

Effect of dietary inulin with hypercholesterolemia

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Abstract

The carbohydrates known as non-digestible oligosaccharides (NDO) include inulin-fructooligosaccharides (FOS), which have been consumed by humans for a very long time. In *vitro* and in *vivo* research have demonstrated that inulin has several nutritional benefits, primarily related to the stimulation of *bifidobacteria*. Similar to dietary fiber, inulin shares all the properties and health advantages of non-digestible polysaccharides (NDP). The normal physical effects of dietary fiber, including significant increases in osmotic pressure, intestinal bulking effects, intensive water holding, and dramatic viscosity building, are not present in inulin.

The capacity of inulin to specifically promote the growth of bacterial genera and species known to be health-promoting in vivo in humans, such as *Bifidobacterium* (apart from *Bifidum*) and *Lactobacillus*, at the expense of potentially harmful microorganisms, accounts for a number of the vitamin's more notable health benefits. Therefore, inulin is typically regarded as a bifidogenic factor prebiotic. Prebiotics, such as inulin, have the advantage of promoting the selective growth of endogenous bacteria in their natural habitat, without being overly impacted by their surroundings, unlike probiotics.

Inulin can be referred to as a "physiologically functional food" or food ingredient, or simply a food with potential health-promoting effects, due to its effects on gut microbiota, blood glucose attenuation, lipid homeostasis, mineral and nitrogen bioavailability, immunomodulation effects, and the ability to add texture and improve rheological characteristics and nutritional properties of food.

Keywords: Hypercholesterolemia, Inulin, Probiotic, Yoghurt.

I. INTRODUCTION

Functional foods

The term "functional foods" was first used in Japan in 1984 as a result of a study of the relationship between food intake and consumer satisfaction, and the physiological changes that these foods cause in human health [11]. The European Federation of Functional Food Science in Europe (FUFOSE) referred in 1999 to the science of functional foods and some of the characteristics that must be available in order for food to be considered functional, which are:

1. It must be in the form of natural food, and the effect of the fortified substance must be in acceptable quantities in the daily diet.
2. It must be a complete natural food or food to which other components have been added or food from which one of the components has been removed by biological or physical techniques.
3. It can be a food in which the bioavailability of one or more specific elements has been modified.
4. Functional food may be beneficial to the entire community or a specific group of it. On the other hand, the International Life Sciences Institute (ILSI) in North America described functional foods as foods that have convincing evidence that they have a beneficial and healthy effect on one or more of the body's functions, unlike traditional foods. Functional foods were also defined by a set of other important definitions, including "foods that contain auxiliary substances or any auxiliary nutritional component or foods that provide a health benefit in addition to nutritional benefits [38], or they are those foods or nutritional elements that provide the body with health and therapeutic benefits in addition to meeting traditional nutritional requirements as nutritional needs.

Dairy products

Lactic acid bacteria have been used in the production of fermented foods, and interest has increased in developed countries due to the health benefits obtained. [16] confirmed that consuming dairy products fermented with lactic acid bacteria (LAB) can control cardiovascular diseases, improve mental health, reduce lactose intolerance, break down phytic acid (an inhibitor of mineral absorption in the intestine), and improve the balance of intestinal microbes.

[1] confirmed in their study on the manufacture of dairy products using lactic acid bacteria, in addition to their role in fermentation and their ability to lower cholesterol levels.

The demand for therapeutic fermented dairy products has increased in recent years due to the development of their manufacturing processes and the belief in the importance of the health-beneficial substances they contain [20]. They also confirmed [25]. Beneficial bacteria resist and expel toxins and strengthen the immune system and can maintain the vitality of starter bacteria for 35 days by adding *Lactobacillus acidophilus*, a type of probiotic bacteria that can be added to fermented milk and loves high acidity. They pointed out [41] that human consumption of dairy products fermented by bacteria helps reduce heart blood pressure in some adults, as proteins in fermented dairy products are broken down into small peptides, which increases their vitality and the body's ability to digest them. These peptides are absorbed in the intestines, thus causing a reduction in blood pressure. Consumption of therapeutic dairy products can also improve difficult immune functions [28].

Cholesterol

It is a sticky, semi-fatty, white, tasteless, and odorless steroid substance that is found in all parts of the body [15].

Cholesterol is found naturally in the brain, nerves, liver, blood, and bile and is essential for the body to function properly [22].

Cholesterol is a type of fat that helps perform some vital functions, but it is harmful if its level in the human body rises above the normal rate for a long time. Cholesterol in the blood is linked to long-chain, unsaturated fatty acids, forming esters, which are transported via lipoproteins through the blood in the body [12].

