

IMPORTANCE OF PREBIOTICS AND PROBIOTICS AS NUTRACEUTICAL

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ABSTRACT

The knowledge of nutraceuticals and its importance gaining increase in current centuries but it is our misfortune that proper chemical and pharmacological evaluation of most of these nutraceuticals have not done till now. Keeping this view, details studies on medicinal importance of prebiotics and probiotics as nutraceutical study have done. It is a very important supplement as a gift of the nature for living beings. In preventive medicinal system, it is used in different troubles as well as it possesses different important pharmacological activities. Nutraceuticals are dietary supplements, utilized to perfect health, delay senescence, prevent diseases, and support the proper functioning of the human body. Currently nutraceuticals are gaining substantial attention due to nutrition and therapeutic potentials. Based on their sources, they are categorized as dietary supplements and herbal bioactive compounds. The global market for nutraceutical is huge i.e. approximately USD 117 billion. Herbal nutraceutical helps in maintaining health and promoting optimal health, longevity, and quality of life. The health benefits imparted by probiotics and prebiotics have been the subject of extensive research in the past few decades. These food supplements termed as functional foods have been demonstrated to alter, modify and reinstate the pre-existing intestinal flora. They also facilitate smooth functions of the intestinal environment. It includes definition of prebiotics and probiotics and their examples, sources, health benefits, risk factors, future aspects etc.

KEYWORDS: Nutraceutical, Prebiotics, probiotics, food.**INTRODUCTION**

Nutraceutical are wonderful origin of traditional & modern preventive medicine, useful for primary health care system. Since diseases have co-existed with life, the study of diseases and their treatment is important part of our ancient plant worldwide. This helps to getting increase knowledge of nutraceutical. Herbal plants are huge sources of nutraceuticals, prevent the different disease or maintain healthy life. In preventive medicinal system it is used in different troubles as well as it possesses different important pharmacological activities.

The quality of life in terms of income, spending and lifestyle has improved with economic development. However, it has also thrown up a major challenge in the form of 'lifestyle diseases'. The first victim of this lifestyle change has been food habits. Consumption of junk food has increased manifold, which has led to a number of diseases related to nutritional deficiencies. Nutraceuticals can play an important role in controlling them. No wonder more and more people are turning to nutraceuticals. The term nutraceutical was coined from nutrition and pharmaceutical (Figure 1) in 1989 by Stephen Defelice, founder and chairman of foundation for innovation in medicine, an American organization which encourages medical health.^[1,2,3,4] According to

him "a nutraceutical is any substance that is a food or a part of food and provides medical or health benefits, including the prevention and treatment of disease."^[5]

Prebiotics and probiotics play a positive role in promoting human nutrition and health. Prebiotics are compounds that cannot be digested by the host, but can be used and fermented by probiotics, so as to promote the reproduction and metabolism of intestinal probiotics for the health of body. It has been confirmed that probiotics have clinical or health care functions in preventing or controlling intestinal, respiratory, and urogenital infections, allergic reaction, inflammatory bowel disease, irritable bowel syndrome and other aspects. However, there are few systematic summaries of these types, mechanisms of action and the promotion relationship between prebiotics and probiotic. Therefore, we summarized the various types of prebiotics and probiotics, their individual action mechanisms, and the mechanism of prebiotics promoting probiotics in the intestinal tract. In Britain, the Ministry of Agriculture, Fisheries and Food has developed a definition of a functional food as "a food that has a component incorporated into it to give it a specific medical or physiological benefit, other than purely nutritional benefit."^[6]

There is a slight difference between the functional foods and nutraceuticals. When food is being cooked or prepared using "scientific intelligence" with or without knowledge of how or why it is being used, the food is called "functional food". Thus, functional food provides the body with the required amount of vitamins, fats, proteins, carbohydrates, etc. needed for its healthy survival. When functional food aids in the prevention or treatment of disease or disorder. Examples of nutraceuticals include fortified dairy products (e.g. milk).^[6] It is impossible to get adequate nutrition from the routine food. Secondly, live in highly toxic environment, filled with pollution and pesticides that throw off our body's ability to regulate it. A number of new ailments that are haunting us are now wide spread in our population. This is more sensible strategy-to strengthen our system or terrain rather than settling for antibiotic which has lost their effectiveness. There are typically side effects from drugs because they are not natural to the body, whereas with good quality supplementation that can be absorbed and utilized by the body can truly strengthen our body and add vitality.

