

Donkey's and Goat's Milk Consumption and Benefits to Human Health with Special Reference to the Inflammatory Status

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Abstract: The environmental impact as well as malnutrition are responsible for an increased incidence of inflammatory diseases with a consequential loss of immune homeostasis. Therefore, administration of nutraceuticals is aimed at reconstituting the immune balance in terms of the so-called immune nutrition. Among many known nutraceuticals, more recently, donkey's and goat's milks have been used as good alternatives to human and bovine milk in various clinical conditions such as allergy, atopy and inflammatory diseases. In fact, both milks possess immunomodulating capacities and release nitric oxide, a potent vasodilator endowed with anti-atherogenic properties. In this review, emphasis will be placed on the consumption of fermented milk and, in particular, on its ability to modulate the aged immune system, even including the intestinal mucosal immune response in elderly. Therefore, for their specific properties donkey's and goat's milk administration to aged people should be encouraged.

Keywords: Donkey, goat, immune response, milk, nitric oxide, probiotics.

INTRODUCTION

Nowadays, nutraceuticals represent an innovative approach to protect, balance or enhance the immune system of mammals [1,2]. Prebiotics, probiotics, antioxidants and oligoelements, even including milk and dairy products, have been object of intensive studies [1,2].

In particular, in the case of milk, emphasis has been placed on the activity of its immunological components among different species (*e.g.*, human, bovine, donkey, goat).

In this review, special attention will be paid to the consumption of donkey's and goat's milk and their beneficial properties to human health with special reference to the inflammatory status in elderly.

In general terms, milk is a vehicle between the maternal immune system and the infant, since it contains cellular and humoral components that enhance the ontogeny of the immune system [3-6]. Moreover, milk contains antimicrobial substances that afford protection to the host against external and internal noxious agents [3-6].

The beneficial effects exerted by milk's components are illustrated in Table 1.

In this framework, special attention should be devoted to the effects of lactoferrin (LF), the most representative protein in milk [7].

LF exhibits antibacterial, antifungal, antiviral, antiparasitic, and antitumoral activities. Moreover, it binds to lipid A of Gram-negative bacteria, hampering their toxic activities. In addition, LF protects the intestinal epithelium, favors bone growth, and the recovery of immune system function in immunocompromised animals. Finally, a proline-rich polypeptide (PRP), derived from LF, promotes T-cell maturation and inhibition of autoimmune disorders. Of note, PRP, as chewable tablets (Colostrinin), could improve or stabilize the clinical conditions of Alzheimer's disease patients [7].

In general terms, all these substances are able to modulate in different ways mononuclear cell function, also enhancing the development of the gut and its functions [8]. For instance, oligo-

saccharides, contained in human milk, inhibit monocyte, lymphocyte and, neutrophil adhesion to endothelial cells. These results underline how human milk can contribute to reduce inflammatory diseases in human milk-fed infants [9].

On the other hand, other milks, such as donkey's milk, are the major substitute of human milk being their components very powerful in the mitigation of allergy state and inflammation [10-12]. In this framework, in infants with intolerance to bovine milk, donkey's milk can be used as the best alternative, since its chemical composition is similar to that of human milk [13].

In addition, donkey's milk is enriched in essential amino acids, and, therefore, it a useful integrator in the diet of aged people [14]. Moreover, donkey's milk plays an important role in the immune response in terms of production of nitric oxide (NO), and proinflammatory cytokines from mononuclear cells, thus contributing to host defense [15].

Also, goat's milk, besides its immunomodulating capacities on human mononuclear cells, is able to inhibit lipopolysaccharide (LPS)-mediated effects such as NO release from monocytes, thus protecting the host in pathological circumstances, such as sepsis. [16].

Further details on the immunological properties of donkey's and goat's milk will be provided in the next sections.

DONKEY'S MILK EFFECTS ON THE HUMAN IMMUNE SYSTEM

Nowadays, consumption of donkey's milk has been reevaluated and several reports have emphasized its beneficial properties to human health.

Among its components, the most represented is lactose, which constitutes an ideal substrate for the intestinal flora [17]. Moreover, its content in lysozyme and LF also enhances the antibacterial activity [18], thus contributing to the host protection in the case of infections.