[17] indicated that there are several factors that affect the level of cholesterol in the blood, namely:

1. Genetic defect in the process of lipoprotein metabolism as a result of internal diseases in the endocrine system, and liver and kidney diseases contribute to causing this defect in cholesterol concentration.
2. Disorder in the secretion of some hormones, including:

A- Thyroid hormone (Thyroxine): It has an opposite effect on cholesterol concentration, so patients who suffer from hyperthyroidism are often accompanied by a significant increase in cholesterol concentration.

B- Female sex hormone (estrogen): It reduces cholesterol levels in the blood.

[33] explained that the level of cholesterol in the blood is classified as follows:

1. The desirable blood cholesterol level, which is less than 200 mg/100 ml.
2. The high blood cholesterol level, which is the dividing line between the desirable and the bad or dangerous, is 200-239 mg/100 ml.
3. The bad or dangerous blood cholesterol level, which is 240 mg/100 ml and above, was previously indicated by [36].

[35] confirmed that the human body produces the cholesterol it needs, so a person does not need to consume it in his diet. Egg yolks, meat, whole milk, and its products are a rich source of cholesterol, while it is not found in fruits, vegetables, grains, nuts, and seeds.

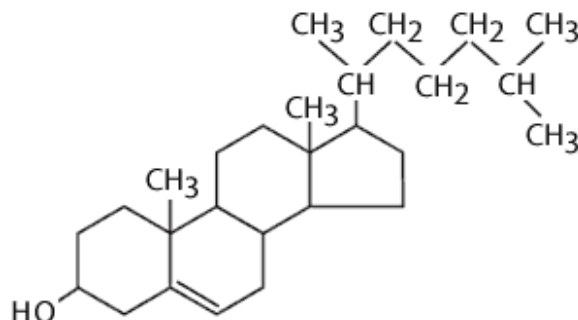
Saturated fatty acids are a major cause of high blood cholesterol, which increases the risk of heart disease. Trans fats are another factor in raising cholesterol levels [52]. Several researchers have noted that consuming oils rich in omega-3 polyunsaturated fatty acids has an effect in reducing blood plasma cholesterol levels and thus protecting against sudden death due to vascular diseases resulting from high cholesterol [37]. The US Department of Agriculture [50] set the dose of cholesterol consumed from food at 200 mg/day and excluded fats from the (Trans) group of meals due to their harmful effect on health.

The Chemical Structure of Cholesterol



The cholesterol molecule consists of 27 carbon atoms arranged in an alcoholic core, consisting of four rings and a tail. Cholesterol contains a saturated phenanthrene core (except for the double bond between C5 = C6) linked to a saturated five-membered ring at positions 13 and 14. It also contains side groups shown in the structural symbol of cholesterol as in Figure (1).

Figure (1). The structural code of cholesterol.



In general, all sterols have the same ring system, but they contain an OH group at position (3) and two methyl groups at positions (18 and 19). They also contain a side chain connected to carbon atom number (17). It is clear from the structural code of cholesterol that the rings are not aromatic rings, as they are all saturated except for ring B, which contains a double bond between carbon atoms (5 and 6) [13].

The harms of cholesterol

Most studies conducted on the relationship between cholesterol and human health have indicated that high levels of cholesterol in the blood are one of the most important factors causing atherosclerosis, which leads to heart and arterial diseases in the body [50] [27].

[44] confirmed that plaques and deposits that occur in the arteries contain a high amount of cholesterol.

[5] explained that high concentrations of a specific type of lipoprotein in the blood, which is low-density lipoprotein (LDL) hyperlipoproteinemia, which contain a high percentage of cholesterol, are closely related to an increased incidence of atherosclerosis, in addition to the fact that its function is to transport this cholesterol from the liver after it is manufactured and transported to the cells of the body's tissues.

The American Heart Association [4] has shown that the presence of cholesterol in the blood at a concentration higher than 150 mg/dL constitutes dangerous signs in the development of hypercholesterolemia and the beginning of atherosclerosis. 96 million people have more than 200 mg/dL cholesterol and 37.8 million have a cholesterol level of 240 mg/dL or more.

High levels of fats, especially cholesterol, in the blood serum are associated with many cardiovascular diseases, as [21] indicated the relationship between high dietary cholesterol and the occurrence of arterial thrombosis when feeding rabbits on a feed containing 1% cholesterol caused damage to the aortic artery with the appearance of narrowing of the blood vessels and thus the possibility of blockage of these vessels and obstruction of blood flow in them, which helps in the formation of a clot.

