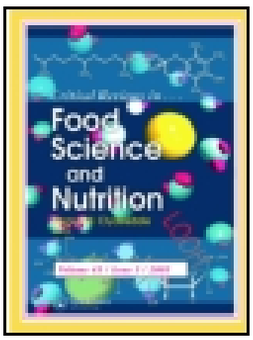

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HUMAN MICROBIOTA IN AGING AND INFECTION: A REVIEW

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Abstract

In most developed countries, ageing of the population started more than a century ago and it seems to be emerged in a wide range of developing countries as well.

Moreover, research into ageing has moved forward in extremely rapidly rhythms nowadays, and the scientific area is of great interest, as implications for nearly all sectors of society, including work, social, economic features, in addition to nutrition and health issues which are involved.

The fragile elder population is affected and experienced more frequently infections than the younger population. Infections in elderly patients are of major medical importance because of hormonal changes, increased production of pro-inflammatory cytokines and chemokines, abnormalities of the telomeres which could cause a dysfunction of the immune system called immunosenescence and malnutrition.

Keywords

Infection, nutrition, ageing, microbiota, probiotics, CYP cytochromes

ACCEPTED MANUSCRIPT

1. *Introduction*

Average life expectancy is rising constantly over the years. At ancient times mean age was defined as 25 to 35 years old just permitting continuation of the mankind. Over the last centuries industrialization and health care seems to rather triple these numbers. However, an increase in the ageing population (EC report, 2012) across the world is registered; the proportion of the elderly population reaching to 22% of the general population following data of WHO (WHO, 2012). Ageing is a natural and inevitable biological process which results in the synergistic effects of genetic and environmental factors (Biagi et al., 2013). Undoubtedly, a number of physiological, immunological and cellular changes is associated to the elderly person and make of the ageing person a prolific territory for infection (Gavazzi and Krause, 2002). Population ageing is registered when the mean age of this population rises as result of an increase in life expectancy .It seems to be strongly associated to declining fertility rates or absence of reproduction. Senescence was firstly reported in the economically developed world but nowadays, it seems also to occur in less economically developed countries (WHO, 2012; High, 2001). Moreover, it is believed that the ageing of the population in the upcoming century will exceed that of the previous centuries, as population encounters less time to adapt to the new changes of the developing world(WHO, 2012).Thus, population ageing becomes a topic of interest today not only in developed countries but also in the least developed countries. In this vein, international focus was sharpening on the different research aspects of the elder population. Our review entails the immunological and clinical related status of the elder population.

2. Origin of the human microbiota

It is known that the elderly are affected and suffer more often from infections than younger people (Marengoni et al., 2011). Microorganisms are omnipresent in the entire ecosystem (Konstandi et al., 2006). There is a close relationship between microbial diversity and ecosystem functioning. Microbial communities keep a key position in all biogeochemical cycles at many diverse habitats, from water, soil, food to the human intestine and other ecosystems (Bezirtzoglou et al., 2000). The human newborn is devoid of bacteria before birth (Bezirtzoglou and Stavropoulou, 2011). Colonization of the neonatal gut occurs primarily during birth when

the neonate comes into contact with the maternal cervical and vaginal flora. In contrast, infants delivered by Caesarean section are colonized by bacteria provided by the environment (Bezirtzoglou et al., 2006). The development of the infant intestinal • microflora is the result of a bacterial species selection process to which the multiple maternal or environmental bacteria that penetrate into neonatal intestines are subjected (Bezirtzoglou et al., 2006).Albeit, it is unknown how the newborn intestine fix on a limited number of microbial species from the enormous diversity offered. Bacteria start to appear in feces within few hours after birth, and a rapid and regular rise of the bacterial count is seen during the Ž first week of life (Bezirtzoglou et al., 2006).Multiple factors are involved at the colonization processes by a given bacterial genus. Hospitalization is implicated in changes of the normal newborn flora (Stark et al., 1993).Feeding seems to modulate the colonization pattern. In humans, breast milk plays a role in passive immunization of the neonatal intestine, and contains factors that promote the growth of *Bifidobacterium bifidum* in the intestinal flora (Bezirtzoglou et al., 1989, 1997, 2011)(Table 1). Formula feeding seems to promote implantation and persistence of *Clostridium perfringens* and clearly enhances intestinal colonization of *C. difficile* in newborns (Fanaro et al., 2003, Falani, 2010). Intestinal bacteria live together and constitute the normal intestinal bacterial flora, referred to as microbiota, which is a powerful barrier to the exogenous microorganisms. However, a plethora of factors may unsettle the mutually beneficial relationship between the microbiota and the human body. When this happens, the barrier is disturbed and bacteria could cause disease (Baumgart et al., 2002). Latest investigations provide information about the ageing influence upon the intestinal microflora which is associated to a decrease in anaerobic bacterial and bifidobacterial population (Benno1984; Balmer/Wharton, 1989; Hebuterne, 2003; Bezirtzoglou and Stavropoulou, 2011) (Table 1) An increase in enterobacterial population is reported as well (Bezirtzoglou and Stavropoulou, 2011; Hebuterne, 2003). Bacterial microbiota changes and the reduced intestinal immunity of the aged may grace gastrointestinal infections that are most common in old persons (Bezirtzoglou and Stavropoulou, 2011; Yoshikawa, 2001). Different nutritional status, extended use of medication with advancing age and the composition of the microbial communities of the human gut (Yoshikawa, 2001).

