We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Bio-Molecular Characteristics of Whey Proteins with Relation to Inflammation

Anwar Ali, Quratul Ain, Ayesha Saeed, Waseem Khalid, Munir Ahmed and Ahmed Bostani

Abstract

Whey proteins in bovine milk are a mixture of globular proteins manufactured from whey which is a byproduct of cheese industry. Whey protein is categorized to contain plethora of healthy components due to wide range of pH, promising nutritional profile with cost effective and diverse functionality. Reportedly there are three categories of whey protein, whey protein concentrate (WPC) (29–89%); whey protein isolate (WPI) 90% and whey protein hydrolysate (WPH) on the basis of proteins present in them. Whey proteins is composed of β-lactoglobulin (45–57%), immunoglobulins (10–15%) α-lactalbumin (15–25%), glicomacropeptide (10–15%), lactoperoxidase (<1%) and lactoferrin nearly (1%). Whey protein plays an important role and is validated to confer anti-inflammatory and immunostimulatory roles related to all metabolic syndromes. According to molecular point of view whey proteins decrease inflammatory cytokines (IL-1α, IL-1β, IL-10 and TNF- α); inhibits ACE and NF-κB expression; promotes Fas signaling and caspase-3 expression; elevates GLP-1, PYY, CCK, G1P and leptin; chelate and binds Fe^{+3}, Mn^{+3} and Zn^{+2}. In this chapter we will discuss significant biological role of whey proteins related to inflammatory health issues.

Keywords: Whey Proteins, Inflammatory Cytokines, Molecular Signaling

1. Introduction

The protein system in bovine milk is made up of two main protein families: casein (insoluble) and whey proteins (soluble). Casein is the major portion 80% of total protein content weight by weight (w/w) and is easy to separate from non-fat milk through isoelectric precipitation (by adding acid or producing it in situ) or rennet-driven coagulation, and the leftover is whey. Whey proteins consists of spherical molecules as well as amino acids either acidic/basic or hydrophilic/hydrophobic in composition of their polypeptide chains that are evenly distributed to form a helical shape [1]. Profiling of whey protein including it chemical and physiological properties like β-lactoglobulin (β-LG), a-lactalbumin (α-LA), immunoglobulins (IG), bovine serum albumin (BSA), bovine lactoferrin (BLF), and lactoperoxidase (LP) along with other constituents are all contained in whey proteins [2]. Whey protein concentrations varies depending on its type (acidic or sweet), milk source (bovine, caprine, or ovine), phase of the year, the kind of feedstuff, lactation phase, and productivity.

2. Components and types of whey proteins

Acid whey, which has a pH of 5.1 or less, is made by acidifying milk directly, as is used in the production of cottage cheese. After rennet-coagulation, sweet whey with a pH of 5.6 or higher is produced, as it is used in most cheese-making processes around the world [3]. Whey protein (protein not precipitated by acid or rennet) accounts for about 0.6 to 0.7 percent of total milk content and accounts for about 20% of overall milk proteins. Whey proteins are high in nutrients that are beneficial to wellbeing of humans. α-lactalbumin, β-lactoglobulin, lactoferin, lactoperoxidase, immunoglobulins, and glycomacropetide are among the proteins present in it [4]. Percentage of each component of whey protein is mentioned in **Table 1**.

The development of processing techniques, particularly those based on selectively permeable membranes, has allowed a range of whey protein constituents to emerge as common food additives in the last two decades. The membrane based processing techniques results in ultrafiltration (UF) to concentrate proteins and diafiltration (DF) to eliminate most lactose, minerals and low molecular weight components and hence producing versatile whey products with distinct qualitative and quantitative profiles of proteins, minerals, lipids, sugars and whey

Sr. No	Component of whey	Amount	specie	Reference
1.	β-Lactoglobulin	3.2 (mg/L milk)	Bovine, buffalo,caprine and equine	[5, 6]
2.	Lysozyme	0.0004 (mg/L milk)	Camel and bovine	[7, 8]
3.	α-Lactalbumin	1.2 (mg/L milk)	Camel,bovine and human	[9]
4.	Lactoperoxidase	0.03 (mg/L milk)	Camel and bovine	[10]
5.	Glycomacropeptide	1.2 (mg/L milk)	Camel and bovine	[11]
6.	Immunoglobulin M	0.04 (mg/L milk)	Camel, bovine and human	[8, 12]
7.	Immunoglobulin G	0.7 (mg/L milk)	Camel, bovine and human	
8.	Immunoglobulin A	0.04 (mg/L milk)	Camel, bovine and human	
9.	Lactoferrin	0.06 (mg/L milk)	Camel, bovine and human	[9, 13]

Table 1.
Approximate concentration of proteins in whey in different species.

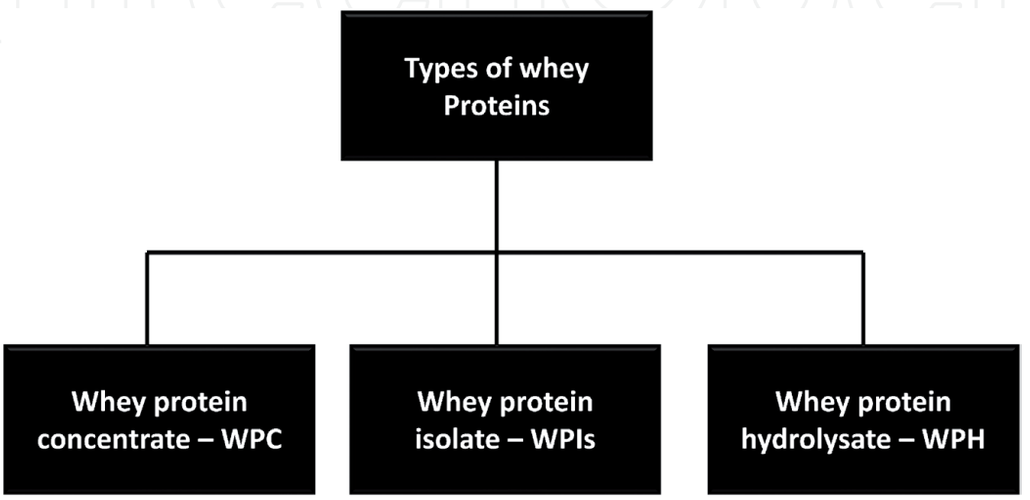


Figure 1.
Types of whey proteins; this classification is based on protein processing and refining [18, 19].

protein concentrate (WPC). There are WPC that produce 35, 50, 65 and 80% (w/w) protein, subject to their concentration. When the protein content reaches 90% (w/w), a whey protein isolate (WPI) is made, that is a high-grade and pure protein concentrate. When added to foods, each of these compounds function as carriers for the stimulation of a variety of biological characters. When whey is heated, α-LA denatures quickly, allowing the fraction to be divided by precipitation [14]. Whey protein hydrolysate (WPH) is the "predigested" type of whey protein since it has already passed through partial hydrolysis, which is needed for the body to consume protein. WPH is easier to absorb than the other two types of whey protein [15–17]. Flow sheet of all types of whey proteins is mentioned under **Figure 1**.