Cholesterol is the main cause of atherosclerosis, which causes coronary heart diseases (CHD) resulting from the observation of a large percentage of cholesterol among the materials deposited on the walls of the arteries, especially in the clot, as cholesterol constitutes 70% of the components of the cells lining the walls of the arteries, in addition to calcium and carbohydrates. This was confirmed by [30] who found that reducing the level of cholesterol in the blood by 1% leads to a reduction in the incidence of heart disease by 2-3%. Coronary heart diseases and fatal heart attacks that occur in patients suffering from high cholesterol levels in the blood (Hypercholesteremic individuals) are among the most serious diseases in the world. [49] explained that the complications of high cholesterol in the blood include:

Atherosclerosis	تصلب الشرايين
Heart Attack	النوبة القلبية
Myocardial infarction	احتشاء عضلة القلب
Hypertension	ارتفاع ضغط الدم
Cerebral coma	السكتة الدماغية
Infarction	احتشاء

Benefits of Cholesterol

Many people consider cholesterol to be a harmful substance that causes serious diseases in humans, and this is the dark side of the truth, as cholesterol has great benefits for the body, the most important of which is helping the digestive system in the process of digestion and absorption of fatty substances. Since cholesterol is one of the basic components of various types of tissues, especially nervous tissue, it helps in the transmission of nerve currents, and without it, nerve cells cannot be stimulated by sensory stimulation, which results in loss of motor ability and speech.

[43] explained that cholesterol is an important basic element for the manufacture of bile acids, steroid hormones, and fat-soluble vitamins such as A, D, E, and K. also confirmed that cholesterol is a type of fat and is beneficial to the body as it helps in performing some vital functions. Many researchers have indicated that cholesterol can act as an antibiotic [47] [2] [19]. It is important within the cell membrane due to its function in cell transport, nerve signals, and nerve conduction [42]. Within the cell, cholesterol is the primary compound for many biochemical processes [53]. In the liver, cholesterol is converted into bile, which contains salts that dissolve fats in the digestive system and aid in the intestinal absorption of fat molecules [54] [50] confirmed that cholesterol is the primary compound for the manufacture of steroid hormones and adrenal hormones such as cortisol and aldosterone, in addition to sex hormones such as progesterone, estrogen, testosterone, and their derivatives. Cholesterol is important for the construction and maintenance of the cell membrane, as it regulates the fluidity of the membrane over physiological temperatures. The hydroxyl group in cholesterol interacts with the polar head groups of phospholipids and sphingolipids in the membrane, and at the same time the fatty part (steroid) and the hydrocarbon chain are immersed in the membrane alongside the nonpolar fatty acid chain of the other peptide. In this structural role, cholesterol reduces the permeability of the plasma membrane to protons and sodium ions [24] [44]. Found that cholesterol enters into the formation of vitamin D by converting cholesterol present under the skin by sunlight into a compound with the properties of vitamin D, which is the vitamin that prevents rickets. Cholesterol also enters into the formation of cholic acid in the liver, which in turn leads to the secretion of bile juice that the body needs to break down fat, which facilitates the work of enzymes in it and its absorption.

Causes of high cholesterol

The level of cholesterol in the blood is not only affected by what we eat, but also by our bodies' ability to quickly produce cholesterol and quickly get rid of it. In fact, the human body produces what it needs of cholesterol, so it is not necessary to consume additional cholesterol through food. [7] explained that there are several factors that help in raising cholesterol levels, the most important of which are:

1-Genetic factors: Genes determine the speed at which the body produces harmful cholesterol and the speed at which it gets rid of it. There is a type of hereditary high cholesterol that usually leads to early heart disease. However, even

if a person does not suffer from any type of hereditary high cholesterol, genes play an important role in determining the level of harmful cholesterol.

2-Food: There are two main types of food that cause high harmful cholesterol:

A- Saturated fat: These are fats found mainly in animal foods such as meat and chicken, as well as in some vegetable oils such as corn oil and palm oil.

B- Cholesterol: We get it only from animal products such as meat, chicken and eggs. There is nothing in food that causes high levels of harmful cholesterol such as saturated fats, so eating large amounts of saturated fats and cholesterol are the main reason for high levels of harmful cholesterol and increased rates of coronary heart disease.

3-Weight: Significant weight gain (obesity) contributes to raising levels of harmful cholesterol.

4-Physical activity: Physical activity may reduce levels of harmful cholesterol and raise levels of good cholesterol.