2. *Human microbiota in the ageing*

Pathogenic attackers such as, bacteria, parasites, viruses and any xenobiotic invader, are expelled out of the body *via* natural barriers formed by our skin, mucosa and intestinal microbiota. If the above natural barriers are disrupted, the immune system with its many components comes into action in order to front possible infection. The intestine itself is considered as an "active organ" due to its abundant bacterial flora and to its large metabolic activity (Bezirtzoglou and Stavropoulou, 2011; Bezirtzoglou, 1997). Inter-species or inter- strains variations recover the multifarious of the genetic polymorphism which regulates the immune system functions (Bezirtzoglou and Stavropoulou, 2011; Bezirtzoglou, 1997). Factors such as, gender, personal habits, alcohol consumption, smoking, food, religion, age, gender, precedent infections and vaccinations seems to have a crucial role (Bezirtzoglou and Stavropoulou, 2011; Bezirtzoglou, 1997). Hormonal status and stress seems to be related to the integrity of the microbiota causing immune system alterations (Mullie et al., 2002; Bezirtzoglou et al., 2008). However, which bacteria are responsible for inducing a proper barrier effect is not yet elucidated, but it is though that the barrier function can be ensured successfully by providing benefic diet supplements called functional foods. In this vein it is stressed the fact that newborn intestinal colonization by microorganisms such as *Lactobacillus spp* and *Bifidobacterium spp* offers protection from many different types of diseases (Bullen/Willis, 1971; Bezirtzoglou, 1997; Mackie, 1999, Harmsen, 2000, Fanaro, 2003, Adlerberth, 2009). Additionally, Adlerberth explains the presence of Staphylococci and specifically *Staphylococcus epidermidis* to the extensive contact with the mother's breast during breast feeding. Moreover, this benefic microbiota dominated but *Bifidobacterium* and *Lactobacillus* support the concept of their ability to modify the gut microbiota by reducing the risk of cancer following their capacity to decrease β-glucoronidase and carcinogen levels (Humblot et al., 2007). As they ask a beneficial role in the human gut, LAB (Lactic Acid Bacteria) are called "probiotics", and efforts are undertaken in order to ensure their use in modern nutrition habits as functional foods (Plessas et al.,2012). Members of *Lactobacillus* and *Bifidobacterium* genera are normal components of the microbiota in the human gut, in which they appeared few hours after birth (Bezirtzoglou, 1997). As already mentioned, within a few hours from birth the newborn develops its normal bacterial flora

(Bezirtzoglou, 1997). As known, human milk frequently contains low amounts of non-pathogenic bacteria like *Streptococcus, Micrococcus, Lactobacillus, Staphylococcus, Corynebacterium* and *Bifidobacterium* (Bezirtzoglou, 1997). Colonization by *Bifidobacterium* occurs generally within 4 days of life under maternal feeding (Bezirtzoglou et al., 2011). Speculations have reported the positive effect of *Bifidobacterium* on infant growth and health. Many authors (Bezirtzoglou and Stavropoulou, 2011; Bezirtzoglou, 1997) stated that several intestinal bacteria have a benefic action on the gut. *Bifidobacterium* is reported to be a probiotic bacterium, having a beneficial effect upon the intestinal microbiota. Moreover, an antagonism has been reported between *B. bifidum* and *C. perfringens* in the newborn gut delivered by cesarean section (Bezirtzoglou et al., 1989) (Table1). The aim of the probiotic approach is to repair the disruption in the gastrointestinal microbiota and enhance the protective effect. Albeit this knowledge, the possible mechanisms involved concerning the influence of probiotics upon the gastrointestinal microbiota are not yet clearly elucidated.

4 .Immune system in the ageing

The human immune system is essential for our survival in a world (Larbi et al., 2013). Human corps has evolved an holistic system of defense, role of which is either to identify and destroy the exogenous attackers or to develop mechanisms permitting to settle harmful actions. The host immune system keeps the capital role to preserve the microbial intestinal balance *via* the barrier effect (Bezirtzoglou and Stavropoulou, 2011). Components of the mammalian immune system appear to have arisen sequentially in phylogeny and have become specialized with evolution. However, the mechanisms involved in this situation are not yet fully elucidated.