Benefits of nutraceutical

- May increase the health value of our diet.
- May help us live longer.
- May help us to avoid particular medical conditions.
- May have a psychological benefit from doing something for oneself.
- May be perceived to be more "natural" than traditional medicine and less likely to produce unpleasant side-effects.
- May present food for populations with special needs (e.g. nutrient-dense foods for the elderly).^[7]

Concept of nutraceutical

In the pharmaceutical development process, it is a requirement to have clinical test results for animal tests and studies and for verification of their therapeutic effects. But in the case of nutrition, there was no verification method for foods in preventing diseases in the past. In recent years however, as food composition has been scientifically proven to cause life style related diseases, and has become a social issue. The nutraceutical products are recognized and produce health benefits like alleviating the risk of cancer and heart disease and also to prevent or treat hypertension, high cholesterol, excessive weight, osteoporosis, diabetes, arthritis, macular degeneration (leading to irreversible blindness), cataracts, menopausal symptoms, insomnia, diminished memory and concentration, digestive upsets and constipation etc.^[8-11]

Variety of nutraceuticals

Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms. These can be grouped into the following categories.^[12]

Nutrient: A feed constituent in a form and at a level that will help support the life of an animal. The chief classes of feed nutrients are proteins, fats, carbohydrates, minerals and vitamins.

Dietary Supplement: A product that contains one or more of the following dietary ingredients: vitamin, mineral, herb or other botanical, amino acid (protein) and also includes the diet as concentrates, constituents, extracts or metabolites of these compounds.

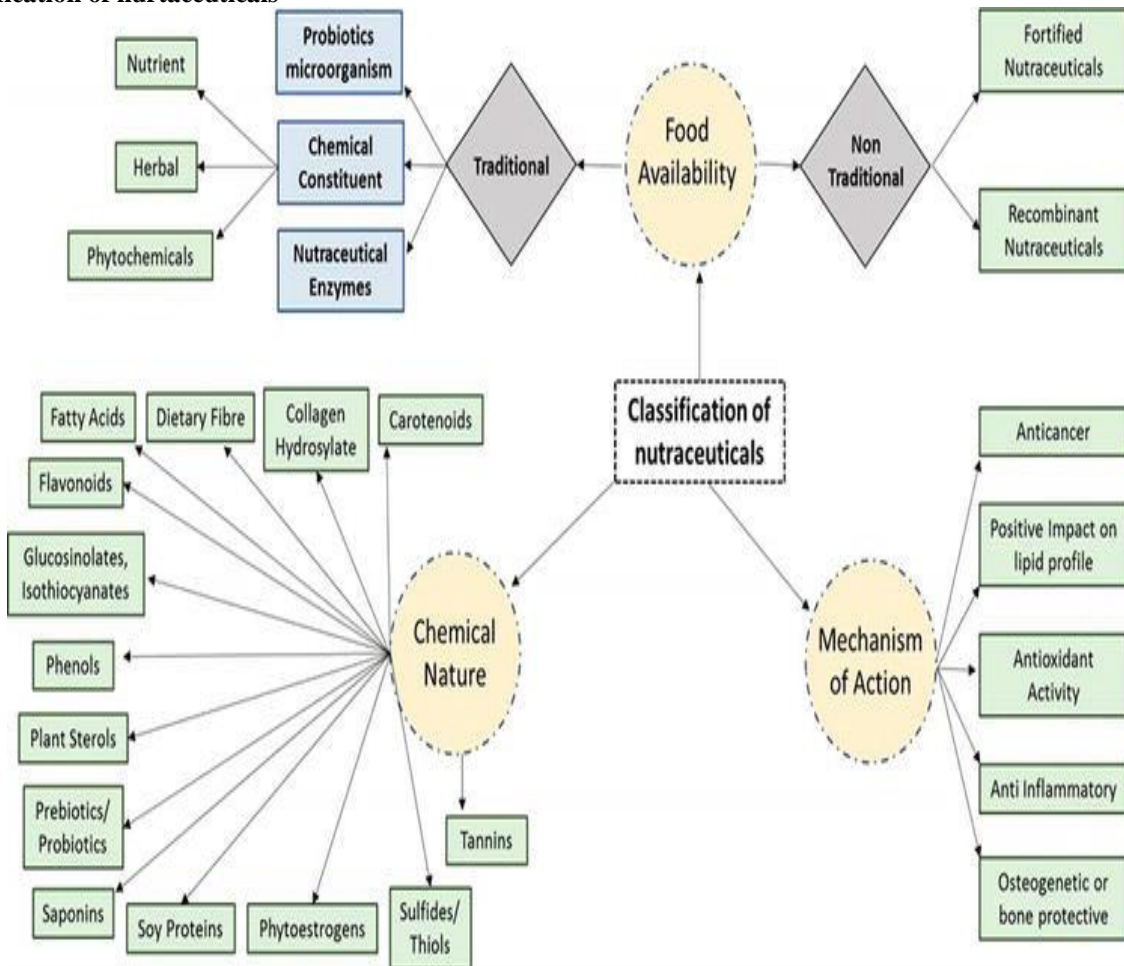
Nutraceutical: Any nontoxic food component that has scientifically proven health benefits, including disease treatment and prevention.