5-Age and gender: The level of total cholesterol before menopause (maturity) in women is lower than its level in men in the same age group, and as men and women age, their cholesterol levels rise.

6-Psychological stress: Several studies have shown that long-term psychological stress leads to an increase in levels of harmful cholesterol, and perhaps the reason for this is that psychological stress affects eating habits, as some people tend to eat fatty foods that contain a lot of saturated fats and cholesterol.

7-Drinking alcohol: Drinking alcohol raises the level of good cholesterol but does not lower the level of bad cholesterol. It is not clear whether this reduces the risk of coronary heart disease. Drinking alcohol causes damage to the liver and heart muscle and leads to high blood pressure and high levels of triglycerides.

The role of microorganisms in reducing cholesterol levels

Cholesterol is one of the important building blocks in the structure of the cell and is also used in the manufacture of hormones and energy production to some extent. Many deaths in the world are attributed to high levels of cholesterol in the blood, leading to cardiovascular diseases such as coronary artery sclerosis in particular [14], as the World Health Organization (WHO) expected the number of deaths from this disease to increase by 40% of the number of deaths in 2020. There are many chemical drugs that have the ability to reduce the level of cholesterol in the blood, but they usually show undesirable side effects, so there was an urgent need to search for an alternative to these drugs by means that would reduce the level of cholesterol in the blood without being exposed to these side effects. In this regard, the use of the bio-enhancer added to dairy products emerged as a means to reduce the level of cholesterol in the blood [23]. Conducted a study in which he demonstrated the ability of *Lb. acidophilus* bacteria to reduce cholesterol levels in MRS-EY medium. He concluded that this bacteria has the ability to reduce cholesterol from 8.41 mg/cm³ in MRS-EY medium before growth to 5.59 mg/cm³ and 5.37 mg/cm³ after 24-48 hours of growth. The percentage of reduction was 33.65% and 36.64% respectively. In a study conducted by [3], which included the isolation of 29 isolates of *Lactobacillus* bacteria from children's stools and the detection of the best among them to reduce the existing cholesterol, he concluded that *Lb. casei* bacteria was the most efficient as it reduced cholesterol to 80.4% after growing it on MRS-EY medium for 24 hours. Hamster rats were also fed milk fermented with *L. plantarum* NTU102 *Lb.*, *L. para casei* subsp. *para casei* *Lb. acidophilus* BCRC 17010 reduced the level of liver cholesterol, blood serum, low-density lipoprotein cholesterol (LDL-C, HDL-C), and total cholesterol in them [9]. This was followed by several studies in this field. [10] added *Lb. plantarum* bacteria to the diet of a group of laboratory rats. He observed a decrease in the level of triglycerides, low-density lipoprotein cholesterol (LDL-Cholesterol), and free cholesterol in the blood of these rats compared to their level in control rats whose diet was free of this bacteria. This type of bacteria was also found to be capable of producing the enzyme that decomposes bile salts (BSH), which means its ability to colonize the intestines. Several studies have indicated that consuming fermented dairy products in certain farms, it led to a reduction in human serum cholesterol, and the removal of cholesterol by microorganisms present in food can reduce the cholesterol ready for consumption by him [56].

[55] found in a study conducted on 32 people whose blood cholesterol levels ranged between 220-280 mg/cm³ that consuming milk containing *Bifidobacterium longum* bacteria at a rate of 300 cm³/day contributed to reducing the level of cholesterol in the blood by 32% after four weeks of consumption.

[26] also explained that feeding rabbits fermented milk products containing *S. thermophilus* and *L. bulgaricus* bacteria caused a significant decrease in the levels of total cholesterol and LDL in the blood serum of rabbits consuming these products after 4 and 8 weeks of feeding compared to the control group consuming skimmed milk. In a study by [34] to investigate the ability of 11 strains of the *Lactobacillus* genus to reduce cholesterol in the culture medium, it was found that these strains have the ability to reduce cholesterol at levels ranging from 12.03-32.25 mg/cm³. Oral administration of laboratory rats with the fermented product containing live cells of the local isolate *L. salivarius* (LP5) at a rate of 10⁹ cfu/ml had a positive effect in reducing the percentage of total cholesterol, low-density lipoprotein values, and triglycerides, with a significant increase in high-density lipoprotein values.