4.1 .The innate immune system in the elderly

Natural immunity is the first front defense of our body against exogenous attackers. During ageing, there is a decreased mode of many functions as barrier effect and epithelial barriers of dermal and mucosal membranes favoring invasion of pathogenic bacteria (Wollscheid-Lengeling and Kerksiek, 2009). Moreover, natural killer cells, natural Killer T cells, neutrophils,macrophages and dendritic cells are playing an important role to the innate immunity. Most scientists all over the world report that there is no quantitative decrease in cells

of the immune system with ageing. However, the natural killers cells, granulocytes, monocytes and macrophages associated to the innate immunity and the B lymphocytes and T lymphocytes associated to the adaptive immunity are shown slightly increased in the ageing (Larbi,2013; Camerini and Ishikawa,2002;Vasto and Caruso,2004). Moreover, in ageing individuals the antigen-presenting function is far from normal, as the dendritic cells show a reduction in antigen presentation-function,reduced chemokine secretion and impaired endocytosis.

Natural killer cells (NK) are responsible to front pathogens and limiting tumors. They keep a capital role in the recognition, cytotoxicity and killing of tumor cells as well as virus infected cells. However, in the elderly there is a low signal transduction associated to an increased expression of killer-inhibitory receptors and a decreased production of chemokines, leading to a decrease in cytotoxicity of the natural killer (NK) cells and a decreased killing capacity. Natural killers numbers are increasing in the healthy elderly probably due to increasing activity of the markers cells CD56dim and CD57.However, their functioning is impaired as cytotoxicity and secretion of cytokines are reduced. The Natural Killer T cells (NKT cells) are important to front microbial and viral attackers. They seem to confer to an increased production of IL-4 and IL-10 and a reduced production of INF-c in the ageing individuals. It is stated that their number in lymphatic organs increases unlike their low proliferative capacity in the peripheral blood (Culley, 2009). As previously stated *neutrophils* remain quantitatively stable in the ageing in the peripheral blood and in the bone marrow but decrease in their functions is registered. While they remain quantitatively stable, they have low phagocytic and killing and bactericidal activity and are more susceptible to apoptosis (Butcher et al., 2000).

Monocytes remain also quantitatively stable in the elderly peripheral blood but decrease in the *Macrophage* function is occurring (Zhang and Wang,2014; Dunston and Griffiths,2010). Decrease in phagocytosis, chemiotaxia and oxidative burst due to the rapid release of reactive oxygen species, as superoxide radical and hydrogen peroxide from different type of cells. Their antigen-presenting capacity is lower and furthermore effective removal of apoptotic cells is not achieved. It is then conceivable that infection in the ageing patient will be long lasting and it is likely to develop a chronic inflammation state. The same picture is presented for the *dendritic cells (DCs)* .Although their stable levels, their functional profile is impaired (Do Nascimento et

al.,2015). Endocytosis, chemiotaxia, production of IL-12 and IFN-I / III are decreased as well as the effective removal of apoptotic cells (Gavazzi and Krause, 2002; Ginaldi, 1999). An increased production of the pro-inflammatory cytokines (TNF-a, IL-6) is observed together with an important reactivity against auto-antigens (Dunn and Swiergiel, 1998). Pro-inflammatory molecules are also used as markers for comorbidities and predictors of mortality (Marengoni et al., 2011). These alterations in the immunological profile of the frail elderly create a "prolific milieu" for development of the chronic disease state called inflamm-aging (Larbi et al., 2013). The innate immune system keeps without any doubt a crucial role in the development of chronic inflammation in the elderly (inflamm-aging). The pro-inflammatory genes that boost against pathogens and have a healing effect lose their efficacy during ageing and offer a prolific territory for different disease states such as cardiovascular diseases, Alzheimer's disease and diabetes. Additionally, macrophages are destined to engulf exogenous attackers and afterwards secreting inflammatory mediators (cytokines) (Zhang and Wang, 2014). Albeit some contradictory studies that yielded the macrophages function to be strictly associated to the chronological ageing, it is generally accepted that macrophages play the key role in the inflammatory discrepancy,that causes "inflamm-aging".

4.2. The acquired immune system in the elderly

The adaptive immune system registers more profound age-related modifications. The maturation of *T-lymphocytes* is completed in the thymus, a gland located behind the breastbone. Soon after birth at the 9th month of newborn life, the *"involution of thymus"* starts (atrophy of thymus) (Lynch et al., 2009) includes thymus reduction in size but also changes in anatomy are occurring, as absence of thymic epithelial cells,increase in adipose tissue and impairment in thymopoiesis. At the same time, pre-lymphocytes, derived from hematopoietic stem cells of the bone marrow are recognizing and facing antigens in the thymus configuring the gloomy picture of specific cytotoxic, helper and regulatory T cells (Chou and Effros, 2013). Additionally, a regression in T-naïve cells is registered increasing with chronological ageing and a surplus of oligoclonal memory and cytotoxic T cells are mentioned (Nikolich-Zugich, 2005). The thymus involution process's ends at around 50 years of life and age-related modifications are more pronounced since then, with notably a prevailing decrease in T-cells populations (Lunch, 2009). This