3. Physiological and biological roles of whey proteins

Whey protein is high in bioactive peptides, which can help with chronic disease control by nutrition. The conventional and evolving implications of whey proteins are elaborated in below para [20, 21].

Whey proteins and their constituents have been found to have a variety of health advantages. In a study, bovine whey proteins showed positive impacts on the lipid profile in serum and liver, including overall lipid and triglyceride alteration and reduction [22]. Enzymatic breakdown (natural digestion in the GI tract, enzyme mediated hydrolysis, milk fermentation) of whey proteins produces antihypertensive peptides (ACE-I) [23]. Whey proteins derivatives like short chain and peptides resistant to water have been shown in studies to reduce blood pressure and stress hypertension by increasing ACE inhibitory action [24, 25]. Whey proteins are a predecessor or foundation of glutathione (GSH) that performs oxidation against reactive oxygen species (ROS), responsible for tissue harm, especially in the central nervous system's neurons and glial cells [26]. Whey proteins are unusual in their capacity to increase glutathione (GSH) levels in different tissues that optimizes the functionality and structure of the immune system [27]. GSH defends cells from free radical destruction, contaminants, chemicals, infection, and UV exposure as part of antioxidant defense mechanism of body [28]. GSH levels are usually low in people who have cancer, HIV, persistent fatigue syndrome, or other immune-suppressing diseases [29]. GSH levels drop with age, and it's thought to play a role in diseases like Alzheimer's, cataracts, Parkinson's, and arteriosclerosis. Whey proteins provide a number of health benefits, including improving the acquired immune system. The most active fractions were whey protein extracts from β-lactoglobulin and α-lactalbumin, which had an additive impact on neutrophils, making them more sensitive to a subsequent stimulus [30]. Supplementing athletes with whey protein during rigorous endurance training can help them boost the immunity in between and afterward of workout and physical activity [29, 30]. In infants, an improved immune response may aid in the prevention of bacteriological and pathological syndromes, as well as illnesses including gastroenteritis. Thus, including whey proteins in one's diet can benefit people of all ages, not just those with a weakened immune system [31]. Whey protein has been shown to prohibit the progression of pathogenic bacteria, suggesting that it may be used to regulate the development and reinfection of *E. coli* (O157:H7)*, Listeria monocytogenes, and Salmonella typhimurium* in ready to eat meat by using WPI as a defensive film covering ingredient [32–35]. Rises in the levels of alanine in plasma and aspartate aminotransferase activities, production of lactate dehydrogenase, and bilirubin concentration that refers to hepatitis indicators, as well as hyaluronic acid concentration which is fibrosis marker can be suppressed by a whey protein-rich diet [36, 37].

The active ingredient of whey protein found to have a vital role in growth and development of bones as well as a possible healing impact on osteoporosis by stimulating osteoblasts [38, 39]. The biochemical role of peptides in whey protein is as food additives is to improve calcium absorption (by preventing calcium phosphate formation) and avoid bone disorders [40]. Branched-chain amino acids (BCAAs) are well-known in whey proteins. While the need for BCAAs rises with endurance activity, whey protein may be used to supplement these BCAAs during the healing process to boost protein synthesis and muscle development [41]. Since both whey and skeletal muscle almost have identical amino acid profiling, it is highly effective to speedup muscle protein synthesis [42]. As a result, whey protein, by its necessary amino acids, aids in the production of skeletal muscle protein and the avoidance of sarcopenia (muscle wasting) after strenuous exercise [43, 44]. Current researches depicts that whey proteins may help athletes with resistance training boost their lean body mass and efficiency [45]. Increased brain tryptophan and serotonin activities boost cognitive function in stress-prone subjects because of efflux of whey protein in α-lactalbumin [46]. In milk, glycomacropeptides (GMPs) and whey protein concentrate may help probiotic bacteria like *bifidobacterium lactis* development. Gut wellbeing has been seen to be improved by a variety of probiotic bacteria [47]. Cancer prevention is essential. Whey protein in the diet can lower serum C-peptide levels and duodenal SREBP-1c mRNA profusion, as well as lessen the risk of duodenal tumors [48, 49]. Growth stimulator established in whey proteins showed positive impacts on various mammalian cells of the culture media. These growth stimulators work by suppressing protein degeneration and enhancing synthesis of protein and DNA inside the cells. As a result, whey protein can aid in tissue regeneration as well as the prevention of psoriasis and ulcers [50]. Incorporating whey protein concentrates and glycomacropeptides (GMPs) into the diet may increase satiety and reduce food consumption. GMP that activates cholecystokinin (CCK), which is a hormone to suppress hunger, is shown to have variety of important roles in gastrointestinal activity, including food intake control [51]. Various other proteins, in the patients suffering from type 2 diabetes, established to be overtaken by whey proteins for the improvement of postprandial lipemia, when taken as a complement to a fat-rich diet, likely due to the development of less chylomicrons or improved clearance of chylomicrons [25, 52] as shown in **Figure 2**.

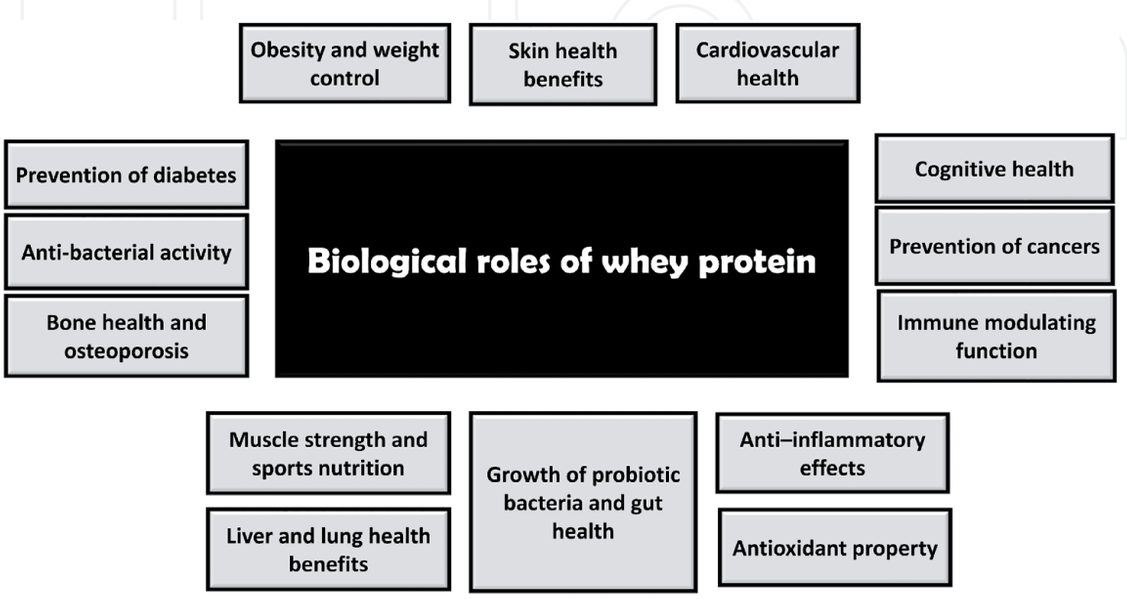


Figure 2.
Biological roles of whey proteins summarized from different literature [53–60].

