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Research Paper

Kefir Brew as A Rebalancing System

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Abstract
Symbiosis is a coordination pattern within different microorganisms, which are capable of readjusting the imbalance of the intestinal microbiota; as a consequence of unhealthy lifestyles. A diet that rich in sugar, salt, and saturated fat is the main cause for change in the microbial equilibrium; which is responsible for gut homeostasis, that contribute to several universal epidemic diseases.

Kefir grains constrain an invisible world within them; that are clusters of complex symbiotic system of beneficial microbial mixture consisting mainly of bacteria and yeasts, which is considered as a probiotic. Kefir brew is a nutraceutical dairy product, that is produced during the fermentation process as a result of the action of probiotics on the milk.
Kefir brew has an ability to modulate the intestinal microbiota balance, and enhance its action. Routinely consumption of kefir brew attains a great promotion to the human health.

In this review, we will discuss the mechanism by which consumption of kefir brew probiotics will modulate this imbalance system and accordingly restrain these diseases. Furthermore, we will highlight the symbiotic system of kefir brew and its significant actions on the human body; including the ability to promote the immune system in order to inhibit tumor formation or cancer progression.
Key words: Kefir, kefir grains; probiotic, lactic acid bacteria; kefiran, microbial diversity.

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I. Introduction:

1.1 Background

Kefir grains are cultures employed to produce fermented dairy milk and other kefir products such as kefir beverage; their beads rich with probiotic micro-organisms that are approved to support the human biosystem [1,2].

Kefir is famous with many names as kefyr, kephir, kefer, kiaphur, knapon, kepi or kippi [3]. The name of kefir comes from Turkish origin, where the term Kef is coming from Keyif which means "well-being" or "living well, that reflects its beneficial nature on general human health [4]. Also, it is referred to fermentation properties of kefir in any type of milk to form curdle brew [5]. In the Caucasus Mountains, former Soviet Union and Central Asian areas, kefir brew has been consumed for thousands of years [6]. In these countries the kefir brew is produced until now from sheep milk, while in European countries the production of Kefir grains is basically produced from cow milk [5]. These kefir grains can be persevered by freezing, lyophilization, and refrigeration [7].

Kefir grains have yellowish-white color, slimy texture and irregular shape that resembles miniature cauliflowers blossoms [5]. It is varying in diameter from 3 to 35 mm. Furthermore, the exterior surfaces of the kefir grains appear to the naked eye to have an irregular foamy surface, but kefir microbiota under electron microscope appeared to consist of fibril rods spread out evenly. [8].

Kefir grains are composed of many and various strains of bacteria up to 30 strains or more [9], growing in association with several types of yeasts[10], which lives in a distinctive symbiotic environment in the kefir grains [11]. There are many types of bacteria inside the kefir grain such as; lactic acid bacteria which classified to four types including; *lactobacilli, lactococci, leuconostocs*, and *Streptococci* [12] and acetic acid bacteria (*Acetobacter sp.*), Surviving together with many types of yeasts as *Candida, Kluyveromyces, Saccharomyces, Torulopsis*, and *Zygosaccharomyces* [7,13].

All of these types of microorganisms (microbiota) within kefir grains live in an exo-polysaccharides matrix called Kafiran [1,11]. These microbiota are considered as Probiotics, which are responsible for the beneficial effect in preventive and curative action of various diseases [14,15].

Probiotics are living organisms that promote host health when administered in adequate amounts. The action of probiotics is mediated by acting together with the host gut microbiota. Probiotics are able to modify the human gastro-intestinal mucosa, thus, modulating the systemic immune responses and protecting the host against pathogens [16].

kefir grains and its brew contain lactic acid, lipid, proteins, sugar, vitamins, minerals and essential amino acids which give the nutritional value for all of the different kefir products [1] [11].

Consequently, fermentation of milk by kefir grains can provide useful approach, as a results of its ability that contribute to changes in the composition of gut microbiota to manage and rebalance the system, which has an influence on several metabolic disorders.

II. What is kefir and what is kefir grains?

2.1 Kefir Chemical Composition

Kefir grains are biological clusters with thick, Yellowish-white and gelatinous characters, which are considered to be a complete world that composed of lipid, proteins and polysaccharide substance.

2.1.1 The Classical Composition of Kefir

The classical composition of Kefir is mainly 89-90% water, 10-14% total dry matter: 24-25% Kefiran, 30-34% proteins [4,5], 3-4% fats, 3-6% carbohydrate, and 1-7% ash (Mineral content). Ash an inorganic precipitate remains as a result of removing water and organic materials using heat, which allows us to measure the content of minerals within the kefir depending on the fact that minerals are not destroyed by heat. [11,17–20]. Kefir brew contains free fatty acids (FFA) produced due to the lipolysis activity of lactic acid bacteria (LAB) during fermentation processes. The predominant FFA in kefir brew is saturated long chain palmitic acid, unsaturated long chain oleic acid, and short chain FFA such as butyric acids and propionic acid.

In addition, it has been found that kefir brew contains several types of proteins; such as casein that can be classified into four main types (α-s$_1$ casein, α-s$_2$ casein, β-casein and κ-casein) which, are breakdown throughout fermentation by the proteolytic activities of yeast and LAB to form free amino acids and bioactive peptides. Similarly, there other types of milk proteins (whey proteins, lactoferrin, lactoperoxidase, and lacto-globulins) that, by probiotic proteolytic degradation, produce more types of bioactive peptides [21].

2.1.2. Bioactive Peptides of Kefir Brew

Remarkably, kefir brew also contains bioactive peptides that have a positive effect on health. Many types of bioactive peptides were identified, as they are not found naturally in milk, but are produced by Kefir microorganisms' proteolytic activity; these bioactive peptides are considered as a specific product for the kefir brew.

The bioactive peptides are identified with a variety of biological functions, including: αs_2- casein f.189–197, αs_2-caseinf.204–212 (α-casein derivatives), casohypotensin, and β-casokinin-7 (β-casein derivatives) are found to have antihypertensive effects. While β-casomorphin-7, β-neocasomorphin-6, Pro$_8$-β-casomorphin-13, Pro$_8$-β-casomorphin-9 (β-casein derivatives) are considered as opioid agonist, unlike casecidin-15, casecidin-17, caseicin B, and caseicin C, which have been established to display an antimicrobial activity [22].

2.1.3 The Specific Kefir Brew Taste and Flavour

Peptides and FFA can turns into other chemical compounds that have evident impact on the taste of the kefir brew [23]. The specific kefir brew taste is due to the presence of different volatile and non-volatile carbonyl compounds, which are mainly produced as fermentation products by the action of lactic acid and acetic acid bacteria. It is also important to mention that the fresh fruit aroma of kefir brew is mainly due to acetaldehyde production, while the buttery aroma of the kefir brew is caused by diacetyl products [10].

2.1.4 Kefiran Matrix

Kefir grains are embedded in a polysaccharide matrix, specifically and solely produced by kefir grains, that's why it was termed as kefiran. Kefiran is a water soluble extracellular heteropolysaccharide (EPS) mainly produced by *Lactobacillus kefiranofacians*. It was found that the kefiran polymer is a disorganized coat that encapsulates all of the Kefir grains microorganisms together in enclosed system and protects them from the environmental factors. [24–26].

It is composed of frequent branched EPS penta or hexasaccharides, mostly (1:1 D-glucose/D-galactose) as shown in (Figure-1), containing different types of linkages, involving linear linkage like; β-D-(1→6) linked, α-D-(1→3) linked, β-D-(1→4) linked, beside to branched linked β-D-(1→2) as shown in (Figure-2). These characteristically different linkages make kefiran resistible to breakdown by human gut enzymes, and allow kefiran to tolerate the different environmental conditions and act as protector to the kefir grains [26,27].