decrease is more pronounced in the sub-population of CD8+ cells comparing to the CD4+ (Deeks, 2011). The development of *B-lymphocytes*, derived from hematopoietic stem cells of the bone marrow, is completed in peripheral lymphoid organs (Demsey, 2014). While their numbers remains constant in peripheral blood, the rate of mnemonic B cells is increasing in an attempt to compensate probably the decrease of B-naïve cells in the ageing person. Moreover, as the hematopoietic tissue in the bone marrow is decreasing during ageing it is stated that the B-lymphocytes should decrease with chronological ageing. Additionally, a decrease in antibody production and impaired activation of the antigen-presenting system is registered in the elderly. This last probably explaining the insufficient production of specific antibodies in response to vaccination in old population (Gavazzi and Krause, 2002). Although all parts of the immune system are influenced by the aging of the organism, the specific immunity particular cellular component (T lymphocytes) showed greater impairment. To summarize, a plethora of changes are occurring within the immune system of the ageing population, with remarkable changes in B and T-cell responses, increasing frequency of memory phenotype cells, clonal exhaustion, thymic involution, and disrupted co-stimulation (Lynch et al.,,2009). Moreover, Interleukin-2 (IL-2) production is reduced, and changes in the Th1-Th2 cytokine balance is disrupted (Dunn et al., 1998).

4.3 Immunosenescence

Ageing related dysfunction of the immune system is reported as immunosenescence (Caruso et al., 2009),which is associated to a high risk of infection. Many research studies state the decreased immune function in old persons. Immunosenescence is mainly characterized by modifications in T-cell phenotype and a reduced number of naïve T cells necessary to fight the exogenous attackers (Caruso et al., 2009). The ageing related dysfunction seems to be a multifactorial complicating the possible explanations of the mechanisms involved in senescence development. Controversy in explaining the Immunosenescence development seems to exist (Caruso et al., 2009). Whether, several authors mention immunosenescence as a complex issue of dysfunction involving the whole host defense system. Other report just specific parameters in the immune remodeling of the human defense system (Caruso et al., 2009). The “damage theory of ageing“ support the theory of the first group of scientists while the effect of the telomere

tucking in the fast dividing of the immune system cells argument the second group of scientists opinions(Freitas and De Magalhaes,2011). The main proliferation control mechanism cells are telomeres (Aubert and Landorp, 2008), small repeat sequences at the ends of chromosomes. Specifically at each cell division the telomeres are reduced until the length reaches a critical size which marks the irreversible cessation of cell proliferation which is ageing .Telomere shortening has been identified in the memory CD8+ T cells CD28-T cells (Shammas, 2011). As lack of telomeres is related to loss of proliferation, telomeres absence is associated to the senescence status (Aubert and Landorp, 2008). In contrast, tumor cells which proliferate indefinitely having active telomerase, which maintains the telomere length, and therefore they do not senesce. Research studies (Freitas and De Magalhaes, 2011 Aubert and Landorp, 2008; Shammas, 2011) have shown that the synergy of telomerase with oncogenes as well as the deregulation of some tumor suppressor genes (p53 and RB) leads cells to immortalization. Unlike, senescent cells are post-mitotic, that have pulled out the cell cycle. In this vein, overexpression of inhibitors (p16, p21 genes) of the cell cycle leads to the faster aging. It is known actually that ageing is related to the changes in expression of multiple genes. Encoded genes associated with cytoskeleton and cell homeostasis keeps a key role in apoptosis and cell survival. Moreover, the role of the proteasome in the development of the phenomenon of aging and the maintenance of cellular homeostasis is confirmed. Proteasome (Chondrogianni and Gonos, 2008) is responsible for the degradation of both normal and oxidized proteins. The *in vitro* aging of fibroblasts exhibit reduced levels of the three main proteolytic activities of proteasome, chymotrypin-like, peptidylglutamylpeptide-hydrolyzing and trypsin-like (Chondrogianni and Gonos, 2008). Moreover, it is observed that the process of inhibition of the proteasome mediated by p53 as specific inhibitor leads to the premature aging in young cells (Chondrogianni et al., 2008). This last argument is in direct relation with the development of targeted telomerase-based therapies in the elderly and seems to be more supported as the former one is not associated to any chance of developing targeted therapies (Kim et al., 2002). However, without any doubt the ageing related dysfunction in the elderly exists. Moreover, the modulation of specific immune system elements during ageing seems to be influenced by both the genotype,the T-cell phenotype and lifestyle of the individual. To summarize, senescence is correlated to a chronic antigenic stimulus of

repetitive viral infections debilitating the immune system. Moreover, the observed decrease in naïve T and B lymphocytes results in attenuated response to the antigens. Simultaneously, increasing in pro-inflammatory cytokines contributes to the chronic inflammation (inflamm-aging).