4. Inflammatory cytokines in inflammatory process

Cytokines are tiny secreted proteins (<40 kDa) that virtually every cell produces to control and affect immune response [20]. The discharge of pro-inflammatory cytokines causes immune cell initiation and development, along with the discharge of additional cytokines [61]. When the word "cytokine storm" first appeared, it was used to describe inflammation as a rapid immediate discharge of cytokines to activate an inflammatory mechanism [62]. Current work of scientists suggests that in every immune reaction, the simultaneous release of pro- and anti-inflammatory cytokines is needed [63]. Interleukins, chemokines, and growth factors are only some of the terms used to describe cytokines [64]. Super families of cytokines exist, which do not actually describe common genes but rather related structures [64]. Furthermore, the same cytokine may be generated by various cell populations. Cytokines have pleiotropic effects and their effects are dependent on the cell they are targeting [65]. Furthermore, various cytokines may have the same impact, making them redundant. However, they could have a synergistic influence. Finally, they can initiate signaling cascades, allowing even tiny amounts of protein to have catastrophic consequences [66].

5. Whey proteins leads to activation and production of pro-inflammatory cytokines

As cellular antioxidants struggle to keep up with ROS, the organism suffers from oxidative stress [67]. Inflammation causes damage to tissue by releasing free radicals from macrophages and neutrophils [68]. By transporting iron, whey proteins are essential for maintaining oxidative stress [69]. They produce the cytotoxic protection mechanism of neutrophils as well as free radicals [70, 71]. Whey proteins are involved in the preservation of inflammation through reducing lipid peroxidation and oxygen radicals via the production of antioxidant glutathione. Inflammatory cytokines are generated in large part by whey proteins. Whey proteins supplementation restored a high degree of IL-1β and TNF-α. IL-1β and TNF-α influenced the expression of chemokines and the adhesion of molecules required for the recruitment of inflammatory cells [72, 73]. According to a review, whey protein can increase neutrophil infiltration by inhibiting oxidative markers and reactive oxygen species. In whey protein treated mice, the number of bone marrow-derived dendritic cells, T-cells, and B-cells increased in response to CCL-21 and CXCL-12 [74]. Cytokines released by neutrophils increase the proliferative and remodeling processes of cells; via this, the earliest signals responsible for the activation of fibroblasts and keratinocytes are produced [75, 76]. Neutrophils are involved in the early stages of the anti-inflammatory cascade by removing bacteria and phagocytosing cellular waste [77]. Various experiments have shown that priming blood neutrophils with proteins can trigger oxidative explosion, chemotaxis, degranulation, and phagocytosis [78]. Whey protein promotes the development of inflammatory proteins such as IL-1β, IL-8, IL-6 and TNF-α in macrophages [78, 79]. The initiation of NF-kB, which contributes to the development of inflammatory cascades and the release of pro-inflammatory cytokines for instance IL-1β, TNF-α, and IL-6 is one of whey protein's anti-inflammatory processes [80, 81]. Inflammatory cytokines such as IL-1, IL-1, IL-10, and TNF-α were shown to be lower in the blood of mice feeding whey protein concentrate. Contrary to this, the amounts of cytokines such as IL-2, IL-4, IL-7, and IL-8, which are accountable for maintaining a healthy immune system, increased. The proliferative capacity of lymphocytes, monocytes, and macrophages in reaction to antigens was intensified [82].

6. Whey proteins role as anti-cancerous agents through production of inflammatory cytokines

Cancer is associated with a high rate of morbidity and mortality. According to a worldwide study, 27 main cancers were responsible for millions of deaths per year [81]. Dietetic modification has been proposed as an encouraging prophylactic strategy. Metabolites that modulate biomarkers of cancer began to emerge. Whey protein seems to be effective in this respect, and the assumptions have been supported by some data. In vitro, isolates of whey proteins had an impact on melanoma B16F10 cells that is cytotoxic in nature, as shown by the release of high caspase-3 [83]. According to a study performed on the rats suffering from gut cancer, fed whey protein hydrolysate, there were less tumor foci [84]. Before and after chemotherapy, a cervical cancer patient received whey protein (10 g three times quotidian) and a monthly testosterone infusion, which increased body lean mass, physical movement, and life quality [85]. Lactoferrin has been shown in vivo to stimulate cytokines in the guts and suppressing cancer growth in colon. Research established that consuming 3.0 g of bovine lactoferrin on a regular basis enhance the IFN levels that reduces the propagation of colorectal polyps [86]. While the available evidence is limited and the conclusion is far from definitive, but it might play a role of foundation for further research regarding anticancer experiments [21].

7. Whey protein as immunomodulators through maintenance of inflammatory cytokines

The complex network of lymphoid glands, effector cells, and molecules that make up the host immune defense is critical for survival [87]. Pathogenesis, metabolic, and degenerative disorders results as immunity lost. Dietary ingredients including probiotics, oligosaccharides, and β-glucans have been shown to have immune-boosting properties [88]. Whey proteins have been found to boost tolerance during childhood and thereby eliminate certain immune problems [89]. Whey proteins, upon digestion, found to activate variation among cells of immune system and recruitment of secondary lymphoid glands, according to a rodent report [89]. A comparative study among child's who fed whey incorporated formula were and the kids who consumed bovine milk, the chances of atopic dermatitis were 16 percent less in the former than later group [90]. Psoriasis patients' skin healed by taking 20 grams of whey protein isolate a day [21]. Although the psoriasis region and intensity score ranged from 4.9 to 28.8, it improved from 0.8 to 8.4 after 3 months of therapy. Higher glutathione levels and reduced systemic inflammation were linked to a reduction in autoimmune disorder symptoms [91].