Proposed mechanisms for the action of lactic acid bacteria in reducing cholesterol

The production of Hydroxymethyl glutarate by lactic acid bacteria may inhibit the enzyme Hydroxymethyl – glutaryl – CoA reductase, which is one of the requirements for the process of cholesterol formation. It can be said that the exact mechanism for reducing cholesterol by lactic acid bacteria is still unknown. There are three proposed mechanisms for reducing cholesterol by lactic acid bacteria, as follows:

The first mechanism stated that the ability of *Lb. reuteri* bacteria to reduce cholesterol is through metabolic processes in which cholesterol is converted into 3-Keto-5B-cholestane and 3-B-Hydroxy-5-cholestane, vital metabolites of cholesterol.

The second mechanism: [18] [32] indicated that the action of reducing blood cholesterol levels by lactic acid bacteria may be through inhibiting the absorption of cholesterol coming with the food mass in the intestine. It is believed that lactic acid bacteria possess a Bile Salt Hydrolase (BSH) system that is effective in reducing cholesterol levels through its interaction with the host's bile salt metabolism, as the dissociation of bile salts by this system produces compounds including Cholestyramine and Colestipol. These compounds bind to bile acids, which prevents their reabsorption in the enterohepatic circulation, resulting in an increase in the demand for cholesterol as precursors for the synthesis of bile salts, leading to a reduction in its percentage in the blood. On the other hand, unbound bile salts do not function functionally as is the case in the bound forms in dissolving cholesterol, and therefore they prevent them. From being absorbed, which leads to a reduction in serum cholesterol concentration.

-The third mechanism: It was noted in the study conducted by [6] that *Lb. acidophilus* bacteria were able to reduce cholesterol from the culture medium, which may be a result of cholesterol incorporation into the cell wall of the bacteria, while the mechanism by which *Lb. casei* bacteria were able to reduce cholesterol from the culture medium was justified by the fact that the bacteria affected the stability of cholesterol micelles, which precipitated with unbound bile salts.

The health importance of inulin

Inulin is characterized by its resistance to digestion and decomposition in the human intestine due to its composition containing beta (2-1) bonds, so it is considered an energy reducer [39] as bacteria benefit from it only when it enters the intestine, as it contributes significantly as a bio-enhancer for the growth of therapeutic bacteria (*Bifidobacteria*) that work to improve general health. Inulin does not cause an increase in the level of absorbable glucose and thus does not increase insulin secretion [51]. Inulin is not digested by digestive enzymes in the stomach, but is fermented by colon bacteria in the large intestine through short-chain fatty acids and carbon dioxide. Inulin is considered a low-calorie carbohydrate because it provides less than 50% of the energy provided by other digestible carbohydrates [46]. [51] indicated a significant decrease in the content of triglycerides in both the blood and liver of laboratory rats when inulin was included in their diet containing saturated fats. Inulin increases the bioavailability of mineral salts, and this may be due to its osmotic effect on the water transported inside the large intestine. It was also noted that there was an increase of about 60% in the levels of calcium and magnesium absorption when rats were fed a diet containing chicory inulin [40].

Effect of inulin on blood lipids and cholesterol Sources have indicated the effect of inulin and its relationship to lipid metabolism. Daily feeding of rats with 10% inulin for one week resulted in a significant reduction in the level of

glycerides in the blood serum [45] confirmed that rats fed a diet containing 10% and 29% polyfructose reduced serum cholesterol levels. He also indicated a decrease in cholesterol, mainly a decrease in very low-density lipoprotein (VLDL), while high-density lipoprotein (HDL) increased. [48] concluded that inulin has the ability to reduce lipid levels when consuming a high-fat diet, as it prevents the accumulation of glycerides and cholesterol and reduces the fat content to a greater extent compared to experimental animals fed a high-fat content. When 10% inulin was added, it reduced glycerides and very low-density lipoprotein (VLDL) by: Inhibition of the key enzyme Glycerol-3-phosphate acetyltransferase in the synthesis of fatty acids. In a study conducted by [31] on two treatments, the first by adding 10% inulin and the second by adding 10% polyfructose to rats' diets for 7 weeks, both of which led to a significant reduction in serum cholesterol as well as abdominal fat and an increase in intestinal length compared to the control treatment. In a study conducted by [29] on rats, 0.2% cholesterol was added to the diets of the treatments containing 1% and 5% chicory extract, as well as the diet containing 5% inulin powder for 4 weeks, it was shown that the percentage of high-density lipoprotein (HDL) in the serum increased significantly, and the percentage of low-density lipoprotein (LDL) liver glycerides decreased significantly in the serum of the three treatments compared to the control. It also significantly increased the excretion of fat, cholesterol and bile salts in the feces of the treatments compared to the control. The effect of inulin on fat metabolism in humans differed according to the presence or absence of chronic diseases. In a study on diabetic patients that lasted for 14 days, with the intake of 8 g of polyfructose with a coffee drink, the cholesterol level was reduced by 19 mg/dl and low-density lipoproteins were significantly reduced by 17 mg/dl. In a study conducted by [8] on 12 males with high cholesterol, serum triglycerides were reduced by 40 mg/dl when 20 g of inulin from chicory extract was consumed, and serum cholesterol was reduced by 11 mg/dl and LDL was reduced. In a study of 21 male and female volunteers with high cholesterol, who consumed 18 grams of inulin daily with a low-fat diet for 4 weeks, there was a significant decrease in LDL by 4.4% and total cholesterol by 8.7%.