3. Hormonal status and ageing

Ageing is characterized by a variety of hormonal changes (Chahal and Drake, 2007). The decline in estrogen levels in women and testosterone in men together with an observed increase of gonadotropins and binding globulin are the most characteristic changes in ageing. These hormonal changes lead to the reduced secretion or decreased sensitivity of the tissues or changes in the rate of their metabolism (Chahal and Drake, 2007). Furthermore, hormonal changes are associated with reduced synthesis of proteins, decrease of muscular and bone mass, an increasing in fat mass. The clinical significance of the above changes being insulin resistance, cardio-vascular risk, anemia, cachexia, depression, reduced libido and erectile function (Chahal and Drake, 2007).

4. Ageing and autoimmunity

Mild autoimmune diseases are present in the elderly. As stated previously, there is an increased production of pro-inflammatory cytokines and chemokines in the elderly. Abnormalities of the telomeres also could cause dysfunction of the immune system, which can lead to autoimmunity (Goronzy, 2012). It is notable the increased incidence of several auto-antibodies,such as antinuclear,antithyroid or rheumatoid factor are observed in the older population,probably due to a disorder in functioning of T and B lymphocyte cells, reduced affinity of the antibodies or mutations which give rise to cellular clones producing autoantibodies (Goronzy et al., 2012).

5. Ageing and infection

The elderly are more frequently and severely affected by infectious diseases than younger people due to an aged immune system which is not able to efficiently recognize and eliminate new attackers and restricting their spread in the elderly (Wollscheid-Lengeling and Kerksiek, 2009). Ageing-induced modifications in the immune system succor to the increased incidence and

severity of infectious diseases. Infections in the elderly are often occurred from intracellular microorganisms and symptoms are not specific or covert by primary chronic diseases. These infections afflicting the elderly population includes the flu, community-acquired pneumonia, CMV, urinary-tract infections, revival of herpes simplex virus and varicella-zoster virus infections, fungal and parasitic infections,staphylococci infections and soft tissue infections. They are associated with a high rate of morbidity and mortality (Marengoniet al., 2011). Respiratory infections are the major infections occurring in the elderly. The most common causes of these infections are *Pneumococcus* and *Influenza* virus. This last remains the leading treat for infection and death among the old persons attributed to the innate immune system disorders. As known, CMV is asymptomatic in healthy population and only in immunocompromised individuals CMV disease revives. The prevalence of CMV varies from 50% to 100% following habits, hygiene conditions, ethnic populations, ageing and religion. As discussed, old individuals carry lower numbers of circulating naïve T cells and presence of CMV memory specific CD8+T cells (Larbi et al., 2013). Memory CD8 T cells grow in size with continuous immunological exposure leading to their progressive dehabilitation. This is associated to the shortening of the telomeres and the loss of stimulatory molecules as CD28 and CD27. The proportion of CD8+CD28-T cells is in direct correlation with CMV infection and response to influenza vaccination (Sauerwein-Teissi et al., 2002).Urinary tract infections are coming in second row .They are correlated more often with application of urinary cacheters or lack of hygiene practices. However, structural or functional abnormalities of the genitourinary tract are associated as well to these infections (50). The most common bacterial species involved are *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Morganella, Providencia, Acinetobacter, Serratia, Enterococcus, Group B Streptococcus (*Nicolle,2005*).* Other prosthetic devices are also associated with infection in the geriatric population. Pyogenic infections remain the main causal agent for such infections coming from urinary cacheters and prosthethic devices (Nicolle, 2005). Endocarditis remains also a major cause of infection (Crossley and Peterson, 1996) in old population. The most common bacterial species involved are pyogenic bacteria as *Staphylococcus spp*, especially *S.aureus or* MRSA. Developing of an infection in the elderly seems to be a multifactorial status. During ageing, the

skin and mucous membranes being more damaging and dehydrating and bacteria can reach easier into the body. In addition, chronic diseases typically present with age, such as arteriosclerosis and diabetes, inhibit wound healing and host defense system function. It seems that chronic diseases have a negative effect upon the immune system which is no more able to quickly react against infection. Old persons are often hospitalized making them more vulnerable to nosocomial infections and infections occurring by antibiotic-resistant bacteria (Gavazzi and Krause, 2002). The longer period of hospitalization of these individuals is stated as the risk of infection is increasing per day of hospitalization. Infections occurred by unusual bacterial species are less frequent but of clinical importance. Pneumonia associated to *Chlamydia pneumonia*, *Legionella pneumophila* and *Mycoplasma pneumonia* as well as tuberbulosis indicates the decrease of the immune system functioning (Gavazzi and Krause, 2002).