8. Whey protein role in metabolic syndrome related to amelioration in pro-inflammatory cytokines

Hormones, cytokines and various other compounds involved to prohibit insulin sensitivity are produced by adipose tissue, an endocrine organ [66]. It is established that in the obese people, there is an increased discharge of adipocytokines through adipose tissue and macrophages [92]. Pal & Ellis [93] found that supplementing whey protein (54 g) for 12 weeks had little effect on pro-inflammatory markers (IL-6, C-reactive protein-CRP, and TNF-α) in overweight and obese participants. In rats with D-galactosamine-induced hepatitis and liver fibrosis, however, whey protein intake significantly decreased plasma amounts of pro-inflammatory cytokines

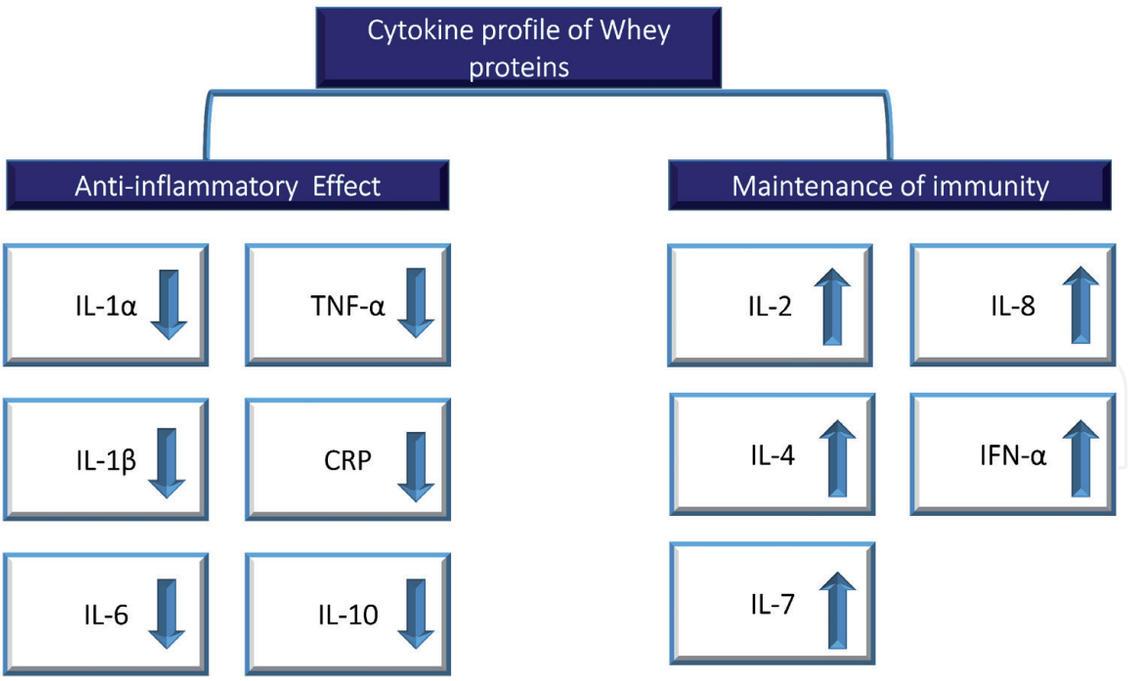


Figure 3.
Cytokine profile related to whey proteins; by inhibiting IL-1α, IL-1β, IL-6, TNF- α, CRP and IL-10 whey protein show anti-inflammatory effect while release of IL-2, IL-4, IL-7, IL-8 and TNF- α showed its immunity related function [60, 96, 97].

(IL-1β: 59 percent and IL-6: 29 percent) as paralleled to casein consumption [37]. Since consuming whey protein and its amino acids, a decrease in pro-inflammatory cytokines can be linked to a reduction in body weight gain [94]. In streptozotocin-induced diabetic rats, whey protein fed in 100 mg amount related to body weight in kg and results showed the decrease in number of oxidative stress markers, like; MDA, nitric oxide, and ROS concentrations, as well as pro-inflammatory cytokines (IL-1, TNF-α, IL-6, and IL-4) and raised glutathione amount [81]. A study in which rats were fed with a food of more carbohydrate content, no fat diet to cause fatty livers (nonalcoholic fatty liver model) plus orally directed whey protein (0.15 g/d/rat) for 28 days resulted in decreased MDA and elevated glutathione levels [95]. Hence it can be concluded that whey proteins plays a vital role to enhance endogenous antioxidant enzymes (glutathione peroxidase, catalase, and superoxide dismutase) and limits oxidative stress markers in obese, diabetic, or stroke patients, along with low expression of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) [94]. TBARs are commonly used to measure lipid peroxidation products in cell and MDA is used as an oxidative stress marker. Summary of all cytokines related to whey proteins is discussed in **Figure 3**.

9. Whey protein hydrolysate downregulate inflammation-related genes

Bioactive peptides with anti-inflammatory effects, as well as amino acids, are used in dairy protein hydrolysates [98]. After the consumption of milk or yogurt, postprandial mRNA levels of inflammatory markers were shown to be lower in an acute clinical trial [99]. These findings indicate that dairy nutrients, as shown in mice, may control the transcriptome [100]. Low-grade systemic inflammation has been related to endothelial dysfunction and the progression of atherosclerosis in obese and/or T2D people [101]. Reduced nitric oxide (NO) supply and hence endothelial nitric oxide synthase (eNOS) activity characterize endothelial dysfunction. The research showed that lower the availability of NO, enhances the invasion

of macrophages linked to adhering molecules like vascular cellular adhesion molecule (VCAM)–1, along with the discharge of proinflammatory cytokines like interleukins (ILs) and tumor necrosis factor (TNF–α) [102]. Antioxidant enzymes including superoxide dismutases (SOD) may even deactivate reactive oxygen species (ROS) that are connected to endothelial dysfunction [103]. Endothelial cells play an important role in inflammation. Dairy products' special protein and amino acid composition can influence cytokine gene expression and development. However, mechanistic experiments comparing various dairy protein compounds are rare [104]. Whey proteins and their chief amino acids, BCAAs, shown an increased anti-inflammatory capacity compared to other proteins.

Whey protein hydrolysate and BCAA have anti-inflammatory properties by lowering TNF and VCAM-1 expression and thereby attenuating TNF-α induced gene expression. Similarly, whey proteins were found to have an anti-inflammatory impact in Caco-2 intestinal cells by lowering IL-8 production [105]. Whey proteins' protective effects may be regulated by BCAAs. In HUVECs, BCAAs reduced the inflammatory reaction caused by TNF. In obese mice, induction of BCAAs, particularly leucine, reduced the appearance of genes involved in inflammation in the adipose tissue and liver, as well as macrophage infiltration [106].

In a rodent model of endothelial dysfunction, glutamine reduced the levels of circulating inflammatory markers (IL-6, IL-1, MIP-1, GM-CSF, MIP-2, IFN, and E-selectin) [107]. SOD2 expression is influenced by whey proteins and amino acids in the absence of TNF stimulation. WPH have been shown in to reduce inflammatory responses by constraining the nuclear factor κB (NF-κB) pathway [108]. Furthermore, glutamine, leucine, and proline have the ability to block the NF-κB pathway [109]. NF-κB is a transcription factor that controls the transcription of several inflammatory genes when it is triggered by proinflammatory signals like TNF-α. TNF, VCAM-1, and SOD2 are among the genes controlled by NF-κB [110], and these were the genes most affected by whey protein combinations in this study. As a result, it is established that by a route of NF-κB pathway, clear reduction in TNF-linked appearance of genes for inflammation through hydro-lysates and BCAAs of whey proteins could be achieved. Whey protein isolate, caseins, and WPC are entire proteins that can require other pathways. Autophagy, for example, has an effect on the functionality of mitochondria and oxidative stress, and that could be stimulated by proteins [111, 112].