Herbals: Herbs or botanical products as concentrates and extracts. Herbals are as old as human civilization and they provide a complete storehouse of remedies to cure acute and chronic diseases. India has the oldest written tradition for the nature's remedies called 'Auyrveda' which possess many effective means of ensuring health care. Numerous nutraceuticals are present in medicinal herbs of key components.

Global demand of nutraceuticals

In the global marketplace nutraceuticals and functional foods have become a multi-billion dollar industry and estimates. Internationally, significant limitations to growth in this area are resulting from a necessity to properly label and assess the health effects of nutraceutical and functional foods. Selection for consistent production of high and low productivity of active plant components within specific ecological regions will allow development of alternative nutraceuticals and functional foods with distinctive and more reliable health and food properties. The United States of America (USA) currently possesses the largest and most rapidly expanding functional food and nutraceutical market in the world.^[13] India is the home of a large number of medicinal herbs, spices and tree species that have a substantially large domestic market. The functional foods and nutraceuticals are available as traditional Indian Ayurvedic Medicines in India and marketed in different brand names. However, no strict pharmaceutical regulations are available for the Ayurvedic and nutraceutical health products in India; they are available to the public as over the counter without any medical prescription. India has a large share of the international functional food and nutraceutical market, and exports products to various countries.

Classification of nutraceuticals^[15]



Traditional and Nontraditional Nutraceuticals

Nutraceuticals on the market today consist of both traditional foods and non-traditional foods. Traditional nutraceuticals are simply natural, whole foods with new information about their potential health qualities. Many if not most fruits, vegetables, grains, fish, dairy and meat products contain several natural components that deliver benefits beyond basic nutrition, such as lycopene in tomatoes, omega-3 fatty acids in salmon or saponins in soy. Even tea and chocolate have been noted in some studies to contain health-benefiting attributes. Non-traditional nutraceuticals, on the other hand, are foods resulting from agricultural breeding or added nutrients and/or ingredients.^[16]

Applications of nutraceuticals

The extensive researches have revealed the involvement of nutraceuticals in the treatment of many disorders such as insomnia, digestion problems, blood pressure abnormalities, cold and cough, depression, delayed gastrointestinal emptying, and many more conditions which need special care. Nutraceuticals are currently receiving recognition as being beneficial in coronary heart disease, obesity, diabetes, cancer, osteoporosis and other chronic and degenerative diseases such as Parkinson's and Alzheimer's diseases etc.^[17]

Prebiotics are substances come from types of carbs (mostly fiber) that humans can't digest. The beneficial bacteria in your gut eat this fiber. Probiotics are live bacteria found in certain foods or supplements. They can provide numerous health benefits.

Prebiotic: Prebiotics are food, ingredients, supplements, products, and more that support the wanted beneficial bacteria in our micro biome by providing an ideal nutritional source for the bacteria.