3. References

- [1] Albano, C. ; Morand, S. ; Silvetti, J. ; Casitraghi, C. ; Manini, F. and Brasca, M. (2018). Lactic acid bacteria with cholesterol lowering properties for dairy.
- [2] Albertes, B.; Bary, D. and Lewis, J. (1999). Molecular biology of the cell.
- [3] Al-Rawi, Zaid Akram. (2005). Isolation and identification of some Lactobacillus species capable of reducing cholesterol and incorporating them into therapeutic lactic ferments. Master's thesis, College of Agriculture, University of Baghdad.
- [4] American Heart Association.(2008)."Cholesterol" applications: In vitro and situ activity. J. Dairy Sci., 101: 10807- 10818.
<http://WWW.americanheart.org/cholesterol/about.Jsp>
- [5] Barter, P. and Kastelein, J. (2006). Targeting cholesteryl ester transfer protein for the prevention and management of cardiovascular disease. J. Am. Coll. Cardio, 47: 492-499.
- [6] Brashears, M.; Gilliard, S. and Buck, L. (1998). Bile salt. Deconjugation and cholesterol removal from media by lactobacillus Casein.J. Dairy Sci.,18:2103-2110.
- [7] Brunzell, J. D.; Davidson, M.; Furberg, C. D.; Goldberg, R. B.; Howard B. V.; Stein, J. H. and Witztum, J. L. (2008). Lipoprotein management in patients with cardiometabolic risk : consensus statement from the American diabetes association and the American college of cardiology foundation.Diabetes Care, 31(4):811-22.



- [8] Causey, J.L., Xin-Chua Y., Tungland, B.C., Feirtage, J.M., Gallaher, D.G. and Slavin J.L. (2014). Effect of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men. *Nutr. Res.*, 20(2):191-201.
- [9] Chiu, C.; Tzu-Yu, Lu.; Yun-Yu, T. & Tzu-Ming, P. (2005). The effects of *Lactobacillus*-fermented milk on lipid metabolism in hamsters fed on high-cholesterol diet. Institute of Microbiology and Biochemistry, National Taiwan University, No. 1, Section 4.
- [10] Chul-Gyu, H.A.; Jin-Kook, C.H.O.; CHI-HO, L.E.E.; Young-Gyu, C.H.A.I.; Young-AE, H.A. & Shan-Hun, S.H.I.N. (2006). Cholesterol lowering effect of *Lactobacillus planterum* isolated from human feces. *J. Biotechnol.* 16(8):1201-1209.
- [11] Damián, M. R., Cortes-Perez, N. G., Quintana, E. T., Ortiz-Moreno, A., Garfias Noguez, C., Cruceño-Casarrubias, C. E., ... & Bermúdez-Humarán, L. G. (2022). Functional foods, nutraceuticals and probiotics: a focus on human health. *Microorganisms*, 10(5), 1065.
- [12] Davidson, M. H. (2006). Mechanisms for the hypotriglyceridemic effect of marine omega-3 fatty acid. *Am. J. Cardiol.* 98: 27-33.
- [13] Dennis, E. and Henk, D. (2000). *Biochemical and biophysical Acta. (bba.)*. Vol. 1529(1-3).
- [14] Dilmi-Bouras, A.; Koiche, M. and Tabti, M. (2007). The effect of *Lactobacillus paracasei* On The Rabbit Cholestolemia. *J. Biotechnol.* 6(24): 2840-2845.
- [15] Emma Leah (2009). Cholesterol lipidomics gateway, doi:10.1038/lipidmaps. <http://WWW.lipidmaps.org/update/2009/090501/full/lipidmaps.2009.3.html>.
- [16] Erginkaya, Z., & Konuray-Altun, G. (2022). Potential biotherapeutic properties of lactic acid bacteria in foods. *Food Bioscience*, 46, 101544.
- [17] Frank, A. (2007). Technological functional of inulin and oligofructose. *British Journal of Nutrition*. 87:5287-5291.
- [18] Gilliland, S. E.; Nelson, C. R. and Maxwell, C. (1985). Assimilation of cholesterol by *Lactobacillus acidophilus*. *Applied and Environmental Microbiology*, 49:377-380.
- [19] Girao, H.; Mota, C. and Pereira, P. (1999). Cholesterol may act as antioxidant in lens membranes. *Curr. Eye. Res.* 18:448-454.
- [20] Goma, M. A. E. (2018). Nutraceuticals impact on probiotics growth: a challenge in synbiotic-yoghurt production. *Journal of Food and Dairy Sciences*, 9(1), 41-49.
- [21] Gordon, D.; Probstfield, L.; Garrison, R. and Tyroler, H. (1989). High-density lipoprotein Cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*, 79(1): 8-15.
- [22] Grass, L.S.; Li, L. and Ford, E.S (2004). Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the us :an ecologic assessment . *Am. J. Clin. Nutr.*;79(5):774-779.