10. IFN-γ, IL-8 and TGF-β expressions are downregulated by whey proteins

The most notable result of cow milk (CM0 whey therapy was the full abolition of interferon gamma (IFN-γ), as shown by extensive research. IFN-γ has a direct anti-proliferative effect on cancer cell lines. Studies have shown that mice lacking IFN-γ or IFN-γ receptor [113] as well as IFN-γ gene knockout (KO) mice grow cancer more quickly [114]. The late colitis stage and early neoplasms are reflected in the mouse examination and sample selection at 12th week. Dextral Sulfate Sodium (DSS) induced colitis was linked to an elevated level of IFN-γ, which was linked to decrease in weight and more death ratio [115]. Thus, the decreased IFN-γ amount results in the prohibition of immune cell recruitment to the inflammatory region and more tissue harm can clarify CM-mediated inhibition of inflammation. As a result, the neoplasm formation in CM-treated mice may have been influenced by lower mucosal inflammation. In a related vein, it has been shown that CM therapy reduced IFN-γ levels in chronic hepatitis B patients [116].

IL-8 has been shown to play a multifunctional role in cancer development, including encouraging tumor cell proliferation, improving cancer cell survival, and controlling adhesion and invasion [117]. Findings showed that cow milk (CM) significantly reduced IL-8 expression in colon tissue, suggesting that these results may reflect CM's anti-inflammatory mechanism. It was found in a report on immunomodulatory function of milk proteins that IL-8 was recruited by Caco2 gut cells lined with the both α-lactalbumin and β-lactoglobulin of a non-fat bovine milk (BM) whey [118]. This phenomenon occurred by the activation of Caco2 cells by IL-1β. However, it is still needs to be confirmed that either the abstinence of β-LG in CM whey has any link to drop the IL-8 scale or graph in the CM treated population in model. Many studies have shown that all milk ingredients have a synergistic role in lowering IL-8 gene expression [118].

In addition, milk whey treatment reduced transforming growth factor (TGF-β) expression. TGF-β, a cytokine has double role in cancer growth and alteration in the TGF-β pathway within epithelial cells, promotes the enlargement and evolution of colonic tumors [118]. TGF-β signaling in tumor-infiltrating T-lymphocytes, on the other hand, led to the growth of dysplastic epithelial cells in experimental colorectal cancers (CRCs), according to contradictory findings [119]. Varying results on the role of TGF-β in CRC models could be described by the phase of cancer studied or the signaling pathway targeted by the cytokine in specific immune cells.

11. Conclusions

An interesting and verified phenomenon of bovine milk whey proteins is that they are known to act as anti-inflammatory and immune-stimulatory agents in connection with inflammatory and metabolic disorders.

According to molecular hypothesis, whey proteins decrease inflammatory cytokines (IL-1α, IL-1β, IL-10, and TNF-α) by molecularly inhibiting ACE and NF-κB expression, promoting Fas signaling, and increasing caspase-3 expression, while elevating GLP-1, PYY, CCK, GIP, and leptin, as well as chelating and binding iron, manganese, and zinc.

In this chapter, we have described about whey proteins' essential significance in the molecular mechanisms associated with inflammatory health conditions. Whey protein also possesses many other impacts on different health issues on molecular level.

Acknowledgements

Authors acknowledge the role Food and Nutrition Society Gilgit Baltistan Pakistan for giving free access to journals.

Conflict of interest

Authors declare no conflict of interest.

Notes/thanks/other declarations

Authors pay special thanks to everyone for contribution.

Abbreviations

ABTS	2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid
ACE	Angiotensin-converting enzyme
α-LA	alpha lactalbumin
AOM	Azoxymethane
B16F10	Murine melanoma cell
BCAA	Branched chain aminoacids
Caco-2	Cells human colon adenocarcinoma
CCK	Cholecystokinin
CM	Cow milk
CRC	colorectal cancer cell
CRP	C-reactive protein
Cxcl-12	Motif Chemokine Ligand 12
DPPH	2,2-diphenyl-1-picrylhydrazyl
DSS	Dextran sulfate sodium
E.coli	*Escherichia coli*
E-selectin	CD62 antigen-like family member E
FRAP	Fluorescence recovery after photo bleaching
GI-tract	gastro intestinal tract
GLP-1	Glucagon-Like Peptide 1
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSH	Glutathione
HIV	human immunodeficiency virus
HSP70	Heat Shock Protein
HUVECs	Human umbilical vein endothelial cells
IL	Interleukin
IFN	interferon
KDa	kilodalton
MDA	methylenedioxymethamphetamine
MIP-1β	Macrophage inflammatory protein
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
PYY	Peptide YY
SOD2	Superoxide dismutase 2
SREBP-1c	Sterol regulatory element-binding protein 1
T2D	type 2 diabetes
TBARS	Thiobarbituric acid reactive substances
TGF-β	Transforming growth factor beta
TNF-a	Tumor Necrosis Factor alpha
UV	ultraviolet
w/w	weight per weight
WPCN	whey protein/casein mixture
(VCAM)–1	Vascular cellular adhesion molecule

DOI: http://dx.doi.org/10.5772/intechopen.99220

IntechOpen

Author details

Anwar Ali[1*], Quratul Ain[2], Ayesha Saeed[2], Waseem Khalid[3], Munir Ahmed[4] and Ahmed Bostani[5]

1 Department of Epidemiology and Health Statistics, Xingya School of Public Health, Central South University, Changsha, China

2 Department of Biochemistry, Government College University, Faisalabad, Pakistan

3 Department of Food Science and Technology, Government College University, Faisalabad, Pakistan

4 Department of Food Science and Engineering, Yangzhou University, Yangzhou, China

5 Department of Tourism and Hospitality Management, Dongbei University of Finance and Economics, Dalian, China

*Address all correspondence to: 206908003@csu.edu.cn

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Madureira AR, Pereira CI, Gomes AM, Pintado ME, Malcata FXJFRI. Bovine whey proteins–Overview on their main biological properties. 2007;40(10):1197-211.

[2] de Castro RJS, Domingues MAF, Ohara A, Okuro PK, dos Santos JG, Brexó RP, et al. Whey protein as a key component in food systems: Physicochemical properties, production technologies and applications. 2017;14:17-29.

[3] Pelegrine D, Gasparetto CJL-FS, Technology. Whey proteins solubility as function of temperature and pH. 2005;38(1):77-80.

[4] Zarogoulidis P, Tsakiridis K, Karapantzou C, Lampaki S, Kioumis I, Pitsiou G, et al. Use of proteins as biomarkers and their role in carcinogenesis. 2015;6(1):9.