To support our gut micro biota, a prebiotic ingredient must.^[18]

- Not be easily digested (or only partially digested);
- Not be absorbed in the small intestine;
- Be poorly fermented by bacteria in our mouth;
- Be well fermented by seemingly beneficial intestinal bacteria;
- Be poorly fermented by potential pathogens in the bowel.

Probiotics: Probiotics are food, ingredients, supplements, products, and more that contain the wanted beneficial bacteria. To support our gut micro biota, as defined by regulatory agencies, a probiotic ingredient must be

- Safe, meaning the ingredient should contain beneficial bacteria that don't cause adverse reactions in the gut.
- Functional, meaning it needs to work as intended and be able to survive and thrive properly in the gut
- Technologically useful, meaning manufacturers can easily replicate, store, and continue to use the ingredients ongoing.

Probiotic and prebiotic concepts are altering the composition of intestinal micro biota by viable bacterial supplements versus non absorbable bacterial substrates.^[19]

Examples of probiotics and prebiotics^[20]

Plants- Based Probiotic Foods

1. Natto

Natto is a popular Japanese soybean product. It is prepared from whole soybeans fermented by *Bacillus subtilis* (var. natto). It represents typical food and staple in the Japanese cooking and diet, frequently served as a breakfast with rice. Natto contains nattokinase, soybean isoflavone, γ -polyglutamic acid, vitamin K2, biogenic amines, superoxide dismutase (SOD), small-molecule polypeptide and so on. Therefore, natto is known as "super healthy food". Nattokinase (EC 3.4. 21.62) is a kind of serine protease.^[21]

Health benefits of natto

- Natto improves your digestion: Natto contains fewer anti-nutrients and more probiotics than non-fermented soybeans. This reduces unpleasant digestive symptoms and helps your body absorb nutrients more easily.^[22]
- It contributes to stronger bones: Natto contains calcium and vitamin K2, both of which contribute to stronger, healthier bones.
- It promotes heart health: Natto contains fiber, probiotics, vitamin K2 and nattokinase. This combination may help reduce cholesterol and blood pressure levels and decrease the risk of heart disease.
- Natto may strengthen your immune system: Natto is rich in probiotics, vitamin C and several minerals, all of which contribute to a healthy immune system.

Kimchi

Kimchi is a unique and traditional fermented ethnic food of Korea, which consists of vegetables such as Chinese cabbage fermented with lactic acid bacteria.^[23]

The mixture ratio for kimchi was as follows: 85% salted-cabbage, 3.3% red pepper powder, 2.7% green onion, 2.5% garlic, 0.4% ginger, 1% anchovy sauce, 1.5% salted shrimp, and 3.6% glutinous rice paste.

Health benefits of Kimchi

Improved digestion: The method of producing fermented foods such as kimchi involves a lacto-fermentation process trusted source that uses the Lactobacilli bacteria

to break down sugar and starches into lactic acid.^[24] Eating fermented foods containing probiotics can help maintain healthy gut flora and reduce the negative symptoms of digestion-related conditions.

Heart Health: Kimchi consumption may reduce the risk of heart disease by lowering cholesterol and inflammation. The mice consuming the kimchi had lower fat levels in the liver and circulating blood than those only consuming the high cholesterol diet.

Immune support: Kimchi can also help remodel the gut micro biome and alter and strengthen the immune system.

Weight Loss:-Kimchi is not only low in calories but may also help with weight loss.

A 12-week randomized clinical trial in 114 adults with obesity suggests that *Lactobacillus sakei* derived from kimchi might help reduce body fat mass and waist circumference.

Tempeh

Tempeh or tempe is a traditional Indonesian food made from fermented soybeans. It is made by a natural culturing and controlled fermentation process that *Rhizopusoligosporus*, *Rhizopusoryzae*, *Hibiscus tiliaceus*.^[24] Tempeh is typically made up of fermented soybeans, wheat, or both. It can be prepared in a variety of different ways and is high in nutrients, making it a popular vegetarian source of protein. Tempeh is a food product that is fermented with *Rhizopusoligosporus* and has a high nutritional composition. Tempeh contains 46.68-52.70% protein, 6.57- 6.12% carbohydrates, 2.01- 2.47% ash content, and 6.21- 6.77% crude fiber (25. Astawan et al. 2013).