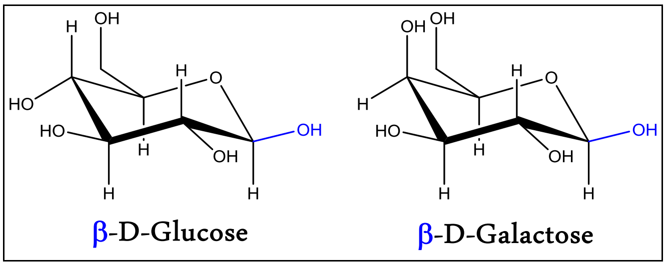

Figure-1 Chemical structure of β-D-glucose and β-D-galactose residues, the basic units for the Kefiran Matrix.

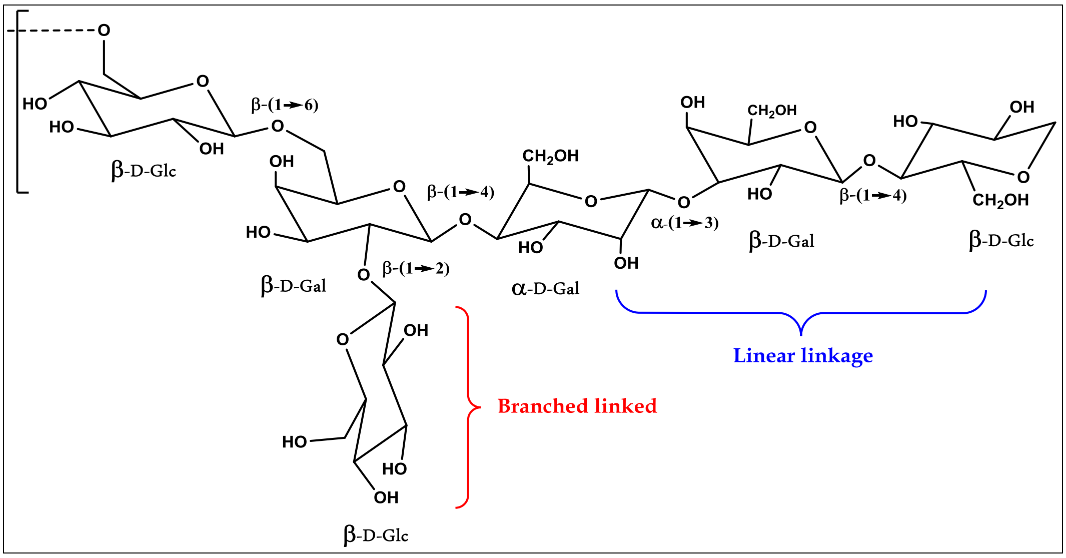

Figure-2 Branched and linear different linkages of kefiran [26].

This kind of bond diversity in the kefiran structure might be responsible for biophysical stability of the kefir grains; which means the kefir grains do not change in terms of microbial composition, as well as biological activity, in which it will sustain during shelf-life of kefir brew [5,26,28].

2.1.5 The Polysaccharide Composition of Kefir

Many types of EPS can be produced by species other than *Lactobacillus kefiranofaciens,* for example *Lactobacillus plantarum* can produced EPS, which is mainly composed of glucose, galactose and mannose. EPS produced by *Lactobacillus plantarum* was found to exhibit an antibiofilm activity, since it is interfering with harmful microorganisms adhesion to the wall of the intestine; and prevents it's pathogenic effect, beside to its antioxidant and antitumor activity [29–31].

In addition, *Lactobacillus* species can produce homopolysaccharides; that are formed from one type of a repeated unit saccharide, can be either fructose or glucose, and are termed: fructans or glucans respectively [25]. There are two types of fructans that can be classified into: β-D-Fru-levan (2,6) and β-D-Fru-inulin (1,2); these two types of homopolysaccharides are found to have Prebiotics besides, antitumor and hypocholesterolaemic effects [32].

It is important to mention that, the kefir microorganisms are identified to ferment milk lactose (milk sugar) to form lactic acid, approximately 0.8-1.2%, also 0.2% of CO_2, and 0.5-0.7% of ethanol result from carbohydrates fermentation (Belletti et al., 2009; Pogačić et al., 2013).

2.2 Kefir Nutritional Facts:

Kefir grains do not have standard nutritional compositions, but usually Kefir and kefir brew comprises of several nutritional ingredients, such as: proteins, fats, carbohydrates, vitamins, and minerals that assist the body to perform its physiological functions.

2.2.1 Protein kefir compositions

As mentioned before kefir brew contains many proteins and bioactive peptides, which are incompletely digested. Thus, these proteins would complete their digestion by the body into free amino acids [11]. Besides to the free amino acid compositions of the kefir brew that varies during the fermentation process like; glutamic acid, isoleucine, phenylalanine, methionine, lysine, and threonine [11]. Tryptophan is one of the essential amino acids and a predominant amino acid in kefir, that has a vital role in the nervous system function [7,11].

2.2.2 Fatty Acids Kefir Compositions

The fermentation process, enhance in nutritional profiles because some of the nutrients in kefir are developed during fermentation, for example many types of fatty acids, including: palmitic acid, which is the most common saturated fatty acid in kefir brew that is considered to be an antimutagenic agent. Besides to oleic acid, which is found in kefir brew has a potential anticarcinogenic effect [34].

2.2.3 Minerals Kefir Compositions

Furthermore, Kefir is an important dietary basis of some minerals for instant, calcium, potassium and magnesium. In addition to that, Phosphorus which is considered to be one of the basic minerals present in kefir by approximately 1.45%. Phosphorus is involved in many vital biological proceeds, for example, digestion of lipids and carbohydrates and production of ATP, besides its important structural role in nucleic acids and cell membranes [11].

2.2.4 Vitamins kefir compositions

kefir is a good source of many vitamins that are not metabolically produced in the human body, that we usually obtain from food. The most important of these vitamins present in kefir are: thiamine, pyridoxine, folic acid, biotin, vitamin C and Carotene (Figure-3)., which in turn play an important role in maintaining and regulating body functions and reinforcement of the immune system [7,11,23].

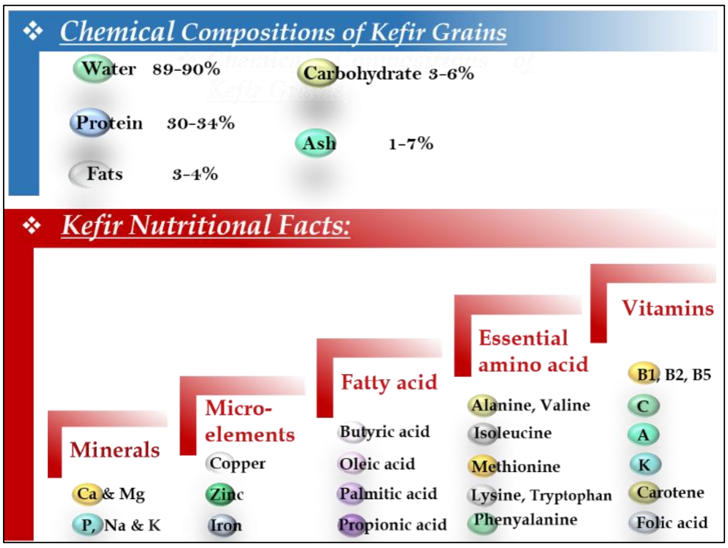

Figure-3 Main Kefir Chemical and Nutritional Compositions.

2.3 Kefir Microbial Composition:

Kefir grains contain a mixture of microbial species, their exact composition is still not intelligible yet; due to the complexity of the interaction between strains of bacteria, yeasts, and fungi [35,36]. The main microbial population found in kefir grains was bacteria, mainly lactic acid bacteria (LAB), but kefir grains also contains acetic acid bacteria (AAB) and many types of yeasts [37]. More than 50 types of bacteria and yeasts have been found in kefir grains , depending on the source of kefir grains and the type of milk used in the fermentation process [17,38].