The lipidic fraction is the most important, with a low content in saturated fatty acids and an elevated concentration of unsaturated fatty acids [19]. In fact, a recent report has indicated that a moderate intake of milk fat reduces the risk of cardiovascular disease, possibly through reduced formation of small dense LDL-particles, despite its inherent tendency to increase total cholesterol [20]. This means that donkey's milk possesses anti-atherogenic and anti-thrombogenic activities higher than those found in bovine milk.

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Table 1. Milk Components and their Effects on Human Health

Substances	Beneficial effects
Secretory IgA antibodies	they bind microbes at the intestinal mucosa surface, thus preventing their penetration and passage into tissue ;
Interferon (IFN)- γ	it potentiates the antimicrobial activity of macrophages, natural killer cells and T cytotoxic cells;
Lysozime	it kills bacteria disrupting cell wall;
Mucins and Oligosaccharides	they bind microorganisms preventing their adhesion to mucosal surfaces;
Fibronectin	it potentiates macrophage microbicidal activity and favors tissue repair;
<i>Bifidus factor</i>	it promotes the growth of <i>Lactobacillus bifidus</i> in the intestine;
Protein Binding Vitamin B12	it reduces levels of this vitamin which represents a growth factor for bacteria;
Fatty Acids	they destroy certain viruses, thus retarding viral replication;
Hormones and growth factors	they facilitate maturation of the digestive tract, impeding entry of microorganisms through mucosal surface.

In donkey's milk, also the concentration of minerals, and in particular, calcium and phosphates are more elevated than the human counterpart, thus leading to a more efficient activation of immune cells [13].

On these bases, in a recent report donkey's colostrum and milk have been tested *in vitro* on peripheral blood mononuclear cells (PBMCs) isolated from healthy blood donors. Cytokine release was evaluated by a cytofluorimetric method, while NO induction was measured on monocytes [16].

Quite interestingly, the ability to induce release of interleukins (IL) (IL-12, IL-1 β and IL-10) and tumor necrosis factor (TNF)- α was confined only to milk, while colostrum was devoid of this capacity. Finally, both colostrum and milk produced NO but milk induced higher levels of NO than colostrum. In particular, NO induction by donkey's milk may be useful in the prevention of atherosclerosis, being a strong vasodilator and an affective antimicrobial agent.

Other details on structure and function of NO are discussed below.

NO is a simple diatomic molecule consisting of one atom of nitrogen and one atom of oxygen, whose physico-chemical and biological properties are determined by its small size (30 kDa), absence of charge and its single unpaired electron [21]. NO is a gas under atmospheric conditions but a solute within cells and tissues [21]. It is generated by a group of cytosolic or membrane-bound isoenzymes, named nitric oxide synthase enzyme constituted by a sequence of 1,294 amino acids. This enzyme converts the terminal guanidine-nitrogen atoms on the amino acids L-arginine into NO and L-citrulline either in mammalian or non-mammalian cells [22,23].

It is well known that NO possesses other anti-atherogenic activities such as:

- inhibition of platelet aggregation [24,25];
- inhibition of adhesion to the vascular wall of proliferating smooth muscle cells [24,25];
- inhibition of gene expression involved in atherogenesis [24,25];
- inhibition of influx of atherogenic monocytes and LDL into the wall of arteries [26];
- inhibition of *Chlamydia pneumonia* [27] and *Porphyromonas gingivalis* [28] growth which represents an important etiological factors in atherosclerosis development.

In conclusion, *in vitro* experiments with donkey's milk further support the anti-atherogenic role of this milk as well as its capacity to maintain immune homeostasis in the host in terms of IL-12: IL-10 ratio.

GOAT'S MILK EFFECTS ON THE HUMAN IMMUNE SYSTEM

Goat's milk consumption is quite common in the Mediterranean area since these animals can be very easily managed for their adaptability to the local vegetation [29]. In particular, the use of intensive systems based on the range vegetation only is mostly aimed at milk and cheese production [29].

One-quarter of goat's milk production in the world derives from the Mediterranean basin in comparison to 16% of cow milk and 4% of buffalo milk [30].

In general terms, as far as the quality of products is concerned 3 types of qualities can be distinguished [30]:

- Hygienic and sanitary quality;
- Dietetic and nutritional quality;
- Gustative and gastronomic quality.