-
- [23] **Greenwald ,C.G.(1999).**Overview of Fat & Cholesterol Reduction Technologies Gulf Publishing ,London .PP.21-34 .
- [24] **Haines, T. H. (2001).**Do sterols reduce proton and sodium leaks through lipid bi layers. Prog. Lipid Res. 40(4):299-324.
- [25] **Huang, J. J., Yang, L. C., & Liu, Y. C. (2022).** Production, purification, and structural characteristics of extracellular polysaccharides derived from *Lactobacillus acidophilus*. *Journal of the Taiwan Institute of Chemical Engineers*, 137, 104189.
- [26] **Hussein, Nawfal Abdul Amir (2004).** Identification and selection of local isolates of probiotic bacteria for use in the manufacture of fermented milk products and a study of their effect on lipid levels in rabbit blood serum. Master's thesis, College of Agriculture, University of Basrah.
- [27] **John, S.; Sorokin, A.V. and Thompson, P.D.(2007).** Phytosterols and vascular disease. Curr. Opin. Lipidol. 18(1):35-40.
- [28] **Khalaf, A. T., Wei, Y., Alneamah, S. J. A., Al-Shawi, S. G., Kadir, S. Y. A., Zainol, J., & Liu, X. (2021).** What Is new in the preventive and therapeutic Role of dairy products as nutraceuticals and functional foods? *BioMed research international*, 2021, 1-9.
- [29] **Kim, M. and Shin, H. K. (2014).** The water-soluble extract of chicory influences serum & liver lipid concentrations, cecal short-chain fatty.
- [30] **Kin-Zhi, L.; Shaw, R.; Man, A.; Thomas, C. and Henry, H. (2002).** Clinical chemistry. 48(3): 499-506.
- [31] **Kozmus,C.E.; Moura, E.; Serrao, MP, Real, H.; Guimarraes,J.T. and Guedes-de-Pinho,P.(2017).**Influence of dietary supplementation with dextrin or oligofructose on the hepatic redox balance in rats.Mol.Nutr.Food Res.55(11):1735-9.
- [32] **Lankapnthra, W.E.,& Shah, V.N.P.(1996).** Survival of *Lactobacillus acidophilus* and *Bifidobacterium ssp* in presence of acid bile salt. Cultured Dairy Products Journal., 30(5).
- [33] **Levy, E.; Spahis, S.; Sinnott, D.; Peretti, N.; Maupas, F.; Delvin, E.; Lambert, M. and Lauoie, M. (2007).** Intestinal cholesterol transport proteins : an update and beyond. Curr. Opin. Lipidol, 18: 310-318.
- [34] **Liong, M. T. & Shah, N. P. (2005).** Acid and bile tolerance and cholesterol removal ability of *Lactobacilli* strain. J. Dairy Sci., 88: 55-66.
- [35] **Lopez, E. (2006).** Consumption of trans fatty acid is related to plasma biomarkers of inflammation and endothelial dysfunction. J. Nutr. 135(3): 562-566.
- [36] **Mackay, J. and Mensih, G. A. (2004).** In the atlas of heart Disease and Stroke Geneva: WHO, pp: 30-31.
- [37] **Marchioli, R.; Barzi, F. and Ceriello, A. (2002).** Early protection against sudden death by n03-polyunsaturated fatty acids after myocardial infarction : time-course analysis of the results of the Gruppo taliano per lo studio della sopravvivenza nell infarto Miocardico (Gissi)-Prevenzione. Circulation, 105: 1897-1903.

