

## Designer Milk - A Milk of Intrinsic Health Benefit: A Review

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### Abstract

The functional and nutraceutical food are more preferred and consumed by the health conscious people. Milk and milk products are considered as complete food containing most of the nutrients required for healthy life. The nutrients contents and its proportion in the milk can be modified by either incorporating required functional ingredients directly into fluid milk/dairy products or modifying the feed formulation of lactating animals to get desired milk composition. The modification of feed formulation not only results in secretion of milk of desired composition but also reduces the chances of incidence of certain diseases in lactating animals. Modification or enrichment in milk/milk products can be done in several ways such as modifications in protein/amino acid composition, modifications in fat/fatty acid profile, alteration in lactose, humanization of bovine milk, eliminating  $\beta$ -lactoglobulin from milk, milk with human therapeutic proteins, decreasing of milk allergies, melatonin enriched milk and many more types of the modified or enriched milk can easily be obtained for the specific proposes.

**Keywords:** Alteration in lactose; Designer milk; Melatonin enriched milk; Milk with human therapeutic proteins

### Introduction

In modern era consumers are very much aware about their health. So the demand of functional foods is increasing day by day at a global level [1]. The optimistic views of increasing demand of functional foods are also supported by number of institutions and health related organizations such as the American Dietetic Association [2]. Among all the foods available, milk is a natural complete and balanced food, which is a rich source of fat, protein, essential vitamins and minerals. In particular, milk is a good source of calcium that is very much essential for the prevention of bone disorders such as osteoporosis [3] and it is also necessary for the growth and development of new born young one, growing children's. Keeping in view the importance and its nutritive value it is considered as complete food. With the changing social and eating behavior, the milk should be of special value so that it can compete with other dairy products and energy drink. To compete with the today's demand of human beings, milk has to be designed in such a way, which increases its properties according to the need of the changing scenario. Designer or enriched milk are those in which the content has been modified from the standard constituent of milk. This milk may be classified as humanized milk, milk with high therapeutic purpose. The most commonly available designer milk is with modified fat and lactose content of the milk. Composition of milk can be modified by nutritional management or through the exploitation of naturally occurring genetic variation among milch animals. By a comprehensive understanding of the biochemistry, genetic makeup and changes in the animals diet that affect milk synthesis and composition, ways and means to manipulate milk composition to suit specific needs can be found. By combined use of these two tools of nutritional and genetic interventions, researchers are now hoping to develop 'designer milk' tailored to consumer preferences or rich in specific milk constituents that have implications in human health as well as processing of milk. This article exposes the readers to the potential that exists in altering the milk composition or 'designing' milk by nutritional and genetic approaches so as to achieve specific health and/or processing opportunities. Some constituents of milk which are not useful rather they are harmful for human consumption, so such constituents of milk can either be reduced or can be removed from the milk to make it much

beneficial for human consumption. Till date the emphasis has been laid to increase the quantity of milk but in present scenario, more emphasis have been laid to increase the quality of milk, thus the designed milk will be boon to the health conscious people. Moreover, it will make the processing friendlier.

### Applications of Designer Milk

The applicability of designer milk can be classified into two categories i.e. in diet and human health measures as well as in processing/technological developments. Among applications of designer milk in diet and human health is that it generates a greater proportion of unsaturated fatty acids (USFA) in milk fat, reduced lactose content that benefits lactose intolerant individuals and removal of  $\beta$ -lacto-globulin from milk. However, its applicability in processing and technological developments includes alteration of primary structure of casein to improve technological properties of milk, production of high-protein milk, accelerated curd clotting time for cheese manufacturing, increased yield and/or more protein recovery, milk containing nutraceuticals and replacement for infant formula etc.

### Technologies Adopted for Development of Designer Milk

#### Modifications in protein

Transgenic cows are able to secrete elevated levels of  $\beta$ -(8-20%) and k-caseins (two fold) which can be produced by genetic engineering [4].  $\beta$ -casein, a most abundant milk protein, is involved in binding calcium

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phosphate and thus controlling milk calcium levels. Higher  $\kappa$ -casein in milk is linked to smaller micelles, better heat stability, and improved cheese-making properties. In the transgenic animals engineered by Brophy's group, the total milk protein increased by 13-20% and total milk casein by 17-35% compared to non-transgenic control cows. This has obviously, a positive influence on the cheese yield and also on the casein and milk protein concentrate industry. Edible casein is used in vitamin tablets, instant drinks and infant formulas, whereas acid casein is used for paper coatings, cosmetics, button making, paints and textile fabrics.