Clostridium difficile-associated diarrhea is a common nosocomial infection in the ageing population with high morbidity and mortality (Duncan and Flint, 2013). Some hepatic cytochromes (CYP 2C8, 2C9, 2C18, 2C19, 2B6, 3A4) in humans object to inflammation and thus may have a critical effect on human drug responses in disease states. In this vein, CYP2C18, is expressed at very low levels in liver tissue, and so it was unaffected by cytokine exposure. It is mentioned previously that the liver decrease in size in the elderly and then quantitavely lower amounts of CYP should be expressed in the older tissues. The response pattern of cytochromes CYP2C9 and CYP2C19 was proven identical as both cytochromes were down-regulated by IL-6 and TGF but not influenced by LPS, TNF, IFN, or IL-1 (Aitken and Morgan, 2007). Moreover, research investigations claim that, alike the overlapping effects of cytokines, human P450s are freely regulated in response to inflammation and infection. Yet, different patterns in inflammatory response to cytokines may be crucial for patient therapeutic treatment, as CYPs are apparently regulated at different stages and by various mechanisms, as result to inflammatory attack or disease. In the light of this, differences in sensitivity of CYP-dependent clearance observed in infectious liver disease (Freie et al., 2006). It is known that vaccines are less effective in older people than in younger adults. Scientists are focusing their research in this direction looking for the causes and hoping to probably produce better vaccines for the elder population (Gavazzi and Krause, 2002). Vaccines are less effective in older people than in

younger adults, as a rapid response to the introduced attenuated antigen is missing (Larbi et al., 2013). Vaccination seems to be ineffective especially in the ill hospitalized or institutionalized elderly. In the light of this, influenza vaccination of medical and health-care personnel have been shown to efficiently protect lives of these patients.

6. Probiotics and ageing

It is known that probiotics exercise a positive influence upon intestinal microbiota function (53). Treatment with *Lactobacillus spp* and *Saccharomyces boulardii* in post-antibiotic *Clostridium difficile* associated diarrhea is highly effective (Simor et al., 2002; Duncan and Flint, 2013; Cusack et al., 2011).

Probiotics derived benefits include increased numbers of enhancement of the innate immunity and reduced inflammation. Inflammation in geriatric patient's intestine is associated with microbiota changes and specifically with dropping of bifidobacterial mucus-adherent populations (Cusack et al., 2011). Scientists state that diet supplementation with probiotics in the elderly patient decrease the impaired immunity due to the ageing (Duncan and Flint, 2013). Probiotic supplementation has been reported to increase the number of Natural Killer cells and phagocytic activity in the elderly. Moreover, they improve the immune and nutritional status of the frail elder by increasing levels of immunoglobulin A and serum albumin. In this vein, benefic *Lactobacillus, Bifidobacterium and Enterococcus* are predominant, unlike the reduced levels of *Enterobacter* (Patel et al.,2014). This may play a positive role to the reduction of infection. However, beneficial effects are usually dependent upon the genus and species of the probiotic microorganism. In this vein, the question is raised if the probiotic strains derived from the human gut should be commercially employed as functional foods. This is clearly a matter of extensive discussion and conflict between scientists and the industrial body.

The vast majority of probiotic bacteria commercially available are *Lactobacillus* and *Bifidobacterium* (Cusack et al., 2011). The dominant bacterial phyla in the elderly population are the *Firmicutes, Bacteroidetes* and *Proteobacteria.* Fresh evidence based on 16SrRNA gene analysis, revealed *Faecalibacterium prausnitzii* to possess anti-inflammatory potential in the human intestine (Patel et al., 2014). The intestinal microbiota provides more species with

beneficial effects potential *via* their metabolic outputs and gene products, as *Lactobacillus* and *Bifidobacterium*. The aged individual microbiota is mainly dominated by putrefactive bacteria, including strict and facultative anaerobes and gram-negative bacteria as *Enterobacter*. A decrease in *Lactobacillus* and *Bifidobacterium* is registered (Bezirtzoglou and Stavropoulou, 2011). In the light of this, increased putrefaction status in the human colon gives a higher susceptibility to infection to the frail aged man.

A benefic effect of probiotics is reported in *Clostridium difficile* associated diarrhea, which consists of a common nosocomial infection to the geriatric patient (Patel et al., 2014).

Prebiotics as well as synergistic combinations of probiotics and prebiotics called synbiotics, when given as diet supplements, ask a beneficial effect to the elderly by increasing numbers of the beneficial microbiota and anti-inflammatory cytokines. In contrast, pro-inflammatory cytokines are decreased resulting in a decrease of intestinal inflammation in old people. As stated previously, scientists are interesting in producing more efficient vaccines for the elder (Patel et al., 2014). However, it should be of interest to determine if the consumption of probiotics is associated to a lower infection rate or a higher effectiveness of vaccines.

Research must be oriented to the use of genetically modified benefic microorganisms to provide epitopes for vaccine delivery in order to improve the immune response (Patel et al., 2014).