2.3.1 Kefir Microbial Classifications

Kefir microbial species are classified as either a homofermentative bacteria; which is capable of producing mainly one chemical compound during fermentation as a final metabolite termed lactic acid, or heterofermentative bacteria which are able to produce more than one chemical compound during fermentation like ethanol, acetic acid, and CO_2 [35,39,40]. In addition, (Irigoyen *et al.*, 2005) [41] has classified the kefir grains according to the yeast fermentation product to, lactose fermented yeasts and non-lactose fermented yeasts.

2.3.2 Kefir Bacterial Composition

The major species that were isolated from kefir grains are lactic acid bacteria, including its all four types*: lactobacilli, lactococci, leuconostocs, and streptococci* [12]. It was found that lactic acid bacteria count to about (83–90%) of the microbial content of kefir grains [42,43] According to [11], the most important types of these bacteria are *Lactobacilli* that makes up about (65–80%) of the total lactic acid bacteria [44]. It was divided into heterofermentative bacteria Include: *Lactobacillus kefiri*, *Lactobacillus parakefiri*, *Lactobacillusbrevis*, *Lactobacillus fermentum* and Correspondingly, homofermetative bacteria Include : *Lactobacillus kefirgranum*, *Lactobacillus delbrueckii*, *Lactobacillus acidophilus*, *Lactobacillus helveticus*,*Lactobacillus casei*,*Lactobacillus Rhamnosus*, *Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus gasseri*,and *Lactobacillus kefiranofaciens;* which according to [45,46] considered as dominant microbiota species [3,19].

Furthermore, there are other types of bacteria found in kefir grains including: *Bifidobacterium bifidum, Leuconostoc mesenteroides subsp*.Cremoris, *Lactococcus lactis* subsp. *cremoris, Lactococcus lactis* subsp.*biovardiacetylactis, Lactococcus garvieae, Streptococcous thermophilus, Streptococcus salivariusn* subsp. *Thermophilus* and *Streptococcus durans* [37,42].

Additionally, kefir grains were found to contain acetic acid bacteria (*Acetobacter species*), which forms approximately 20% of total microbial content, however increases in their quantity is typically in correlation with the increase on length of the fermentation period [2,10,47] It's important to mention the proportions of these type of bacteria compared to each other important for the living and the stability of grains [35].

2.3.3 Kefir yeasts Composition

The yeasts count in kefir grains are about 10-17% [48], the most common genera belong to: *Candida, Kluyveromyces, Saccharomyces, Torulopsis, and Zygosaccharomyces*.

The predominant species of yeasts are: *Kluyveromyces marxianus*, *Kluyveromyces lactis*, *Candida kefyr*, *Candida lipolytica*, *Dekkeraanomala* and *Debaryomyces hansenii*, which are found to be lactose fermented yeasts. While *saccharomyces cerevisiae*, *Saccharomyces boulardii*, *Torulaspora delbrueckii*, *Pichia fermentans*, *Kazachstania unispora*, *Zygosaccharomyces rouxii*, *Debaryomyces occidentalis*, *Yarrowia lipolytica*, *Issatchenkia orientalis*,*Saccharomyces turicensis*,and *Kazachstania exigua*are non-lactose fermented yeasts [3,49,50] It should be emphasized, that there is only one type of fungi *Geotrichum candidum*, that is present in kefir grains, which forms approximately 0.1% of total microbiota [17,19,44,47].

2.3.4 Nothing Can Exist Individually: Microbial Interactions within Kefir Grains:

The microbiota of kefir grains lives in an obligatory symbiotic relationship; which is an essential natural environment for enabling the kefir to release many of the compounds responsible for enhancing the survival of all the species together and giving the kefir brew its medicinal value [3,45,46] Consequently, according to [35], the interaction between kefir species can be done in two ways, either by direct contact between the microbiota or indirect by secreting some chemical compounds which enhance or inhibit the growth of some other microbiota inside the kefir grains.

Firstly, the direct contact between the microbiota due to auto-aggregation and co-aggregation during fermentation process its enhances their survival, for instant: *Saccharomyces cerevisiae* promotes the survival of *Lb. Rhamnosus* within the acidic environment. Furthermore, the direct contact between a yeasts-type *Saccharomyces cerevisiae* with a bacteria *Lactobacillus kefiranofaciens* improves kefiran production; which in turn maintains the stability and life of the grains [25,51,52].

Equally important, the indirect effect is represented in yeasts, which plays an important role in the life expectancy of kefir; as it provides appropriate conditions for the survival of bacteria, since it is considered as a source nutrients, such as fatty acids and amino acids by lipolytic and proteolytic activities respectively [45]. likewise, bacteria sharing in symbiosis with yeasts; as the compounds resulting from their activities become available to the yeasts, which use them as an energy source [53]. For example, LAB are able to convert lactose into lactic acid. Non-lactose fermented *Saccharomyces Cerevisiae, Debaryomyces hansenii, and Yarrowia lipolytica* yeasts can consume that lactate and use it as a carbon source; which leads to reduced harmful acidity and this, in turn, would maintain the appropriate pH for kefir viability [4,35,54] Furthermore, Vitamin B produced by *Acetobacter* spp. and yeasts promotes growth of microbiota in kefir grains [3]. Additionally, another type of interaction within the kefir grains found in *K. marxianus*has an important role in supporting the survival of *Bifidobacterium* (Figure-4), where *K. marxianus* discharge substance; due to metabolic activity, considered as a nutritional source for *Bifidobacterium*; therefore the level of *Bifidobacterium* increase in kefir grains [42].

On the whole, it seems that strong contact between all of these microbiota types, makes the identification and the isolation of each species alone is a very challenging process, where it may affect the natural harmonization that is present in the kefir media. Also the isolation can damage these microbiota, and as a result of this, it is complicated to collect reliable information from pure isolated cultures [45,46].

Figure-4 Microbial Interactions within Kefir Grains: Natural Harmonization.

However, a blend of culture-dependent and independent approaches are used to understand the microbial compositions of kefir and kefir brew. Culture-independent procedures; includes extraction of DNA from kefir grains or kefir brew. Then, Polymerase chain reaction (PCR) amplification and sequencing of 16S rRNA genes is used. While, culture-dependent procedures were achieved by inocubating sample from the kefir grains and kefir brew to the appropriate culture [38,44,55].

III. Kefir production

3.1 Incubation

Kefir dairy brew can be produced from immersion of kefir grains in pasteurized milk for example: (cow, goat, sheep, camel, or any type of milk). The milk pasteurization process occur at 90°C for 15 minutes and followed by cooling of milk to 25°C, by using water circulation via a heat exchanger or by leaving it at room temperature for a period of time [23,56]. The ideal ratio between kefir grains and the milk is (1:30 to 1:50 w/v) [57].

3.2 Cultivation

Simply, kefir cultivation, is done by adding kefir grains to the milk in glass or a pottery jar using wooden spoon, then cover it with gauze for partial ventilation and allow kefir breathing [23]. After that, incubate kefir grains at room temperature 25-28°C and relative humidity (70 to 75%), for (18-40 hours). Usually, 24 hours is the preferred incubation time for the fermentation process to takes place. Furthermore, full prudence and carefulness must be taken during preparation of the kefir culture to avoid any dust or contamination as much as possible [23,58].

3.3 Fermentation

During the fermentation process, the most energetic grains move to the surface of the milk. Then, begin to take and store the nutritional material from the milk inside the grains. Later, secrete its metabolites such as enzymes, Co_2 and acids to the milk, which cause alteration in the milk components such as (proteins, lipids and sugars) to form the healthy kefir fermented brew [58].

3.4 Kefir Brew Collection and Storage

After the fermentation process, kefir grains are separated from the fermented milk by a filtration process using a clean plastic sieve [59]. The healthy fermented brew will be obtained which can be consumed directly or stored at 4°C by refrigeration for later consumption. Then, the kefir grains are washed with water and reserved to be used to another fermentation process[56,60], or stored in -20°C by freezing [61], or, to be stored for a long period of time reaching up to months; by lyophilization of kefir grain (dehydration by freeze drying technique for 24h) [62].