Caseins, particularly the  $\beta$ -,  $\alpha_1$ - and  $\alpha_2$ -caseins, being easily digestible are quite sensitive to plasmin, a serine protease occurring naturally in milk along with plasminogen. Plasmin activity leads to limited proteolysis in milk. This offers a dual disadvantage of decreasing the curd yield in cheese and inducing organoleptic defects and gelation of ultra high temperature-treated milk. Milk augmented with specific inhibitors of either plasmin or plasminogen activator would therefore be a boon to the process industry [5].

### Modifications in fat

The 'ideal' milk fat for human health would contain <10% poly unsaturated fatty acids (PUFA), <8% saturated fatty acids (SFA), and >82% mono saturated fatty acids (MUFA) [6]. Although it may not be possible to achieve this 'ideal' milk fat composition, manipulation of composition of milk fat is possible through altering the feeding practices for dairy cows and also through genetic interventions.

**Decreasing the level of saturated fat in the milk:** Ashes et al. [7] reported feeding of unsaturated fats in an encapsulated or protected form results in prompt rise in the degree of unsaturation of the serum lipids, tissue fat and milk fat. Feeding of highly unsaturated oils (e.g. soybean oil) caused depression in milk fat, but increased the proportion of USFA to SFA in milk ([www.extension.iastate.edu](http://www.extension.iastate.edu)). A study at the University of Alberta [8] revealed that feeding canola oil in the encapsulated form (to protect it from biohydrogenation by the rumen microorganisms) leads to increase in linoleic (18:2) and linolenic (18:3) acids as compared to feeding of unprotected oil seeds. As the melting point of milk fat containing USFA is less, the spreadability of butter made from such milk is improved tremendously. An Australian study on feeding of a special blend of canola and soybean meal in the protected form resulted in doubling in the spreadability of butter [9]. When taken out of a fridge at 5°C, the butter was nearly as spreadable as margarine, without losing its special eating qualities.

Studies at the University of California (Davis) are focused on the desaturase gene to produce milk with decreased levels of SFA. Efforts are underway to determine if genetic differences among breeds and individual animals are translated into ratios of SFA and USFA.

**Escalating conjugated linoleic acid levels in milk fat:** Dairy products are rich in conjugated linoleic acid (CLA), a product synthesized in the rumen during the bio-hydrogenation of linoleic acid. Diets rich in linoleic acid lead to increase the CLA levels in milk fat two fold [10]. Incorporation of CLA along with soy oil in the diet of cows increased the CLA levels and simultaneously decreasing the SFA in milk fat. Furthermore, milk from grass-fed cows has five times greater CLA as milk from a grain-fed animal [11].

CLAs reportedly inhibit carcinogens, proliferation of leukaemia, colon, prostate, ovary and breast cancers. They are the only natural fatty acids accepted by the National Academy of Sciences, USA as exhibiting reliable antitumor properties at levels as low as 0.25-1.0% of total fats

[12]. The other valuable health beneficial effects of CLA are supported by biomedical studies with animal models are anti-atherogenic effect, altered nutrient partitioning and lipid metabolism, anti-diabetic action (type II diabetes), immune enhancement and improved in bone mineralization [13].

**Enhancement of Omega fatty acids:** Scientific research indicates that PUFA content in modern diets (nearly 30% of calories) is far too high. It is suggested that our PUFA intake should not be much greater than 4% of the caloric total, in approximate proportions of 2% w-3 linolenic acid and 2% w-6 linoleic acid [14]. Milk from pastured fed cows contains an ideal ratio of essential fatty acids (EFAs).

It is evident that replacing grass in the diet with grains or other supplements increases the proportion of w-6 to w-3 fatty acids. Too much w-6 in the diet creates an imbalance that can disrupt the production of prostaglandins leading to increased tendency to form blood clots, inflammation, high blood pressure, irritation of the digestive tract, depressed immune function, sterility, cell proliferation, cancer and weight gain. On the other hand, deficiency in w-3 is associated with asthma, heart disease and learning deficiencies. There are reports that roughly equal amounts of these two fats in the diet will result in lower risk of cancer, cardiovascular disease, autoimmune disorders, allergies, obesity, diabetes, dementia and some mental disorders [15].

**Reducing fat content in milk as a variation to altering the fat composition:** The genetic makeup of an animal can be modified to enable it to produce milk with 2% fat would reduce the cost of feed per kg milk by 22% [16]. In changing the fat composition, targeting enzymes that influence the synthesis of fat is important. As an example, reduction of Acetyl CoA carboxylase that regulates the rate of fat synthesis within the mammary gland would translate to a drastic reduction in the fat content of milk and reduce the energy required by the animal to produce milk [17].