7. Ageing and drugs

Current research shows that polypharmacy is common in the elderly population due to the mosaic of chronic disorders affecting this population (Segi et al., 2011). However, the frail elder is more effective to the effects of many drugs and frequently these drugs are taken for long periods of life increasing the chance of adverse effects and suppressing the immune system (Cusack et al., 2011). Additionally, the frail elderly presents significant changes in the physiology of his organs (Segi et al., 2011). As result, the drug pharmacokinetic profile is influenced. In the light of this, significant reduction in liver size and blood flow with age are registered (Segi et al., 2011).Drug clearance seems to decrease with reduce liver size in the ageing population.

Ageing can influence drug disposition and therefore decreases their therapeutic efficacy and safety (Segi et al., 2011; Kinirons and O'Mahony, 2003). The cytochrome *P*-450 (CYP450) is a family of enzymatic proteins which catalyze the oxidation of substrates. Many endogenous substances, as well as a large number of foreign substances (xenobiotics), including medicines, are metabolized in multiple sites by CYP450 through an oxidative transformation (Bezirtzoglou, 2012).

As known, cytochromes P450 (CYPs) enzymes metabolize a colossal pool of xenobiotic substances. CYPs are responsible for the majority of phase I drug metabolism reactions. Changes in the intestinal digestive tract during development characterize transition to adult life (Johnson et al., 2001). The human gut is a notable metabolic site and place of drug biotransformation (Stavropoulou and Bezirtzoglou, 2015; Midtvedt, 2003). Although, knowledge associated to the developmental change of intestinal phase I and II xenobiotic metabolizing enzymes are confined.

Cytochromes are distributed in many different tissues of the human body showing preponderance in intestinal and hepatic tissues. Taking in account the marked abundance of P450s in these tissues, we could essentially understand the functioning of the extrahepatic metabolism balance and specifically the reduced hepatic function following liver disease states (64). Effect of ageing and different disease states seems to determine the expression and the activity of the intestinal CYP3A4 and other P450s enzymes (Stavropoulou and Bezirtzoglou, 2015; Prior and Baker, 2002; Benedetti and Baltes, 2003; Wauthier, 2017).

Age dependent variations in xenobiotic enzyme expression, induction and DNA adduct formation during maturation processes of the tissues were registered upon rat intestine. Yet, notable differences were shown in fetal and postnatal gut, which could be mainly affected by maternal factors and the placental barrier, as well as the tissue specific metabolism and the minor modifications in postnatal maturation of the intestinal tissue. Variable patterns in metabolic ability and genotoxic injury could be related to the aged-gut in rat intestine (Patel et al., 1998). The high metabolic capacity of the intestinal flora is due to its enormous pool of enzymes, which catalyzes reactions in phase I and phase II drug metabolism. Phase I states basically an oxidation, reduction or hydrolysis reaction, while phase II focuses on conjugation of the xenobiotic

compound with a molecule (Stavropoulou and Bezirtzoglou, 2015).It is then understandable that the quality of the gut microbiota counts considerably in ensuring its metabolic capacity. Intestinal microflora seems to be modified by ageing. The gut epithelial cells are derived from pluri-potential stem cells near the base of the crypts, and particularized as they migrate to the luminal surface. Additionally, as the enterocytes move towards the villus surface, the expression of the mitochondrial genome is corrupted during cellular maturation in the intestinal epithelium. Nevertheless, knowledge of regulation processes concerning mitochondrial gene expression in developing and senescent cells is yet under study. Persistent ulcers in adults have been associated to the presence of aging cells in the injured site, as senescence may intrench the degree of tissue repair by inhibiting fibrosis.

In response to the inflammatory stimulis, important changes in mRNA introduce changes in protein levels of rats. These changes may lead to an enhanced toxicity or loss of competence of cytochromes targeting drugs (Aitken and Morgan, 2007). In this direction mere extensive studies were carried out in animal models, unlike studies in humans seems to be limited.

The presence of hydrolase activity in the gastrointestinal brush border membrane is crucial for the maturation of digestive capacity in newborns. Hydrolase activity is induced by cytochromes P450. This activity is registered tenuous during the early life and increase with ageing due to the intestinal maturation. Yet, it seems to be a gender dependent activity as males have usually twice the activity of females.

Ageing and different disease states seem to influence the expression and activity of the intestinal CYP3A4 and other P450s enzymes (Segi et al., 2011; Kinirons and O'Mahony, 2003) expressed in the gut. Variable registered profiles in drug distribution could be clarified by the ageing influence which induce changes of the circulating endogenous compounds in plasma, total body fluids, extracellular water, fat, and protein concentration in plasma leading to another pattern of membrane permeability (Johnson et al., 2001; Stavropoulou et Bezirtzoglou, 2015; Midtvedt, 2003; Krishna and Klotz, 1994; Prior and Baker, 2002; Benedetti and Baltes, 2003; Wauthier et al., 2017). Additionally, those changes may have significant impact on human health and being closely related in maturation processes (Benedetti and Baltes, 2003; Wauthier et al., 2017).