3.5 Theories Beyond Kefir Multiplication

Kefir grains after fermentation process, have a size larger than original starter grains before fermentation by up to 25% [28]. Besides, after fermentation, kefir grains form very small biological masses of new grains; which indicate that the kefir multiplication and growth in the milk is continuous [35,37] has revealed some theories beyond kefir multiplication;

- They explained the theory behind the forming of new small grains and increasing the size of kefir grains; that it is mainly due to self-aggregation on each other species of Lactobacillus upon each other such as *L. kefiranofaciens*, *L. Kazachstania* and *L. turicensis*, as well as to auto and co-aggregation of lactobacilli and yeast with each other
- Also they mentioned; that LAB and AAB support the production of polysaccharide as well as the ability of biofilm formation.
- Furthermore, they elucidated that, yeast has an important function in the increasing of complexity and expansion of networks among the probiotics [35].

IV. Impact of Environmental Factors on Kefir Grains:

The microbiota of kefir grains is significantly stable, maintaining its activity for many weeks if conserved under suitable cultural and physiological conditions [35]. Since the fermentation process is very important to motivate the microbiota present in the kefir grains. Thus we should pay attention to all the factors that are affected in the fermentation process; starting from the type of milk used in the process to several other factors that affected in the progress of the process such as: incubation size, incubation temperature, and incubation time [37,63].

4.1. Milk Nature

Kefir grains are highly affected by nature and fat compositions of the milk. Kefir must be made up from fat-bearing milk, otherwise, a kefir brew with humble quality in terms of dry matter, fat, protein and carbon dioxide content; will yield as a result of using skim milk [64]. Therefore, using whole milk or high-fat milk would raise the acidity and CO_2 in the resulting kefir brew and this has a major influence on the flavor, microbial diversity, and biological activity of kefir brew (Tomar et al., 2020).

4.2 The Incubation Size and the pH of Kefir Brew

It was found that the acidity of kefir brew increases with an increase in the grains to milk ratio used at the beginning of the fermentation process; this is due to high content of lactic acid bacteria. Moreover, increase in incubation size leads to an alteration in microbial growth within kefir brew, whereas it leads to an increase in the levels of yeasts and acetic acid bacteria over *Lactococci* and *lactobacilli* levels. This means that the growth of the yeasts and acetic acid bacteria is directly proportional to the increase in acidity of kefir brew [41]. Furthermore, [10,66], agreed that in 5-10% incubation size, will get the appropriate result for pH and Consistency of kefir brew.

4.3 Incubation Temperature

Equally important, is the incubation temperature: it has an effect on kefir brew by its control on pH for instance. It was found that with a rise in incubation temperature the time taken to drop the pH is decrease. Nevertheless, the increase in temperature should be limited up to a certain extent because the excessive increase in temperature leads to melting of the kefiran, which negatively affects in the microbiota of kefir brew. Also, excessive temperature can alter in the form and microbiological composition of the kefir grains. As well as, incubation temperature also has the potential to increase the proteolytic degree of casein in the kefir brew [67,68]. It was established that, the optimum temperature used in the fermentation process ranged from 25°C to 28°C, which is the appropriate range that provides a suitable pH (4.4) for microbial activity (Figure-5),; as it increases biomass of the grains and increases kefiran production [15,36,69,70].

4.4 Miscellaneous Factors

Additionally, there are different factors that influence the kefir grains; because they have a direct impact on the production of kefiran like carbon and nitrogen content. Carbon is considered as an important source of kefiran biosynthesis; because it has a key role in the growth of cells responsible for producing kefiran, and constitutes the structural unit used by these cells to synthesize kefiran. While, nitrogen affects on the production of kefiran due to its effects on bacterial growth [18,71]. Lactose was found to be the best carbon source that bacteria use in producing kefiran [41]. Perhaps this is due to the fact that kefiran is made up of glucose and galactose.

Furthermore, aeration rate is an important parameter to consider; as the rate of ventilation is one of the factors affecting the growth of bacteria, especially the type responsible for producing kefiran (*L. Kefiranofaciens)* [24].

4.5 The Incubation Time

It is important to mention, with regard to the incubation time, that the kefir grains biomass appears to grow rapidly in the first 22-24 hours of fermentation (Figure-5), then we notice a gradual decrease in the growth rates due to the exhaustion of nutrient quantities or acidic rise due to the excessive activity of microbiota of the kefir gains. Therefore, changing the medium (milk) daily is necessary to maintain the survival of kefir grains. Moreover, increasing the rate of stirring helps increase the biomass of the kefir grains; the reason for this may be that stirring ensures a good distribution of nutrients, which means that they reach all of the species within the kefir grains [36].

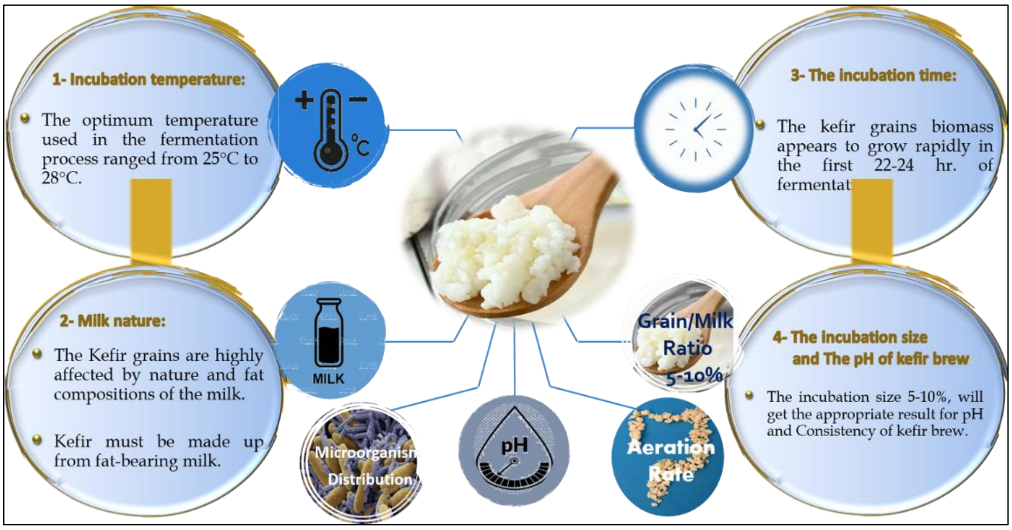

Figure-5 Impact of Environmental Factors on Kefir Grains.

V. Concealed Treasure of the Kefir (Kefir as A Probiotic Source)

The term, Probiotics, is originated from the Latin language, means "for life" [72]; which refers to the matter released from any organism to enhance the growth of another organism [73]. Probiotics are considered to be a set of non-pathogenic living microorganisms (bacteria and yeasts) that, when administered to the human in a sufficient quantity, will improve the gut microbial balance [74]. Also, they can modulate the epithelial cell function and the immune system [75,76]; as a consequence of these actions probiotics reinforce the health benefits of the human body [77,78].

To maintain the survival of these valuable microorganisms, special types of nutritional material are required, called Prebiotic; which is considered to be a non-digestible substance, augments the benefit of the human health by increasing the level of beneficial microorganisms (Probiotics) (Aspri et al., 2020; Valentini Neto et al., 2020).

5.1 Kefir as Symbiotic System

Unification of both probiotics and prebiotics together form a unique system termed symbiotic system; which is the system responsible to restore the homeostasis of the body in case of a disordered situation [73]. Moreover, the consumption of this system frequently gives rise to the boost of several physiological functions in the aim of maintaining the body in a healthy state [81].

Kefir grains and kefir brew are sources highly rich with probiotics; because they contain a complex of symbiotic community [37]. As mentioned before in microbial composition of kefir, they have a mixture of beneficial microorganisms with different species and subspecies, and this diversity is responsible for comprising the symbiotic system within the kefir grains and fermented brew [35].