Health benefits of tempeh

Like other soy foods, tempeh has isoflavones. These are chemicals called phytoestrogens that have cancer-fighting and antioxidant properties. There is also evidence that soy products like tempeh benefits are

- Improve your cholesterol.
- Lower your blood pressure.
- Protect your heart.
- Improve insulin resistance.
- Lower inflammation.
- Help relieve hot flashes from menopause.
- Promote bone health.^[26]

Coconut kefir

Coconut kefir is coconut water that has been fermented with kefir grains. Like dairy kefir, it provides fuel for the beneficial bacteria in your gut. These good bacteria fight potentially harmful bacteria as well as infection. They also help stimulate digestion and boost your immune system. Coconut water kefir contains about as much potassium as a banana. Potassium can help prevent the loss of bone mineral density and reduce the risk of

osteoporosis. Kefir lactic acid bacteria also ferment the milk and form many compounds such as organic acids, hydrogen peroxide, acetaldehyde, carbon dioxide, and bacteriocins, which have an antibacterial effect against many pathogenic organisms.

Health Benefits of Coconut Kefir

Supports Digestive Health:- kefir milk benefits digestive health by supplying the gut with a hearty dose of anti-inflammatory, gut-boosting bacteria.

Some research suggests that probiotics could also improve symptoms of irritable bowel syndrome and inflammatory bowel disease as well.

Provide Allergy Relief:-That probiotics could help provide relief from allergy symptoms by altering the production of immune cells that are involved in inflammation and reducing the body's immune response to reduce symptom severity.

Boosts Immune Function:-It helps maintain intestinal homeostasis and triggers protective responses by the immune system, all of which can aid in the prevention and treatment of certain chronic health conditions.

Strengthens Bones: Milk kefir is a stellar source of calcium and vitamin D, two minerals that play a key role in bone health.

Fights Cancer Cell Growth: One of the most impressive milk, coconut and water kefir health benefits is its potential impact on cancer development. test-tube studies show that probiotics could help block the growth of breast, stomach, colon and cervical cancer cells.

Enhances Weight Loss:Kefir is low in calories but loaded with protein and other important nutrients, making it an awesome addition to a healthy weight loss diet.^[27]

Miso

Soybean miso is prepared from soybeans and salt, and it is fermented and aged with soybean Koji. Mixed miso can be made with a mixture of rice, barley, and/or soybean Koji. Miso is still widely used in both traditional and modern cooking in Japan and has been gaining worldwide interest.

It is used for sauces and spreads, pickling vegetables, fish, or meats, and mixing with dashi soup stock to serve as miso soup, a Japanese culinary staple. Miso is high in protein and rich in vitamins and minerals.^[28] Miso is a Japanese traditional paste produced by fermenting soybean with fungus *Aspergillus oryzae* and salt, and sometimes with rice, wheat, or oats. It contains vitamins, minerals, proteins, carbohydrates, isoflavones, and lecithin.^[28]

Health benefits of miso

Support gut health:-the production of miso promotes levels of beneficial bacteria, known as probiotics. These bacteria are thought to help a range of health issues, including digestion and gut health.

Promote vitamin levels:-Studies in 1997 and 2013 have shown these beneficial bacteria in the gut manufacture vitamins (primarily vitamins K and B12) as a by-product of their metabolism. This means that by improving the balance of your gut microbes through the consumption of fermented foods, an indirect benefit may be enhanced nutritional status.

Enhance immune function:-Regularly consuming a variety of fermented foods like miso may minimise your need for antibiotic therapy when fighting infection.

Support brain health:- the consumption of fermented foods in cognitive health, including anxiety and depression.^[29]

Plants- Based Prebiotic Foods

Asparagus: Asparagus (*Asparagus officinalis* L.) is a member of the Liliaceae family whose origin is believed to be the eastern Mediterranean and further east, in the Mountains. It is a perennial and monocotyledonous plant that is grown for its edible stems (spears) It's common name is satavari.^[30] The active constituents are steroidal saponins, such as, Shata-varin I-IV (0.1–0.2%). The aglycone unit is sarsapogenin. The other compounds isolated from *A. racemosus* are β -sitosterol, stigma sterol, their glycosides, sarsapogenin, spirostanolic acid, furostanolicsaponins, 4, 6-dihydroxy-2-O-(2'-hydroxy-isobutyl) benzaldehyde, undecanyletanoate and polycyclic alkaloid asparagamine A.^[32]

Health Benefits of Asparagus

Blood Clotting: Vitamin K helps blood clot properly, and a vitamin K deficiency can lead to problems like uncontrolled bleeding after an injury.