Microbial colonization or infection in the human gut can influence significantly the cellular and humoral immunity of the intestinal system during normal development. Knowledge of the microbial-host gut mucosal interactions and their outcome stand in need of new or alternative approaches as the therapeutical treatments. Many authors (Bezirtzoglou and Stavropoulou, 2011; Bezirtzoglou, 1997; Cusack et al., 2011; Patel et al., 2014) reported the benefic action of certain bacteria upon the intestinal ecosystem. The aim of the probiotic approach is to repair the defects of the gut flora and install a protective capacity. In the light of this, there is an observed multi-factorial relation of the CYP (P450) cytochrome role in the different diseases states, environmental toxic effects or chemical exposures, ageing and nutritional status.

In the evidence of the fact that many intestinal bacterial strains possess P450 enzymes, the question is raised that if live probiotics express a P450 activity, which of them could presumable affect the drug metabolism and bioavailabity? (Bezirtzoglou, 2012)

8. Malnutrition

Malnutrition is related to the ageing and to the prevalence of the disease risk. The major causes of malnutrition are medical, social, and psychological (Hickson, 2006).

Body composition changes in the malnourished elder and sarcopenia occurs as result. Moreover, increasing up the ageing year's appendicular fat mass seems to be decreased in the elder population (Kyle et al., 2001).

Cytokines seems to be involved in sarcopenia mechanisms through the pro- inflammatory cytokines IL1, IL6, TNFα, interferon gamma and serotonin (Roubenoff, 1999). Theses cytokines have as role to stimulate the release of the acute phase proteins, the proteins breakdown in muscle, and the breakdown of fats in adipose tissue.

9. Conclusions

An increase in the ageing population is registered worldwide during the last years combined with the lower birth rate and life elongation of humans. Diseases are more frequently in the aging population as the recovery of the frail geriatric patient is usually longer due to the loss of immune functions. This loss of immune functions in the elder population is called

‘immunosenescence’. Alterations in cells of the innate immunity lead to a limited response in the specific antigen. Moreover, changes are registered in adaptive immunity, including T and B lymphocytes associated to the immune memory and enabled to give a rapid effective response to the antigen. As result, increased susceptibility to infection and poor response to therapeutical treatment and vaccination is reported in the ageing population. Infection in geriatric patients is frequent and a common cause of increased morbidity and mortality.

Hospitalization, living in a nursing home, the community or a specialized care center seems to increase the chance of infection .Life-threatening infections occurring in the frail elderly are often associated to invasive diagnostic procedures and urinary and venous catheters are involved. The higher incidence of infectious diseases is registered for pneumonia, influenza and urinary tract infections. Type 2 diabetes and cardiovascular disease as well as other disease states as rheumatoid arthritis or cancer aggravate the situation.

Probiotics and prebiotics supplements seem to have a beneficial role in preventing certain disease conditions and ensuring a healthy human ecosystem. Probiotics have been shown clearly to boost the immunity in the old individual, unlike its clinical significance needs to be elucidated.

From another aspect, knowledge of the cytochromes mechanisms involved in drug interactions is capital, not only in preventing drug toxicity or adverse effects, but also in drawing new more effective therapeutic schemes and vaccines.

Conflict of Interest

The authors whose names are listed immediately below report that they don’t have any conflict of interest or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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Table 1: The young children microbiota under bottle and artificial feeding

Author(year of study)	Breast Feeding	Artificial Feeding
Bullen/Willis (1971)	*Lactobacilli*	*E.coli*
Mata/Urrutia(1971)	*Veillonella*	*Bacteroides*
Bezirtzoglou(1989)	*Bifidobacteria, B.bifidum*	*C.perfringens,B.fragilis*
Benno(1984)	*Bifidobacteria*	*Bifidobacteria,Clostridium perfringens,Bacilli,Bacteroides*
Balmer/Wharton(1989)	*Bifidobacteria*	*B.fragilis*
Bezirtzoglou(1997)	*Bifidobacteria, B.bifidum*	*C.perfringens*
Mackie(1999)	*B.infantis*	*B.fragilis*
Harmsen(2000)	*Bifidobacteria*	*C.perfringens, B.fragilis*
Fanaro(2003)	*Bifidobacteria*	*B.fragilis*
Adlerberth(2009)	*Staphylococcus, S.epidermidis*	*Clostridium,Streptococcus,E.coli*
Falani(2010)	*Bifidobacteria*	*B.fragilis*
Bezirtzoglou/Stavropoulou (2011)	*B.bifidum*	*C.perfringens*
Bergstrom(2014)	*Bifidobacteria, Lactobacilli*	*Clostridia,Bacteroides(*COMPLEMENTARY FEEDING*)*
Laursen(2017)	*Bifidobacteria*	*Lachnospiraceae, Ruminococcaceae , Bacteroidaceae (*FAMILY DIET*)*

