement of digestion, mineral absorption, regulating sugar and cholesterol level in the blood, boosting up immune system and several health benefits.

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