VI. Health benefits of Kefir

Kefir products have an unlimited range of health benefits in prevention and treatment of various types of diseases as well as maintenance of the human body in a good healthy status; this is due to its unique structural diversity of valuable probiotic and prebiotic as mentioned before [82].

Probiotic organisms can employ their beneficial properties by two mechanisms: direct effects of the live microbial cells, or indirect effects through their metabolites (biogenic) [83]. Biogenics are nourishment substances that result from a microbial activity which is responsible for health benefits [1,18].

The health benefits of probiotics and prebiotics of kefir will be demonstrated in this review including; enhancement intestinal barrier function, antibacterial effects, immunomodulatory effect, hypocholesterolemic effect, hypotensive effect, antioxidant effect, anticarcinogenic effect, healing effect and effect on lactose intolerance patients (Figure-6).

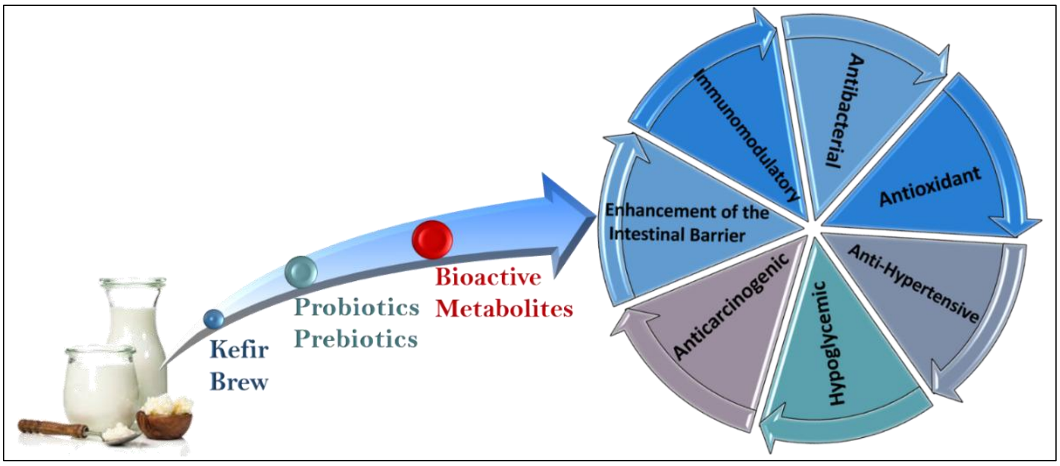

Figure-6: Health benefits associated with the consumption of probiotics and prebiotics in the kefir brew.

6.1 Symbiotics Kefir Mechanisms of Actions in Health Promoting

The beneficial synergistic effect on the human health of probiotics and prebiotics (symbiotic system) occur as a result of various and complex mechanisms that take place inside the human body (Valentini Neto et al., 2020). The health benefits of probiotics and prebiotics of kefir will be demonstrated in this review include the following:

6.1.1 Enhancement of the Intestinal Barrier Function

An increase in the permeability of the epithelial barrier in the gastrointestinal tract (GIT), is intended to be the main cause of chronic inflammatory disorders such as: diarrhea, gastroenteritis, irritable bowel syndrome, and inflammatory bowel disease (IBD; Crohn's disease) [84]. Probiotics in kefir products maintain the function and the structure of intestinal epithelial barriers in healthy state [85].

In normal physiological situations, goblet cells continually secrete mucin to maintain the mucus barrier; but goblet cell function can be interrupted by several causes (such as microbes, microbial toxins, and cytokines) that can interrupt the integrity of the mucus barrier. Consequently, the arisal of several pathological situations such as inflammatory disorders would be increased [84].

Probiotics can heal the intestinal damage by increasing mucin secretion from goblet cells directly or by triggering a gene expression pathway. Subsequent with improve the GIT tight junctions, enhance mucosal immunity [86,87], through up-regulation of the epidermal growth factor receptors; to increase proliferation and maintenance of immune cells function [18].

6.1.2 Antibacterial Effect

Probiotics in fermented kefir products can inhibit pathogenic bacterial GIT adhesion. Since, adhering of pathogenic bacteria to mucosal surfaces of GIT mediated by the interaction between bacterial adhesins (a protein on the bacterial surface) and particular mucosal receptors; is referred to be the first stage of intestinal infection. Some probiotics have the ability to compete with pathogenic bacteria on the mucosal surface of the GIT, by kefiran assisting, where probiotics can adhere to the mucosal surface [57] and prevent the attachment of pathogens with the intestinal mucosa [18].

Besides enhancing the barrier function, probiotics interact with Toll-Like Receptors (TLRs) that are expressed on the intestinal epithelial cells as well as on the dendritic cells, thus inducing the secretion of pro-inflammatory cytokines such as (IL-1β, IL-6, and TNF-α); consequently, enhancing the immune response against the pathogen [42]. Furthermore, these cytokines can affect the nervous system, subsequently increasing gut motility to expels the pathogen [86].

Additionally, antibacterial activities of probiotics from kefir origin, come from a combination of other multiple factors including;

- Competition for accessible nutrients between lactic acid bacteria (LAB) and harmful pathogens [88].
- LAB of probiotic secrete lactic acid substance leading to a decrease in the pH of intestinal media; where most of the pathogenic bacteria cannot grow and survive in such acidic media [89].
- Kefir fermentation probiotics produce active metabolites that have a direct effect on the pathogen elimination process; these metabolites include: organic acids, hydrogen peroxide, acetaldehyde, CO_2, and bacteriocins. Bacteriocins are peptides synthesized by ribosomes in probiotic cells, which are considered as antibiotics; due to the fact that they have bactericidal activity against pathogenic bacteria when secreted from probiotic microorganisms [90].
- Probiotics in kefir products stimulate enterocytes to secret β-defensins; which are groups of antimicrobial peptides synthesized by enterocyte ribosomes and secreted as a defense mechanism [18,87].

6.1.3 Immunomodulatory Effect

The modulation of the gastrointestinal immune system is considered as one of the major ways of promoting health benefits by probiotics. Lactobacillus species of probiotics during brew fermentation by kefir cause proteolytic degradation of many proteins such as (whey proteins, lactoferrin, lactoperoxidase, casiens and lacto globulins) to produce several types of bioactive peptides. These bioactive peptides can promote the humoral immune system, by inducing lymphocyte proliferations and stimulating secretion of immunoglobulin A (IgA) from lymphocytes of lymph nodes in the Payer's Patches, mesenteric lymph nodes, the spleen, and the intestinal lamina propria [21,42]. Furthermore, these bioactive peptides; can also modulate innate immune response and adaptive immune response [21].

Probiotics such as *Lactobacillus helveticus* and its metabolites; can promote an innate immune system which is a first line defense system in the human body; by increasing the activity of natural killer cells, macrophages, monocytes and neutrophils leading to an increase in phagocytosis of pathogens [21]. Furthermore, *Bifidobacterium* cell wall contains lipoteichoic acid, which induces nitric oxide (NO) synthase enzyme; to increase synthesis of NO, which is produced by macrophages after TNF-α secretion. NO enhance pathogen-infected cell death program, also NO lead to up-regulation of phagocytosis receptors such as [FcγRIII and tool-like receptor (TLR)] [91].

Probiotics have been approved to promote the adaptive immune system through several mechanisms; including:

- Activation the innate immune system, as previously mentioned, leads to activation of antigen-presenting cells (APCs) such as dendritic cells and B cells, to allow presentation of antigens to T cells, and migration of APCs towards secondary lymphoid organs [91,92].
- Casein derived peptides hydrolyzed by *Lactobacillus rhamnosus* stimulate proliferation, differentiation and activation of T and B cell to produce antibodies [21,91]
- Activation of cell mediated immunity; which stimulates T cells to be divided into T helper cell (Th) containing $CD4^+$ receptors and cytotoxic T cell contain $CD8^+$ receptors to recognize antigen presenting by APCs and destroy it [91].