Rich in Antioxidants: Asparagus is also a good source of antioxidants like Vitamin A and Vitamin E. These antioxidants help the body fight off "free radicals," or oxygen particles that cells produce as waste.

Blood Pressure Control: Another benefit of eating enough fiber is that it helps regulate cholesterol. Too much cholesterol in your diet can cause and heart disease.

Others: The root is alterative, antispasmodic, aphrodisiac, demulcent, diuretic, galactogogue and refrigerant. It is taken internally in the treatment of infertility, loss of libido, threatened miscarriage, menopausal problems, hyperacidity, stomach ulcers and bronchial infections. Externally it is used to treat stiffness in the joints. The root is used fresh in the treatment of dysentery.

Garlic

Garlic is the ripe bulb of *Allium sativum* Linn. Belonging to family Liliaceae.

Allicin, a yellow liquid responsible for the odour of garlic, is the active principle of the drug. The other constituents reported in Garlic are alliin, volatile and fatty oils, mucilage and albumin.

Health benefits of Garlic

It provides an impressive number and amount of nutrients relative to its low-calorie count, making it a nutrient-dense (read: very healthy!) ingredient. By consuming garlic, you'll treat your body to some key nutrients such as manganese, vitamin B6, zinc, sulfur, iron, vitamin C, potassium, calcium, magnesium, selenium, and more.

It helps reduce your risk for heart disease. Substantial research has found that garlic plays a role in reducing the risk of cardiovascular diseases like heart attack and stroke, namely by lowering high blood pressure and regulating cholesterol levels (including lowering LDL, or "bad," cholesterol)

Antioxidant-rich foods can help guard your cells against free-radical damage, which in turn can decrease your risk for diseases associated with chronic stress and inflammation: cancer, heart disease, diabetes, Alzheimer's, and more.

It has antifungal and antibacterial properties. *More recent scientific interest in garlic's antimicrobial powers has uncovered its potential to protect against viruses, bacteria, and fungi, thanks in large part to allicin.*

It gives your immune system a boost.

In addition to making it harder for pathogens to take hold, garlic may also help fortify your immune system to fight them off by boosting the white blood cell response.

Banana

Banana is an edible fruit and is herbaceous flowering plant belonging to the genus *Musa* and the family Musaceae. The scientific names of most cultivated bananas are *Musa acuminata*, *Musa balbisiana*, Chemical Constituents of Energy 371 kJ (89 kcal) Water 74.91 g, Carbohydrates 22.84 g, Sugars 12.23 g, Dietary fibre 2.6 g, Vitamins, Pantothenic acid (B5) 0.334mg (7%), Pyridoxine (B6) 0.4mg, (31%), Choline 9.8mg, (2%), Vitamin C 8.7mg, (10%), Minerals, Magnesium 27mg, (8%), Phosphorus 22mg, (3%), Potassium 358mg, (8%) Sodium 1mg, (0%), Zinc 0.15mg,^[33]

Health Benefits Of Banana

Improve digestion

Banana is rich in soluble and insoluble fibres that play an essential role in digestive health. Soluble fibres help to control blood sugar levels and may reduce cholesterol

levels. Insoluble fibres may soften your stool and regulate intestinal movements.

Helps to improve heart health: Banana is essential for your heart health. It is rich in potassium, minerals, and electrolytes that help to maintain your heart health.

Helps muscles to recover after exercise: Banana is rich in potassium which helps to recover your muscles after a workout. Consuming bananas after exercise may help to strengthen your muscles and it allows you to work out more.

Supports bone health: Though bananas are not high in calcium but they can help to maintain your bone health.

Helps to reduce bloating: Bloating makes you feel uneasy. Banana may help you in this situation, fight back against gas and water retention. It might increase the bloat-fighting bacteria in the stomach.