**Alteration in lactose:** Lactose, the milk sugar, cannot be transported to the blood stream directly whereas the monosaccharide glucose and galactose, which result from the enzymatic hydrolysis of lactose, can. For many human beings, the level of the hydrolyzing enzyme lactase or  $\beta$ -galactosidase ( $\beta$ -gal) declines early in life to the point of virtual absence in adulthood. When such individuals ingest milk or milk products, the lactose remains undigested and mal-absorbed in the gut, where it causes retention of water due to its osmotic effect. This water retention together with the bacterial production of large volumes of carbon dioxide leads to intestinal distress and dehydration [18]. As milk is a most important component in the human diet, lactose intolerance limits the utilization of valuable nutritional source for many people. In addition, since milk can provide much of the required calcium for maintaining bone healthiness, lactose intolerance may be associated with osteopaenia in later life – an issue of increasing importance in old people [19]. The consequences of intolerance can be limited by nutritional changes such as avoidance of dairy products or through the use of  $\beta$ -gal-replacement (pre-harvest) or hydrolyzed low-lactose (post-harvest) products. Each of these management strategies requires dietary supplementation and varies in its efficiency. Not only is there an associated economic cost, but such strategies also do not adequately satisfy the world's nutritional needs.

**Pre-harvest methods of lactose reduction:**  $\alpha$ -lactalbumin ( $\alpha$ -LA) is one of the most important milk proteins present in almost all mammalian milk. It interacts with  $\beta$ -1,4-UDP-galactosyltransferase (UDP-gal) to change substrate specificity of this enzyme, virtually creating a inimitable binding site for glucose and leading to the synthesis of lactose [20].

The pre-harvest methodologies of decreasing lactose involve either the removal of  $\alpha$ -LA and gene 'knock-out' methodologies or introducing the lactase enzyme into milk via mammary gland-specific expression. Although these successful approaches provide valuable tools to address milk physiology, they decrease the overall sugar content of milk, resulting in highly viscous milk. Studies on mice have revealed that reduction of lactose via  $\alpha$ -LA deletion was inappropriate because it impaired milk volume regulation. The milk of such mice was highly viscous with high protein (88%) and fat (60%), no  $\alpha$ -LA and no lactose Karatzas and Turner [21] knocking out the UDP-gal gene in mice also produced milk with no lactose, but high viscosity [20].

**Post-harvest methods of lactose reduction:** An alternative to produce low-lactose milk are over expression of  $\beta$ -gal in milk. However, the monosaccharide produced within the formed milk increase the osmotic pressure within the alveolar lumen, thereby drawing more water and resulting in further dilution of other milk components [22] explained an in vivo technique for low-lactose milk production. They generated transgenic mice that selectively produced a biologically active  $\beta$ -gal in their milk. In these transgenic mice, the lactose content of the milk is at least halved, even though the  $\beta$ -gal expression levels were relatively low. The authors claim that it is likely that at least twofold greater levels of lactose-reduction could be achieved. In contrast to the previous studies by Karatzas and Turner [21] these experiments led to reduction in the lactose content while retaining most of the monosaccharide content of the milk. In addition, transgenic expression did not affect the milk protein levels, thus helping maintain a balanced nutrient supply as reflected in the similar growth curve reared on transgenic or control milk. It is likely that transgenic low-lactose milk production could offer a more balanced approach to managing lactose intolerance than post-harvest or lactose-replacement products. It is also technically feasible to produce transgenic livestock carrying this transgene. It is likely that similar or better expression levels could be achieved.

**Humanization of bovine milk:** It is said that mother's breast milk is the ultimate designer food for babies. However, due to varying reasons, a number of infants are fed formulas based on bovine milk. The composition of these formulas could be greatly improved to suit the needs of the infant by incorporation of ingredients that resemble to human milk which is achieved by 'humanizing' the bovine milk.

**Lactoferrin (LF):** the iron-binding protein has antimicrobial properties and may also mediate some effects of inflammation and have a role in regulating various components of the immune system. Its level in human milk is about 1 g/l (in human colostrum about 7 g/l). As the levels of LF in cow's milk is only about one-tenth that in human milk, this has caught the attention of those involved in designing human milk replacement formulas. Pharming, NV (Leiden, The Netherlands) developed the first transgenic bull in late 1980s and a line of transgenic cows to produce several proteins, including human LF (HLF) [23].

**Human milk contains 0.4 g/l of lysozyme (LZ):** Enzymes possess antibacterial activity. Active human lysozyme (hLZ) has been produced in the milk of transgenic mice at concentrations of 0.78 g/l [24]. On the processing front, the expression of LZ in milk results in the reduction of rennet clotting time and greater gel strength in the clot. A double transgenic cow that co-expresses both hLF and hLZ in milk may also reduce the incidence of intra-mammary infection or mastitis. Yet another application of transgenic technology could be to produce the human lipase, which is stimulated by bile salt in the milk of bovines. The lipase thus produced could be used as a constituent of formulas to increase the digestibility of lipids, especially in premature infants who

have low b-gal activity [25]. From a study involving African-Americans between the ages 12 and 40 years, Johnson et al. [26] concluded that the cause of milk intolerance in as many as one-third of the subjects claiming symptoms after ingestion of a moderate amounts of milk was not due to its lactose content.