Probiotics can promote both, innate and adaptive, immune systems through its ability to regulate cytokine, chemokine, tumor necrosis factors (TNFs), and transforming growth factor (TGF) secretion from immune cells (lymphocytes, granulocytes, macrophages, mast cells, epithelial cells, and dendritic cells) [87].

Casein hydrolyzed peptides, by action of *Lactobacillus rhamnosus*, increase the production of anti-inflammatory cytokines from Th1 lymphocytes and decrease production of pro-inflammatory cytokines from Th2 lymphocytes; leading to inhibition of inflammation reactions [21,91]. Moreover, bioactive peptides derived from beta-lacto globulin hydrolyzed by *Lactobacillus paracasei* stimulate production of interleukin-10 (IL-10) from monocytes which have anti-inflammatory cytokine, and inhibit IL-4 production which is pro-inflammatory cytokine [87].

L. paracasei and L. acidophilus stimulate production of TNF-α to increase secretion of NO, as mentioned before, and enhances the phagocytosis process [91].

Lactobacillus sakei induces the production of pro-inflammatory chemokines such as (IL-1β, IL-8, and TNF-α) to bring immune cells to the site, where the pathogen infects the body [87], while *Lactobacillus johnsonii* induces the production of TGF-β which is an anti-inflammatory cytokine, to decrease the inflammation at the site of the infection [91].

In conclusion; there are difference in the action of each individual subspecies of probiotics and its metabolites on the immune system; accordingly, that will create an integral action of immunomodulation of symbiotic system in the kefir brew.

6.1.4 Antioxidant Activity

It was established that Kefir probiotics, especially LAB, have the ability to inhibit lipid peroxidation [93–96]. Besides, *Bifidobacterium spp.* probiotics bacteria act as scavengers for different kinds of radicals like; [hydroxyl radicals, superoxide radicals and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical]. Particularly, *Bifidobacterium spp*., which releases anti-oxidases enzymes and metabolites such as folic acid and derived peptides, that have a great binding capability to these free radicals peroxidation [93,97].

In addition, kefir brew contains different types of free amino acids, mainly (glutamic acid, tryptophan, lysine, leucine, cysteine, glycine and valine) producing as a result of proteins breaking down during the fermentation process; which are considered as precursors for glutathione synthesis (glutamyl-cysteinyl-glycine peptide), which is acting as a free radical scavenger and membrane stabilizer.

Moreover, probiotics in kefir lead to up-regulation of glutathione peroxidase, catalases and superoxide dismutase enzymes. They also, reduce malondialdehyde to levels that prevent the induction of oxidative stress. Accordingly, probiotics are considered as a potential tool in the control of oxidative stress [98] Thus, the antioxidative activity of kefir can reduce DNA damage, which leads to a reduction in the incidence of the mutagenicity and tumor formation for kefir consumers [4].

6.1.5 Anticarcinogenic Activity

The intestinal microflora and immune system stimulation; have an important role in the modulation of cancer cell development [28,42].

The kefir fermented brew can prevent and suppress tumor formation in the early stages via the effects of probiotics and bioactive compounds such as protein modified peptides, could be by several mechanisms [84].

Additionally, these peptides, regulate cell growth through inducing un-functioned cell lysis by of apoptotic pathway of the cell. Apoptosis induction is not limited to proteolytic peptides, but also when α-lactalbumin protein form a complex with oleic acid in the acidic media associated with LAB. This transformed protein has the ability to induce apoptosis in malignant cells [21]. Likewise, [21] has mentioned, that cancer cells are more susceptible to apoptotic induction by symbiotic action than normal cells.

Furthermore, probiotics inhibits ErbB2 and ErbB3 expression (ErbB receptors are a family of tyrosine kinase receptors that are responsible for proliferation and survival of cells) [99].

[100] has evidence in human studies that showed, that the; ingestion of dairy products containing *Lactobacillus* or *Bifidobacterium* of probiotics can prevent colon cancer development. Several mechanisms have been suggested as possible explanations to inhibit cancer progress; these involve inducing production of inflammatory cytokines (IL-6, TNF-a) in the human, altering enzyme activities (NADPH-cytochrome P-450 reductase, glutathione-S-transferase, COX-2) in the colon, reducing the mutagenicity by inhibiting the uptake of potential carcinogens or producing antiproliferative and antitumorigenic compounds. Thus, these mechanisms display kefir milk can be used as a chemo-preventive therapy.

Furthermore, the antimutagenic activity of kefir milk is evaluated by using the Ames test. Kefir showed a significant reduction in the mutagenicity induced by methyl-methanesulfonate, sodium azide, and aflatoxin B1; and this is can be elucidated by the higher levels of linoleic, butyric, palmitic, palmitoleic, and oleic acids of the kefir milk; which were found in relation to the antimutagenic activity [101].

6.1.6 Anti-Hypertensive Activity

Released bioactive derived peptides such as (Casein modified peptides) [21] and kefiran [50] during kefir fermentation; cause inhibition of angiotensin-converting enzyme (ACE) activity (ACE is an enzyme that converts angiotensin I to angiotensin II, which is a powerful vasoconstrictor). This leads to reduced formation of angiotensin II and decreased blood pressure [21,50].

6.1.7 Hypocholesterolemic Activity

Consumption of fermented kefir products was able to reduce cholesterol levels by up to 50% [14], through several biochemical mechanisms including:

- The LAB strains prevents the absorption of exogenous cholesterol in the intestinal lumen; via its capability to bind to, then integrate the cholesterol inside own cell [86].
- A large amount of short-chain fatty acids (SCFA) produced by probiotics bacteria including: Acetic acid, Propionate, Butyrate [86], reduce the production of cholesterol by many mechanisms such as:
  - Inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase enzyme activity. Hence, cholesterol in the plasma is re-distributed to the hepatic tissue.
  - Enhancing the activity of the 7α-hydroxylase enzyme to increase the synthesis and the secretion of bile acids and also, improving the cholesterol regulation.
  - Inhibition of intestinal gene expression required for the biosynthesis of cholesterol.

Some studies established the hypocholesterolemic effect of kefir by using Hamsters, fed with hypercholesterolemic diet linked with kefir product; they noted a significant reduction in triglyceride levels and atherogenic index. Also, they display excretion of high levels of cholesterol and triglycerides in feces of Hamsters [4,102].[25] has mentioned many studies, comparing between non-consumers and kefiran exopolysaccharide consumers, with the latter exhibiting a decrease in total cholesterol, low-density lipoprotein cholesterol (LDL), and triglycerides in plasma serum, as well as cholesterol and triglycerides in hepatic tissue in comparison to the average non-consumer [103].

The intestinal microbiota is the main cause for atherosclerosis, associated with the substance called trimethylamine oxide (TMAO). Red meats, egg and animal source diet contain Lecithin and L-carnitine choline and betaine [82,104], which, under the action of intestinal microorganisms can be transformed to trimethylamine (TMA), which is absorbed from intestine and is transported to hepatic tissue, where it transforms TMA to TMAO by action of flavin monooxygenase (FMO) enzyme. TMAO induces the release of inflammatory cytokines such as IL-18 and IL-1β, as well as stimulating platelet activity and thrombosis formation [104]. Consequently, as the levels of TMAO increase, it can progress of atherosclerosis and development of cardiovascular diseases [105].

[106] demonstrated two comparison studies that monitor the levels of TMAO in urine and blood showing; lower in the levels of TMAO in the individuals whom consume fermented dairy products, compared to others with a diet consisting of non-fermented dairy products. So, the symbiotic system (probiotics and prebiotics) of kefir fermented products can reduce TMAO formation by modulating the intestinal microbiota compositions to reduce formation of TMA metabolites and serum TMAO [104]; leading to a decrease in atherosclerosis formation and a decrease in the risk of cardiovascular disorder [82].