In this respect, the benefits of goat's milk in terms of human digestion and metabolism have been ascribed to [31]:

- The small milk fat globules, so-called naturally homogenized goat milk;
- The polymorphisms of milk proteins different from those of cow milk which generate a softer curd on digestion and in cheese-making;
- Higher contents in short chain, medium chain, mono- and poly unsaturated fatty acids than cow milk and its cheese.

Nowadays, recent researches have emphasized the properties of goat's milk in comparison to human, bovine, and donkey's milk.

In particular, goat's milk seems to be more easily digested than bovine milk also because of its higher content in essential fatty acids and, in comparison with human milk, it exhibits a higher content in conjugated linoleic acid and a lower percentage of casein α [32].

In a recent research, the effects of goat's milk on human PBMCs and polymorphonuclear cells (PMNs) in terms of NO release and cytokine production were evaluated [16].

For this study goat's milk derived from the following breeds: Saanen (Switzerland), Jonica (Apulia, South Italy), Priska (Greece) and from an Italian commercial product were used as a stimulus for PBMCs and PMNs.

Results demonstrated that goat's milk was able to activate innate immunity in terms of NO release from both monocytes and PMN as well as innate and adaptive immunity via triggering of cytokine production, such as IL-10, TNF- α , and IL-6. At the same time, the commercial preparation could inhibit LPS-induced NO production by monocytes, thus limiting exaggerated release of noxious mediators in the host.

These new data obtained on the effects of goat's milk on the human immune system should encourage its larger consumption as an alternative to bovine milk in view of its beneficial activities to human health.

FUTURE TRENDS

The increasing interest in a healthy diet is stimulating innovative development of novel scientific products in the food industry. In particular, many studies have been conducted on fermented milk.

Numerous probiotic microorganisms (e.g. *Lactobacillus rhamnosus* GG, *L. reuteri*, *Bifidobacteria* and certain strains of *L. casei* or the *L. acidophilus*-group) are used in probiotic food, particularly as fermented milk products.

Probiotics are defined as live microbial food supplements, which beneficially influence human health [33-35]. Nowadays, the concept of functional foods, including probiotic food and dietary supplements, implies their ability to beneficially influence body functions in order to improve the state of well-being and health and reduce the risk of disease [36].

A prebiotic is "a selectively fermented ingredient that modifies both the composition and/or activity in the intestinal microflora, thus conferring benefits to human health", whereas synergistic combinations of pro- and prebiotics are called synbiotics [37].

Well-established probiotic effects are indicated in Table 2 [33].

Table 2. Probiotic Effects in Humans

Beneficial effects on rotavirus-induced or antibiotic-associated diarrhea and lactose intolerance
Reduction of cancer-promoting enzymes and/or bacterial metabolites in the gut
Amelioration of gastrointestinal disorders in healthy people
Beneficial effects on <i>Helicobacter pylori</i> infection or bacterial overgrowth
Prevention or mitigation of allergies and atopic diseases in infants
Prevention of respiratory tract and urogenital infections
Balance of the mouth flora and caries prevention
Prevention or therapy of cardiovascular diseases
Improvements of autoimmune diseases (e.g. arthritis).

The viable lactic acid bacteria in fermented milk products have been associated with increased lactose tolerance, a well-balanced intestinal microflora, antimicrobial activity, stimulation of the immune system and antitumoral, anticholesterolemic and antioxidative properties in human subjects [20,32]. In this respect, a pilot study with goat's milk fermented with *Lactobacillus fermentum* strain (ME-3) was developed to test the effect of the

fermented probiotic goat's milk on oxidative stress markers (including markers for atherosclerosis) in healthy human blood and urine and on the gut microflora [38].

The following beneficial effects were observed at the end of the trial:

- anti-atherogenicity;
- resistance of the lipoprotein fraction to oxidation, low levels of peroxidized lipoproteins, oxidized LDL, 8-isoprostanes and glutathione redox ratio;
- enhancement of total antioxidative activity.

Fermented goat's milk also modified the equilibrium of lactic acid bacteria (LAB) in the gut flora of the subjects.