**Eliminating  $\beta$ -lactoglobulin from milk:** Cow milk allergenicity in children is often caused by the presence of  $\beta$ -lg, which is absent in human milk. Elimination of this protein by knocking out  $\beta$ -lg gene from cow's milk is unlikely to have any detrimental effects on either cow or human formula and might actually overcome many of the major allergy problems associated with cow's milk. Further, as milk protein allergenicity studies demonstrate that all food proteins are potential allergens and that allergenic structures are widely spread throughout the protein molecule, milk is a good model in the search for means of characterizing allergenic structures in food [27]. Therefore, while developing strategies for the identification and evaluation of potential allergenicity in novel foods, many of the technological practices used in the assessment of milk protein allergenicity can be adapted.

**Milk with human therapeutic proteins:** Industrial interest has focused on the production of high value, low volume therapeutic proteins in the milk of domestic animals. In this context, several human proteins have already been expressed with success. GTC Biotherapeutics uses both goats and cows to produce more than 60 therapeutic proteins, including plasma proteins, monoclonal antibodies and vaccines. One product that is in late stages of testing is recombinant human antithrombin III (produced in goat milk), an anti-coagulant protein found in blood [23]. GTC is also working on a project to develop a malaria vaccine from goat milk. It is understood that a litter of goat milk can contain up to 9 g of the transgenic protein and that eight goats can produce enough vaccine to inoculate 20 million people. The cost to produce a transgenic protein in goat milk can thus be 3 to 30 times cheaper than the current method using mammalian cell culture. PPL Therapeutics (Edinburgh, UK and Blacksburg, VA) is working with rabbits and sheep to produce a-1-antitrypsin, fibrinogen, and a lipase to treat pancreatic insufficiency in digesting dietary lipids. Products such as insulin and growth hormone have also been obtained from the milk of transgenic cows, sheep or goats [28]. Transgenic animals can also secrete proteins such as blood clotting factors needed by human hemophilia-sufferers in their milk [29].

**Decreasing of milk allergies:** A study conducted on African and Americans (age group 12-40 years), the lactose content of milk was not the cause of milk intolerance in one third of consumers [26]. In children, mostly the milk allergy to bovine's milk is due to b-lg protein, which is absent in human milk. Thus, removal of this protein by knocking out gene responsible for b-lg from bovines is suspicious to have any detrimental effects on bovine and might overcome milk allergy problems associated with bovine milk.

**Melatonin enriched milk:** Sleep disorders like insomnia can be treated by consumption of melatonin enriched milk. Melatonin is a potent antioxidant that acts as a terminal antioxidant which is now used in mitigation of various life-style diseases. The release of melatonin is three to four times higher in milk which is let down before sunrise than in the milk which is obtained during day time [30]. The resources of melatonin are both animals as well as plants [31]. The secretion of melatonin in different individuals varies according to their age, gender, and seasons and in certain diseases condition [31]. The level of melatonin decreases with the advancement of age of an individual although its secretion is higher in older women than elderly men. The concentration of melatonin varies with the seasonal variations

| Minerals/vitamin                         | Function   | Reference |
|--|--|-----------|
| Calcium and Vitamin D3                   | Reduces Bone Loss  | [33]      |
| Phytosterol-enriched milk with vitamin A | Reduce serum Triglyceride, Low-Density lipoprotein cholesterol and Apolipoprotein-B levels | [34]      |
| Lutein-Fortified Milk                    | Effective utilization of lipids  | [35]      |
| Vitamin E                                | Enriches human plasma lipoproteins   | [36]      |

**Table 1:** Some fortified milk and their functions.

[32]. The concentration of melatonin is reported higher in winters as compared to summers. The concentration of melatonin also varies with the type of milk in fashion of conjugated linoleic acid in different milks [31] (Table 1).

## Conclusion

In this age of customized product, milk in spite of being a biological product can be designed to meet the specific needs of the people. Intervention at different stages of production can easily help to design milk of various functions and utility. With an increasing interest in functional foods and nutraceuticals designer milk holds a promising future. But to give a real dimension to the designer milk; still a lot of research and its simultaneous field application is need of the time. The efforts in this field are started but a thorough study on these aspects is required and human trials are also needed to prove the facts or to authenticate the benefits achieved from designer milk. Some essentials compounds (carotene and Phytosterol) required for the normal body function cannot synthesize by the human body may easily fortify and supplemented through designer milk.

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