- [38] Martirosyan, D., Lampert, T., & Ekblad, M. (2022). Classification and regulation of functional food proposed by the Functional Food Center. *Functional Food Science*, 2(2), 25-46.
- [39] Mohammed, E.; Mahmoud, A.; Muhammad, A. and Kuldeep, D. (2017). Chicory (*Cichorium intybus*) herb: Chemical composition, pharmacology, nutritional and health applications. *Inter. J. of Pharmacology*. ISSN 1811-7775: 1-10.
- [40] Nicola, D.G.; Anne, D. and Gary, S.F. (2015). A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes. *J. Nutr. Metab.* 12:36:PP:33-42.
- [41] Papakonstantinou, E., Manolopoulou, E., Papamichalopoulos, A., Kounenidaki, C., Mitrogeorgou, T., Georgalaki, M., & Tsakalidou, E. (2022). Short-term effects of goat milk yogurt containing ACE-I peptides and two raisin varieties on subjective appetite, blood pressure, and glycemic responses in healthy adults. Results from a randomized clinical trial. *British Journal of Nutrition*, 1-24.
- [42] Paulina, Wojciech; Ross, Michael, W. (2006). *Histology: A text and Atlas: with correlated cell and molecular biology*. Philadelphia: Lippincott Williams and Wilkins.
- [43] Pearson, A.; Budin, M. and Brocks, J. J. (2003). Phylogenetic and biochemical evidence for sterol synthesis in the bacterium *Gemmata obscuriglobus*. *Proc. Natl. Acad. Sci. U.S.A.* 100(26):15352-7.
- [44] Ridker, P. (1999). Evaluation novel cardiovascular risk factor: Can we better predict heart attack? *Annals of Internal Medicine*, 130:933-937.
- [45] Schonewille, J. F.; Boer, D. and Mele, L. (2016). Statins increase hepatic cholesterol synthesis and stimulate fecal cholesterol elimination in mice. *J. of Lipid Research*, vol. 57 no. 8 pp.1455-1464.
- [46] Shehzad, A.; Husnain, R.; Hafiz, R. and Azam, S. (2017). Inulin: Properties, Health benefits and food application. *Carbohydrate Polymer* 147:444-454.
- [47] Smith, L. L. (1991). Another Cholesterol hypothesis: cholesterol as antioxidant. *Free Radic. Bio. Med.* 11(1):47-61.
- [48] Stellaard, F. and Lütjohann, D. (2017). The Interpretation of Cholesterol Balance Derived Synthesis Data and Surrogate Noncholesterol Plasma Markers for Cholesterol Synthesis under Lipid Lowering Therapies.
- [49] Tabass, I. (2002). Cholesterol in health and disease. *J. Clin. Invest.* 110:583-590.
- [50] United State Department of Agriculture (2005). My pyramid: steps to a healthier you. Accessed at WWW.mypyramid.gov.accessed.
- [51] Vandeputte, D.; Gwen, F.; Sara, V.; Jun, W.; Manuela, S.; Stephan, T.; Kristin, V. and Jeroen R. (2017). Prebiotic inulin-type fructans induce specific changes in the human gut microbiota. *J. Food and Health*. Doi:10.1136:1-7.
- [52] Wang, N.; Chem, L.; Mulgund, J.; Roe, M. and Delong, E. (2009). Hypercholesterolemia paradox in relation to mortality in acute coronary syndrome. *Clinical Cardiology*, 32(9): 1002-1009.

- [53] Williams, K. J.; Feig, J. E. and Fisher, E. A. (2007). Cellular and molecular mechanisms for rapid regression of atherosclerosis : from bench top to potentially achievable clinical goal. Curr. Opin. Lipidol., 18: 443-450.
- [54] Wolkoff, A. and Cohen, D. (2003). Bile acid regulation of hepatic physiology: 1-Hepatocyte transport of Bile acids. Am. J. Physiol. 284(2): 9-12.
- [55] Xiao, J.; Kondo, S.; Takahashi, N.; Miyaji, K.; Oshida, K.; Itirmastus, A.; Watsuki, K.; Kokubo, S. and Hosono, A. (2003). Effect of milk products fermented by *Bidobacterium longum* on blood lipids in rats and healthy adult male volunteers, J. Dairy Sci., Vol. 86, No. 7:2452-2461.
- [56] Ziarnom, M. (2007). The Influence of cholesterol & biomass concentration on the uptake of cholesterol by Lactobacillus from MRS broth. Acta sci. POL, Technol. Aliment. 6(2)29-40.