[5] Elagamy EJFC. Effect of heat treatment on camel milk proteins with respect to antimicrobial factors: a comparison with cows' and buffalo milk proteins. 2000;68(2):227-32.

[6] Guimont C, Marchall E, Girardet J, Linden G, Otani HJCRiFS, Nutrition. Biologically active factors in bovine milk and dairy byproducts: influence on cell culture. 1997;37(4):393-410.

[7] El-Agamy EI, Nawar M, Shamsia SM, Awad S, Haenlein GFJSRR. Are camel milk proteins convenient to the nutrition of cow milk allergic children? 2009;82(1):1-6.

[8] Ustunol Z. Applied food protein chemistry: John Wiley & Sons; 2014.

[9] Badr G, Ramadan NK, Sayed LH, Badr BM, Omar HM, Selamoglu ZJIjobms. Why whey? Camel whey protein as a new dietary approach to the management of free radicals and for the treatment of different health disorders. 2017;20(4):338.

[10] Konuspayeva G, Faye B, Loiseau G, Levieux DJJoDS. Lactoferrin and immunoglobulin contents in camel's milk (*Camelus bactrianus*, *Camelus dromedarius*, and Hybrids) from Kazakhstan. 2007;90(1):38-46.

[11] El-Hatmi H, Girardet J-M, Gaillard J-L, Yahyaoui MH, Attia HJSRR. Characterisation of whey proteins of camel (*Camelus dromedarius*) milk and colostrum. 2007;70(2-3):267-71.

[12] Laleye L, Jobe B, Wasesa AJJoDS. Comparative study on heat stability and functionality of camel and bovine milk whey proteins. 2008;91(12):4527-34.

[13] Legrand D, Pierce A, Elass E, Carpentier M, Mariller C, Mazurier JJBcom. Lactoferrin structure and functions. 2008:163-94.

[14] Kelly P. Manufacture of whey protein products: Concentrates, isolate, whey protein fractions and microparticulated. Whey proteins: Elsevier; 2019. p. 97-122.

[15] Streicher C, Nguyen NH, Anema SGJIDJ. Modifying whey protein concentrate/isolate by heating in the presence of cysteine. 2020;105:104675.

[16] de Sousa JP, de Araújo Torres R, de Azerêdo GA, Figueiredo RCBQ, da Silva Vasconcelos MA, de Souza ELJIjofm. Carvacrol and 1, 8-cineole alone or in combination at sublethal concentrations induce changes in the cell morphology and membrane permeability of *Pseudomonas fluorescens* in a vegetable-based broth. 2012;158(1):9-13.

[17] Bounous GJAr. Whey Protein Concentrate (WPC) and Glutathione Modulation in. 2000;20:4785-92.

[18] Creusot N, Gruppen H, van Koningsveld GA, de Kruif CG, Voragen AGJIdj. Peptide–peptide and protein–peptide interactions in mixtures of whey protein isolate and whey protein isolate hydrolysates. 2006;16(8):840-9.

[19] Butré CI, Wierenga PA, Gruppen HJJoa, chemistry f. Effects of ionic strength on the enzymatic hydrolysis of diluted and concentrated whey protein isolate. 2012;60(22):5644-51.

[20] Hayes A, Cribb PJJCOiCN, Care M. Effect of whey protein isolate on strength, body composition and muscle hypertrophy during resistance training. 2008;11(1):40-4.

[21] Patel SJJoFF. Functional food relevance of whey protein: A review of recent findings and scopes ahead. 2015;19:308-19.

[22] Vermeirssen, V., Van Camp, J., Devos, L., & Verstraete, W. (2003). Release of angiotensin I converting enzyme (ACE) inhibitory activity during in vitro gastrointestinal digestion: From batch experiment to semicontinuous model. Journal of Agricultural and Food Chemistry, 51, 5680-5687.

[23] Vermeirssen V, Van Camp J, Verstraete WJJotSoF, Agriculture. Fractionation of angiotensin I converting enzyme inhibitory activity from pea and whey protein in vitro gastrointestinal digests. 2005;85(3):399-405.

[24] Park J-Y, Park M-N, Choi Y-Y, Yun S-S, Chun H-N, Lee Y-SJJotKSoFS, et al. Effects of whey protein hydrolysates on lipid profiles and appetite-related hormones in rats fed high fat diet. 2008;37(4):428-36.

[25] Sharma R, Shah NJN. Health benefits of whey proteins. 2010;9(4):39-45.

[26] Tseng Y-M, Lin S-K, Hsiao J-K, Chen J, Lee J-H, Wu S-H, et al. Whey protein concentrate promotes the production of glutathione (GSH) by GSH reductase in the PC12 cell line after acute ethanol exposure. 2006;44(4): 574-8.

[27] Rusu D, Drouin R, Pouliot Y, Gauthier S, Poubelle PEJTJon. A bovine whey protein extract can enhance innate immunity by priming normal human blood neutrophils. 2009;139(2):386-93.

[28] Pérez-Cano FJ, Marin-Gallen S, Castell M, Rodríguez-Palmero Ma, Rivero M, Castellote C, et al. Supplementing suckling rats with whey protein concentrate modulates the immune response and ameliorates rat rotavirus-induced diarrhea. 2008; 138(12):2392-8.

[29] Saint-Sauveur D, Gauthier SF, Boutin Y, Montoni AJIDJ. Immunomodulating properties of a whey protein isolate, its enzymatic digest and peptide fractions. 2008;18(3):260-70.

[30] Peng HJ, Su SN, Tsai JJ, Tsai LC, Kuo HL, Kuo SWJC, et al. Effect of ingestion of cow's milk hydrolysed formulas on whey protein-specific Th2 immune responses in naïve and sensitized mice. 2004;34(4):663-70.

[31] Yuan H, Lingju G, Zhiqing C, Yifei WJJCIFST. The effect of whey protein administration on the immune function of athletes in the intensive endurance training. 2007;7:13-20.

[32] Gadang V, Hettiarachchy N, Johnson M, Owens CJJoFS. Evaluation of antibacterial activity of whey protein isolate coating incorporated with nisin, grape seed extract, malic acid, and EDTA on a turkey frankfurter system. 2008;73(8):M389-M94.

[33] Min S, Harris LJ, Krochta JMJJofp. Inhibition of *Salmonella enterica* and

Escherichia coli O157: H7 on roasted turkey by edible whey protein coatings incorporating the lactoperoxidase system. 2006;69(4):784-93.

[34] Seydim A, Sarikus GJFri. Antimicrobial activity of whey protein based edible films incorporated with oregano, rosemary and garlic essential oils. 2006;39(5):639-44.

[35] Min S, Krochta JMJJoFS. Inhibition of Penicillium commune by edible whey protein films incorporating lactoferrin, lacto-ferrin hydrolysate, and lactoperoxidase systems. 2005;70(2): M87-M94.