6.1.8 Hypoglycemic Activity

In Vivo studies of kefir consumption on hyper-glycemic experimental rats; had showed supplementation of kefir were able to reduce plasma glucose level, due to the ability of phenolic compounds in kefir products; that reduce postprandial hyperglycemia and control of blood sugar in type II diabetes mellitus patients [101]. In addition, [18] has mentioned that adding kefir products to the life style; will increase the sensitivity of the tissue for insulin, and enhance the quality of life for type II diabetes mellitus patients. [107].

Moreover, most of Lactobacillus spp., showed Dipeptidyl Peptidase IV (DPP-IV) inhibiting activity (Figure-7), which is an enzyme that, when inhibited, it leads to an increase in the level of incretins (peptides that enhance glucose-dependent insulin release, and suppress the secretion of pancreatic glucagon and delay the gastric emptying). Accordingly, kefir probiotics promote the incretins effect; which applies the same strategy as the novel antidiabetic drugs (vildagliptin, saxagliptin, alogliptin, and linagliptin). Strategies have been developed, to produce more safer drugs with a lower risk of side effects, compared to traditional antidiabetic agents. [108].

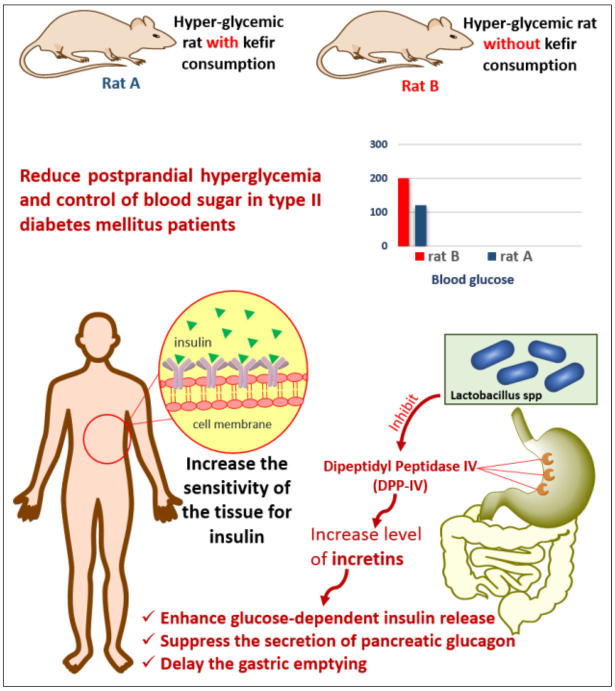

Figure-7 kefir brew consumption and hypoglycemic effect.

6.1.9 Anti-Allergic Activity

Kefiran is capable of inhibiting the degranulation of mast cells, which reduces release of inflammatory mediators. Thus, kefiran is considered to be a promising therapy, that has beneficial activity in the prevention and treatment of allergic diseases mediated by mast cells [109].

6.1.9.1 Effect on Lactose Intolerance Patients

Lactose is a milk sugar; that is a disaccharide (glucose and galactose), found in milk in high concentrations. For Lactose to be absorbed from the intestinal mucosa, is required hydrolysis of the disaccharide into monosaccharide by action of β-galactosidase enzyme [50]. Some of the people cannot digest lactose due to inadequate activity of intestinal β-galactosidase. This enzyme is present in the kefir grain naturally [1], which causes a decreases in the lactose content of the milk in fermentation process [52]. Therefore, the final product of milk kefir can be taken by lactose intolerance patients. [101].

6.10 Healing Activity

Recent studies have demonstrated the beneficial effects of probiotics aside from benefits due to the gastrointestinal consumption of probiotics. Some of these novel benefits include skin health-promoting, alleviation of eczema, atopic dermatitis, burns, healing of scars, and skin rejuvenation.

The healing effect of kefir was evaluated in vivo with an experimental animal burn, and treated with kefir product for two weeks. After the two weeks, noted healing of the burned area and reduced the percentage of inflammation in animals treated with kefir products was observed when compared with animals treated with silver sulfadiazine cream [101].

[18] has mentioned study about the healing activity of kefiran extracts from kefir; they demonstrate that kefiran extracts is effective and facilitate wound healing.

VII. Yeast related benefit

As mentioned previously; after the fermentation process, kefir grains and brew contain a large population of unique species of yeast, which have characters of probiotics such as *Saccharomyces boulardii*, *Saccharomyces cerevisiae*, *Kluyveromyces marxianus* and *Issatchenkia spp* [110].

7.1 Solidarity of the Kefir Symbiotic System

Kefir isolated yeast in vitro studies, has shown the capability to enhance the probiotic properties of different bacterial species in the kefir [52]. Likewise, they can enhance the propagation of bacterial species for long intervals in simulated gastric and intestinal fluid, as well as enhance the adhesion of LAB with the gastro-intestinal barrier [42].

Ultimately, this is clarifying the solidarity of symbiotic system of the kefir, not only for survival in the media of the kefir, but also the solidarity in the action inside the human body.

Most species of probiotic yeast have protective effects against pathogenic bacterial infection through a general mechanism; most of them have the adhesive property for the entero-pathogenic bacteria on the surface of the yeast cells, which traps the pathogen to be recognized and destroyed by the immune system [111,112]. Furthermore, most of probiotic yeasts have antitoxin effects for common bacterial toxins such as Clostridium difficile toxins, A and B, Cholera toxin, and Escherichia coli LPS [112].

7.2 Benefits of*Saccharomyces Boulardii*

In patients with *Clostridium difficile* bacterial infection; a kefir brew species of yeast, *S. Boulardii*, has been shown to reduce the symptoms of *C. difficile* associated diarrhea [113], where the *S. boulardii* reduce inflammation by inhibiting secretion of proinflammatory cytokines [114] in the gastro-intestinal tract caused by *C. difficile*. Moreover, *S. boulardii* has the ability to increase the immunological state in the gut; by stimulating the secretion of IgA from gut lymphocytes [111,115]. Several clinical trials studies, mentioned by (Czerucka, Piche and Rampal, 2007) (Czerucka et al., 2007), determine that the probiotic yeast, *S. Boulardii*, can treat and prevent antibiotics associated diarrhea; this is due to its ability to stimulate the brush-border membrane enzymes (BBE) to enhance the digestion and enhance absorption of digested substances.

7.3 *Saccharomyces cerevisiae*

[117] has mentioned a study that demonstrates; the useful interaction effect between *Saccharomyces cerevisiae* and *Candida albicans* fungi; which confirm *Saccharomyces cerevisiae*, the probiotic yeast, as a treatment for vaginal infection with *Candida albicans*. Since, *S. cerevisiae* prevents the adherence of the fungus, *C. Albicans*, to vaginal epithelial cells, it also leads to inhibition of candida induced damage for epithelial cells, thus promoting the healing or prevention of Candidiasis disease development.

7.4 *Kluyveromyces Marxianus*

K. marxianus has been shown to have an immunomodulatory activity; where a decrease in the secretion of pro-inflammatory cytokines such as IL1β, IL2. IL8 and TNF, was observed [118,119]. Furthermore, *K. Marxianus* is also shown to have the ability to increase the expansion of *Bifidobacterium*; where *K. marxianus* secretes metabolites that feed *Bifidobacterium*, and allow the *Bifidobacterium* to survive, leading to an increase in the level of *Bifidobacterium*, which has good probiotics properties [120]. Some strains of *S.cerevisiae, K.marxianus* and *Issatchenkia spp* are able to inhibit expression of the ccl20 receptor gene; which is the gene responsible for stimulating formation of Salmonella flagellar protein in case of Salmonella infection (Figure-8) [42,118].