In another study, in BALB/c mice, receiving the *Lactobacillus casei* DN114001 or the probiotic fermented milk (PFM) [39], the immune response was studied in the intestinal tissue as well as in the supernatants of intestinal cells (IC).

Results demonstrated that probiotic bacterium interacted with the IC.

Furthermore, the PFM-stimulated IC released IL-6 within the gut. Moreover, the increase in T lymphocytes and IgA+ B lymphocytes, and expression of cell markers related to both innate and adaptive response (macrophages) were observed. Finally, PFM activated the enzyme calcineurine responsible for the activation of the transcriptional factor NFAT.

Different LAB have often been administered to middle-aged people to enhance immune system activity. In one study [40] the effects of a *Lactobacillus casei* DN114001 fermented milk consumption was tested in middle-age volunteers and an upregulation of the innate immune response was observed.

Furthermore, in another group of middle-aged volunteers, daily intake of fermented milk containing *Lactobacillus casei* increased the oxidative burst capacity of monocytes [41].

In sum, these strategies are indicated in the maintenance of immune competence in elderly.

As far as the mechanisms involved in the fermented milk-mediated immune regulation are concerned, the following hypothesis can be formulated. Ingested fermented milk with all its components is able to perform a strong impact on the Gut-Associated Lymphoid Tissue (GALT), which represents the largest contingent of lymphoid tissue in the human body and provides the whole immunological competence into the host [42,43].

It is well known that the intestinal immune machinery response occurs in different compartments as aggregated follicles and Peyer's patches (PP) and immune cells are also widely distributed within the mucosa, the intestinal epithelium, and secretory sites [42,43]. The main components of GALT are highlighted in Table 3.

Finally, the induction of gut-seeking B cells, i.e., by milk components may influence mucosal immunity beyond the secretion of IgA.

In this immune scenario, we postulate that ingestion of fermented milk with probiotic bacteria is able to reinforce the gut mucosal defences by limiting local generation of proinflammatory mediators and enhancing the systemic production of IFN- γ for host protection.

CONCLUSION

All these data suggest that the consumption of fermented milk should be encouraged in clinical applications on a larger spectrum of populations.

In this respect, there is evidence for an altered GALT immune response in senescence in terms of reduction of lymphoid tissue, specific IgA response and lack of oral tolerance [44].

Table 3. Main Functions of GALT

Epithelium:
The specialized follicle associated epithelium contains M cells that form pockets as a niche for Antigen Presenting Cells (APCs), T and B lymphocytes.
In addition, M cells are devoted to uptake and transport of luminal antigens (food antigens and microorganisms).
Lymphoreticular tissue:
PP contain follicles (with a prevalence of B cells) and parafoallicular regions (with a predominance of T cells).
Two/third of T cells with an $\alpha\beta^+$ T cell receptor are T helper (h)1 and Th2.
One/third of $\alpha\beta$ T cells are CD8 ⁺ cells with cytotoxic activity.
In addition, different subsets of T regulatory (T reg) cells are present in the parafoallicular regions.
Finally, different dendritic cells (DCs) as APCs are present as follows:
1. CD11c ⁺ and CD8 ⁺ immature DCs;
2. Mature interdigitating CD11c ⁺ , CD11b ⁺ and CD8 ⁺ DCs.
DCs play a role in the triggering of mucosal immunity as well as of inflammation or tolerance

Therefore, in view of donkey's and goat's milk properties their use in fermented milk preparation is envisaged for the reconstitution of the mucosal immunity in elderly.

ACKNOWLEDGMENTS

Paper supported by INTERREG III A Greece-Italy (I 210130), MIUR and MINISTRY OF HEALTH (Rome, ITALY).

ABBREVIATIONS

GALT	=	Gut-Associated Lymphoid Tissue
Ig	=	Immunoglobulin
IL	=	Interleukin
IFN- γ	=	Interferon- γ
LAB	=	Lactic Acid Bacteria
LPS	=	Lipopolysaccharide
NO	=	Nitric Oxide
PBMC	=	Peripheral Blood Mononuclear Cell
PFM	=	Probiotic Fermented Milk
PMN	=	Polymorphonuclear cell
TNF- α	=	Tumor necrosis Factor α

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Received: October 1, 2009

Accepted: October 28, 2009

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