[36] Lothian JB, Grey V, Lands LCJIjofs, nutrition. Effect of whey protein to modulate immune response in children with atopic asthma. 2006;57(3-4): 204-11.

[37] Kume H, Okazaki K, Sasaki HJB, biotechnology,, biochemistry. Hepatoprotective effects of whey protein on D-galactosamine-induced hepatitis and liver fibrosis in rats. 2006;70(5):1281-5.

[38] Xu RJJods. Effect of whey protein on the proliferation and differentiation of osteoblasts. 2009;92(7):3014-8.

[39] Kim S, Lim JJA-ajoas. Calcium-binding peptides derived from tryptic hydrolysates of cheese whey protein. 2004;17(10):1459-64.

[40] Rui XJIjodt. Calcium binding of peptides derived from enzymatic hydrolysates of whey protein concentrate. 2009;62(2):170-3.

[41] Anthony TG, McDaniel BJ, Knoll P, Bunpo P, Paul GL, McNurlan MAJTJon. Feeding meals containing soy or whey protein after exercise stimulates protein synthesis and translation initiation in the skeletal muscle of male rats. 2007;137(2):357-62.

[42] Candow DG, Burke NC, Smith-Palmer T, Burke DGJIjosn, metabolism e. Effect of whey and soy protein supplementation combined with resistance training in young adults. 2006;16(3):233-44.

[43] Elia D, Stadler K, Horváth V, Jakus JJEjon. Effect of soy-and whey protein-isolate supplemented diet on the redox parameters of trained mice. 2006;45(5):259-66.

[44] Volpi E, Kobayashi H, Sheffield-Moore M, Mittendorfer B, Wolfe RRJTAjocn. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. 2003;78(2):250-8.

[45] Wolfe RRJTAjocn. Protein supplements and exercise. 2000;72(2):551S-7S.

[46] Markus CR, Olivier B, de Haan EHJTAjocn. Whey protein rich in α-lactalbumin increases the ratio of plasma tryptophan to the sum of the other large neutral amino acids and improves cognitive performance in stress-vulnerable subjects. 2002;75(6):1051-6.

[47] Vasiljevic T, Jelen PJIFS, Technologies E. Production of β-galactosidase for lactose hydrolysis in milk and dairy products using thermophilic lactic acid bacteria. 2001;2(2):75-85.

[48] Xiao R, Carter JA, Linz AL, Ferguson M, Badger TM, Simmen FAJTJonb. Dietary whey protein lowers serum C-peptide concentration and duodenal SREBP-1c mRNA abundance, and reduces occurrence of duodenal tumors and colon aberrant crypt foci in azoxymethane-treated male rats. 2006;17(9):626-34.

[49] Middleton N, Reid J, Coolbear T, Jelen PJIdj. Proliferation and

intracellular glutathione in Jurkat T cells with concentrated whey protein products. 2003;13(7):565-73.

[50] Drouin R, Lamiot E, Cantin K, Gauthier SF, Pouliot Y, Poubelle PE, et al. XP-828L (Dermylex), a new whey protein extract with potential benefit for mild to moderate psoriasis. 2007;85(9):943-51.

[51] HUANG XF, Liu Y, Rahardjo GL, McLennan PL, Tapsell LC, Buttemer WAJN, et al. Effects of diets high in whey, soy, red meat and milk protein on body weight maintenance in diet-induced obesity in mice. 2008;65:S53-S9.

[52] Nilsson M, Holst JJ, Björck IMJTAjocn. Metabolic effects of amino acid mixtures and whey protein in healthy subjects: studies using glucose-equivalent drinks. 2007;85(4):996-1004.

[53] Badr G, Badr BM, Mahmoud MH, Mohany M, Rabah DM, Garraud OJBi. Treatment of diabetic mice with undenatured whey protein accelerates the wound healing process by enhancing the expression of MIP-1α, MIP-2, KC, CX3CL1 and TGF-β in wounded tissue. 2012;13(1):1-9.

[54] Badr G, Ebaid H, Mohany M, Abuelsaad ASJTJonb. Modulation of immune cell proliferation and chemotaxis towards CC chemokine ligand (CCL)-21 and CXC chemokine ligand (CXCL)-12 in undenatured whey protein-treated mice. 2012;23(12):1640-6.

[55] Becker C, Fantini MC, Schramm C, Lehr HA, Wirtz S, Nikolaev A, et al. TGF-β suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. 2004;21(4):491-501.

[56] Charo IF, Ransohoff RMJNEJoM. The many roles of chemokines and chemokine receptors in inflammation. 2006;354(6):610-21.

[57] Parkin J, Cohen BJTL. An overview of the immune system. 2001; 357(9270):1777-89.

[58] Seydim A, Sarikus GJFri. Antimicrobial activity of whey protein based edible films incorporated with oregano, rosemary and garlic essential oils. 2006;39(5):639-44.

[59] Sharma R, Shah NJN. Health benefits of whey proteins. 2010;9(4): 39-45.

[60] Patel SJJoFF. Functional food relevance of whey protein: A review of recent findings and scopes ahead. 2015;19:308-19.

[61] Schaper F, Rose-John SJC, reviews gf. Interleukin-6: biology, signaling and strategies of blockade. 2015;26(5):475-87.

[62] Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MGJM, et al. Into the eye of the cytokine storm. 2012;76(1):16-32.

[63] Geginat J, Larghi P, Paroni M, Nizzoli G, Penatti A, Pagani M, et al. The light and the dark sides of Interleukin-10 in immune-mediated diseases and cancer. 2016;30:87-93.

[64] Charo IF, Ransohoff RMJNEJoM. The many roles of chemokines and chemokine receptors in inflammation. 2006;354(6):610-21.

[65] Dinarello CAJAroi. Immunological and inflammatory functions of the interleukin-1 family. 2009;27:519-50.

[66] Ibrahim JN, Jeru I, Lecron J-C, Medlej-Hashim MJC, reviews gf. Cytokine signatures in hereditary fever syndromes (HFS). 2017;33:19-34.

[67] Shen W, Shi D, Wand D, Guo Y, Hai S, Yue ZJEa. Quinestrol treatment induced testicular damage via oxidative stress in male mongolian gerbils

(*Meriones unguiculatus*). 2011; 60(5):445-53.

[68] Niki E, Yamamoto Y, Komuro E, Sato KJTAjocn. Membrane damage due to lipid oxidation. 1991;53(1):201S-5S.

[69] Marchetti M, Pisani S, Antonini G, Valenti P, Seganti L, Orsi NJB. Metal complexes of bovine lactoferrin inhibit in vitro replication of herpes simplex virus type 1 and 2. 1998;11(2):89-94.

[70] Kawasaki Y, Isoda H, Shinmoto H, Tanimoto M, Dosako Si, Idota T, et al. Inhibition by κ-casein glycomacropeptide and lactoferrin of influenza virus hemagglutination. 1993;57:1214-5.