Supports eye health: Banana is rich in vitamin A, vitamin E, lutein and antioxidants that help keep your vision healthy. Lutein is a nutrient that may help to reduce the risk for macular degeneration.^[34]

Chicory Fruits

Choriumintybus, a perennial herbaceous plant of the Asteraceae family, has been used for ages as livestock forage in various parts of the world. Popularity of chicory is steadily growing owing to its numerous medicinal, culinary, and nutritional qualities.^[35]

Chicory root contains some phytochemical such as insulin (starch-like polysaccharide), coumarins, flavonoids, sesquiterpene lactones (lactucin and lactucopicrin), tannins, alkaloids, vitamins, minerals, and volatile oils.^[36]

Health Benefits Of Chicory Fruits

Packed with the prebiotic fiber inulin, It acts as a prebiotic, meaning that it feeds the beneficial bacteria in your gut. These helpful bacteria play a role in reducing inflammation, fighting harmful bacteria, and improving mineral absorption.

Bowel movements-Due to its inulin content, chicory root fiber may help relieve constipation and increase stool frequency.

Improve blood sugar control-inulin and other compounds in chicory root may help improve blood sugar control, especially in people with diabetes.

Support weight loss-Chicory root fiber may aid weight loss by reducing appetite and curbing calorie intake, though more studies are necessary.^[37]

Risks and side effects of prebiotics and probiotics

The Centre's for Disease Control and Prevention (CDC) point out that the use of commercial prebiotics and probiotics is generally safe for healthy people. But there are rare instances where a healthy person becomes sick after ingesting certain types of bacteria contained in probiotics. Probiotics aren't regulated according to "drug" standards by the U.S. Food and Drug Administration (FDA). This means that some of the live bacteria being used in probiotics haven't been evaluated according to strict safety measures. That's something important to keep in mind when considering prebiotics and probiotics.

There is one side effect of probiotics that is known to be dangerous: having an allergic reaction to the bacteria that are being added to your body. If you break out in hives or experience extreme stomach pain after ingesting a prebiotic or probiotic, stop taking the supplement. Contact a doctor to determine if you're having a reaction.

Sometimes probiotics are recommended for children that are taking antibiotics. But you should talk to your child's doctor before you give probiotics to a child under the age of 12. Probiotics and prebiotics are also believed to be generally safe during pregnancy and breastfeeding. Get the all-clear from your doctor before beginning any new supplement during pregnancy and post-delivery.^[38]

In healthy people, prebiotics and probiotics are usually safe to consume and rarely cause health problems. However, some people may temporarily experience gas and intestinal discomfort when adding more into their diets. In people with severe illnesses or compromised immune systems, probiotics may increase the risk of infections. In these cases, consult your doctor or health professional for further advice.^[39]

Future of prebiotics and probiotics

The current and emerging influences on probiotics and prebiotics, including novel sources, new discovery and evaluation techniques, manufacturing and formulation advances, regulatory and policy changes, and influences on implementation in nutrition and healthcare. It is important to note that developments in one area influence growth in others – for example, the discovery of novel probiotic genera necessitates evolution in manufacturing techniques and regulatory frameworks.^[40]

CONCLUSION

The various microorganisms in our gut have a crucial role in our health and well-being. Prebiotics feed the good bacteria already existing in your gut while probiotics directly introduce new strains of beneficial microbes that may result in health benefits. Both pre- and probiotics show promising health affects each person however can help to establish and maintain a healthy and diverse gut micro biota by consuming a balanced diet with a high variety of plant-based foods. Above mention the parts of nutraceuticals and related to prebiotics and

probiotics discussed about related the nutraceuticals. Although the different nutraceuticals like prebiotics and probiotics has numerous pharmacological importance but medicinal application and clinical application can be made only after extensive research on its bio-activity, mechanism of action, pharmacotherapeutics and extensive safety studies. It also require to research on pharmacognostical, phytochemical and pharmacological aspect. However research going on it would be easier to develop new drugs after extensive studies on mechanism of action & pharmacological effects. It is expected that it may find application as a novel drug/ nutraceuticals in the future to control various diseases or prevention of disease.

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