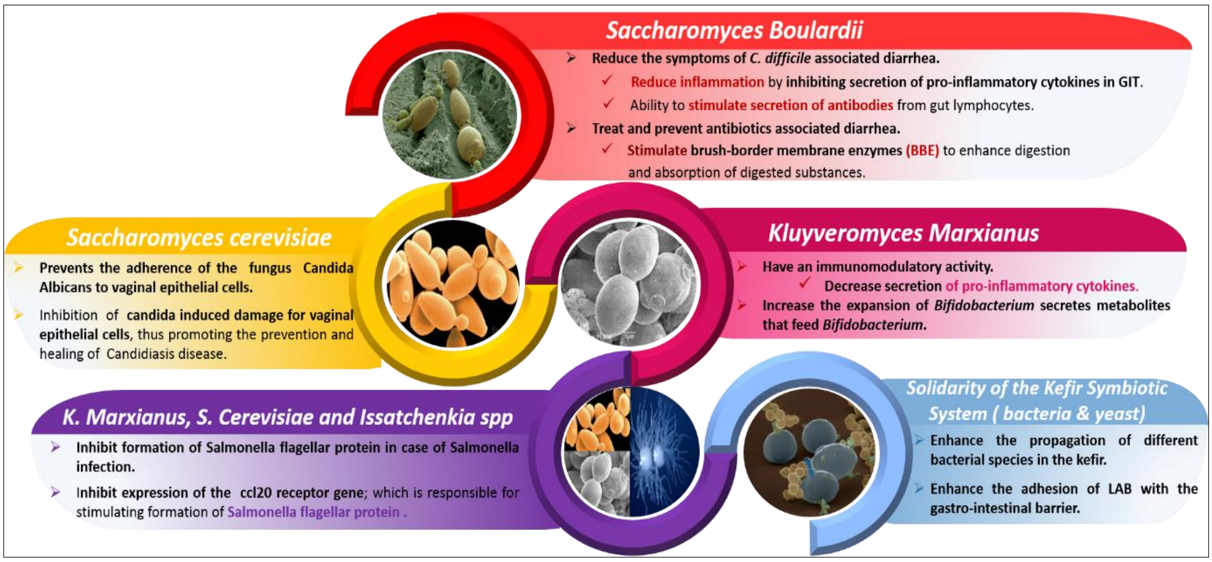

Figure-8 Summary of The Kefir Brew Yeast Related Benefit.

VIII. Conclusion:

This review demonstrates the prospect about kefir, as a whole (grains and brew) and its compositions, since, its contain significant components which have a positive effect on human health. Kefir is a self-motivated fermented dairy item that is formed during the fermentation process by exploitation of kefir grains in the milk. Kefir grains contain symbiotic popularity of bacteria and yeasts comprising a diversity of up to 50 species.

This microbial ecosystem lives in coexistent harmony, sealed off within a sac of exopolysaccharide "termed kefiran" which is constitutes protection for the kefir grains from the ecological stress and the enzymatic degradation.

Meanwhile, detecting the exact microbial composition of kefir poses a great task, as the presence of these microbiota within the complex symbiotic community makes the survival of each strain individually is unmanageable. Actually, the consortium is attributed to the ability of each species to excrete metabolites, which plays an important role in the life of another species. Therefore, the interactions between kefir microbiota are necessary to maintain the grains in a good integrity.

The microbiota within kefir grains have the capability to liberate numerous enzymes responsible for lipolytic and proteolytic activities on the milk to give FFA and bioactive peptides respectively. Whereby, these biochemical compounds are liable to pharmaceutical values of kefir brew, hence making it more precious than ordinary dairy products.

In this review, we have concluded that, in order to attained a suitable kefir brew of high quality; the following optimum conditions should preferably be taken into considerations:

In the beginning of the fermentation process, utilize pasteurized milk that is rich in fat, and the incubation temperature must be controlled so that it does not to exceed 28°C and does not fall lower than 25°C. An appropriate incubation size ranging from 5 to 10% should be used. Kefir grains should be fermented for sufficient incubation time, a period of not less than 24 hours, after that it can be reused or even stored in a refrigerator at 4°C for future use. In the context of that, all previous factors have a direct impact on the pH of kefir. We have discussed, that any deviation from the optimum pH (4.4) could be cause alteration in the microbial composition of kefir.

The spacious extent of health benefit related to the symbiotic community exists inside the kefir through continuous consumption of kefir product. The symbiotic system of kefir has the ability to improve the GIT barrier through the increasing of the mucin secretion and the enhancement of mucosal immunity to maintain off

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the GIT barrier's function and prevent the chronic inflammatory disorders. Furthermore, probiotics of the symbiotic system exert antibacterial effects through various mechanisms; chiefly by preventing pathogenic bacterial adhesion to the GIT surface as well as excreting bacteriocins. In addition, most of probiotic yeasts can catch up the pathogenic bacteria on its wall to be detected by the immune system. Also, some probiotic yeasts can secrete bacterial anti-toxins.

Probiotics of kefir brew and its metabolites have an immunomodulatory outcome regarding the alliance of the species and subspecies of probiotics; by means of promoting the innate and adaptive immune response via its ability to activate and proliferate immune cells. Likewise, probiotics have proficiency in regulating immuno-mediators through cytokines and chemokines secretion.

Moreover, kefir brew contains probiotics and prebiotics that deem as powerful utensils in oxidative stress resistance; attributable to their activities in suppression of lipid peroxidation, free radicals picking up and liberating anti-oxidase enzymes, then preventing tumor consistence and proliferation. On the other hand, the anticancer effects of the symbiotic system in kefir resulted from different mechanisms; which is can induce initiation of the apoptotic pathway of malignant cells, along with the inhibition of tyrosine kinase receptors leading to constraint in growth and propagation of cancer cells.

Regular consumption of kefir brew has been shown to cause a decreases in levels of serum LDL and hepatic cholesterol; as a result of inhibition of exogenous cholesterol absorption and endogenous cholesterol synthesis. The modulation of intestinal microbiota by kefir probiotics prevents TMA absorption to the liver, therefore leading to a decrease in the formation of TMAO, which is the main cause for atherosclerosis development that is followed by cardiovascular disorder.

Inclusively, Kefiran and some bioactive peptides of kefir are capable of reducing the action of the ACE enzyme, to minimize formation of vasopressor peptides that fulfil the task of causing a decline in blood pressure for hypertensive patients. Among additional things, kefir brew has a hypoglycemic effect in type II diabetic patients relating to the inhibition of glucose absorption from GIT. Besides some species of probiotics that have DPP-IV inhibiting activity to elevate insulin secretion, as well as some probiotics' metabolites able to enhance the insulin sensitivity in tissues. Correspondingly, during fermentation process kefir grains liberate β-galactosidase enzyme to the milk, whereby converting lactose (milk sugar) to lactic acid, forming brew with less lactose concentration that enhances the quality of life for lactose intolerant patients if they consume kefir brew frequently instead of conventional dairy products.

In denouement, kefir products are an efficient nourishment with unlimited potentials. Several observed physiological effects support the health promoting benefits of kefir products. The symbiotic system of kefir has a significant influence in prevention and treatment of prevalent diseases due to its nutritional and therapeutic characteristics. Resultantly, it is recommended for ordinary people to reduce the risk of chronic diseases and also for patients with many disorders.

IX. Future prospect

We pay attention to the fermented kefir products as interest in it widespread globally, which is considered to be an important source of probiotics as we mentioned earlier; these probiotics act as a remarkable gut microbial rebalancing agents to promote the digestive health assistance.

After working on this review, several questions have been raised; like, how microbiota inside grains interconnect with each other, how this microbial system remains sustainable and survival for a long time, and how these microorganisms are distributed within the kefir grain. In the future prospective studies, several experiments should be performed to answer such questions.

We found kefir grains in Libya but unfortunately, they have an unknown origin. Consequently, in the near future studies, we plan to analyze this kefir sample; with a particular focus on identifying and being acquainted the types of probiotics present in the kefir sample that is found in the Libyan market after their isolation.

In view of that, our aim is to access to a healthy diet regimen for the Libyan society; through intensification of the awareness of individuals to the benefits and safety of kefir and kefir products to expand the popularity of consumption of kefir products among Libyan consumers. In addition, increasing the Libyan market potential of kefir by adding it to the national commercial dairy products during manufacturing.

In a short summary, the growing healthy kefir products consumption habits can guarantee for humans a healthier lifestyle.

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