[71] Wong CW, Watson DLJJoDR. Immunomodulatory effects of dietary whey proteins in mice. 1995;62(2):359-68.

[72] BouNoUs° G, Batist G, Gold PJCIM. Mice: Role of glutathione. 1989;12:154-61.

[73] Zhang X, Kohli M, Zhou Q, Graves DT, Amar SJTjoi. Short-and long-term effects of IL-1 and TNF antagonists on periodontal wound healing. 2004;173(5):3514-23.

[74] Badr G, Ebaid H, Mohany M, Abuelsaad ASJTJonb. Modulation of immune cell proliferation and chemotaxis towards CC chemokine ligand (CCL)-21 and CXC chemokine ligand (CXCL)-12 in undenatured whey protein-treated mice. 2012;23(12): 1640-6.

[75] Hubner GJDrop-icdwhin, Cytokine g-tm. Brauchle M, Smola H, Madlener M, Fassler R, and Werner S. 1996;8:548-56.

[76] Nian MJIc, Res pirC. Lee P, Khaper N, Liu P. 2004;94:1543-53.

[77] Park B-K, Lee S-H, Seo J-N, Rhee J-W, Park J-B, Kim Y-S, et al. Protection of burn-induced skin injuries by the flavonoid kaempferol. 2010;43(1):46-51.

[78] Rusu D, Drouin R, Pouliot Y, Gauthier S, Poubelle PEJTJon. A bovine whey protein extract stimulates human neutrophils to generate bioactive IL-1Ra through a NF-κB-and MAPK-dependent mechanism. 2010;140(2):382-91.

[79] Pradhan L, Cai X, Wu S, Andersen ND, Martin M, Malek J, et al. Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing. 2011;167(2):336-42.

[80] Lim Y, Levy M, Bray TMJTJon. Dietary zinc alters early inflammatory responses during cutaneous wound healing in weanling CD-1 mice. 2004;134(4):811-6.

[81] Ebaid H, Salem A, Sayed A, Metwalli AJLih, disease. Whey protein enhances normal inflammatory responses during cutaneous wound healing in diabetic rats. 2011;10(1):1-10.

[82] Badr G, Badr BM, Mahmoud MH, Mohany M, Rabah DM, Garraud OJBi. Treatment of diabetic mice with undenatured whey protein accelerates the wound healing process by enhancing the expression of MIP-1α, MIP-2, KC, CX3CL1 and TGF-β in wounded tissue. 2012;13(1):1-9.

[83] Castro G, Maria D, Bouhallab S, Sgarbieri VJJods. In vitro impact of a whey protein isolate (WPI) and collagen hydrolysates (CHs) on B16F10 melanoma cells proliferation. 2009;56(1):51-7.

[84] Attaallah W, Yılmaz AM, Erdoğan N, Yalçın AS, Aktan AÖJP, Research O. Whey protein versus whey protein hydrolyzate for the protection of azoxymethane and dextran sodium sulfate induced colonic tumors in rats. 2012;18(4):817-22.

[85] Dillon EL, Basra G, Horstman AM, Casperson SL, Randolph KM,

Durham WJ, et al. Cancer cachexia and anabolic interventions: a case report. 2012;3(4):253-63.

[86] Alexander DD, Schmitt DF, Tran NL, Barraj LM, Cushing CAJNr. Partially hydrolyzed 100% whey protein infant formula and atopic dermatitis risk reduction: a systematic review of the literature. 2010;68(4):232-45.

[87] Parkin J, Cohen BJTL. An overview of the immune system. 2001;357(9270):1777-89.

[88] Wichers HJA, Chemistry B. Immunomodulation by food: promising concept for mitigating allergic disease? 2009;395(1):37-45.

[89] Badr G, Mohany M, Metwalli AJLih, disease. Effects of undenatured whey protein supplementation on CXCL12- and CCL21-mediated B and T cell chemotaxis in diabetic mice. 2011;10(1):1-8.

[90] Alexander DB, Iigo M, Hamano H, Kozu T, Saito Y, Saito D, et al. An ancillary study of participants in a randomized, placebo-controlled trial suggests that ingestion of bovine lactoferrin promotes expression of interferon alpha in the human colon. 2014;10:305-17.

[91] Prussick R, Prussick L, Gutman JJTJoc, dermatology a. Psoriasis improvement in patients using glutathione-enhancing, nondenatured whey protein isolate: a pilot study. 2013;6(10):23.

[92] Luhovyy BL, Akhavan T, Anderson GHJJotACoN. Whey proteins in the regulation of food intake and satiety. 2007;26(6):704S-12S.

[93] Pal S, Ellis VJO. The chronic effects of whey proteins on blood pressure, vascular function, and inflammatory markers in overweight individuals. 2010;18(7):1354-9.

[94] Sousa GT, Lira FS, Rosa JC, de Oliveira EP, Oyama LM, Santos RV, et al. Dietary whey protein lessens several risk factors for metabolic diseases: a review. 2012;11(1):1-9.

[95] Hamad EM, Taha SH, Abou Dawood A-GI, Sitohy MZ, Abdel-Hamid MJLih, disease. Protective effect of whey proteins against nonalcoholic fatty liver in rats. 2011;10(1):1-7.

[96] Da Silva MS, Bigo C, Barbier O, Rudkowska IJNR. Whey protein hydrolysate and branched-chain amino acids downregulate inflammation-related genes in vascular endothelial cells. 2017;38:43-51.

[97] Al-Omari MM, Al-Ghariebeh RB, Alhaija AAA, Al-Zoubi H, Al-Qaoud KMJEJoF, Agriculture. Camel milk whey inhibits inflammatory colorectal cancer development via down regulation of pro-inflammatory cytokines in induced AOM/DSS mouse model. 2019:256-62.

[98] Ricci-Cabello I, Olalla Herrera M, Artacho RJNr. Possible role of milk-derived bioactive peptides in the treatment and prevention of metabolic syndrome. 2012;70(4):241-55.

[99] Sagaya FM, Hurrell RF, Vergères GJTJonb. Postprandial blood cell transcriptomics in response to the ingestion of dairy products by healthy individuals. 2012;23(12):1701-15.

[100] Bruckbauer A, Gouffon J, Rekapalli B, Zemel MBJLG. The effects of dairy components on energy partitioning and metabolic risk in mice: a microarray study. 2009;2(2):64-77.

[101] Rocha VZ, Libby PJNRC. Obesity, inflammation, and atherosclerosis. 2009;6(6):399.

[102] Potenza MA, Addabbo F, Montagnani MJAJoP-E, Metabolism. Vascular actions of insulin with

implications for endothelial dysfunction. 2009;297(3):E568-E77.

[103] Madamanchi NR, Vendrov A, Runge MSJA, thrombosis,, biology v. Oxidative stress and vascular disease. 2005;25(1):29-38.

[104] Da Silva MS, Rudkowska IJMn, research f. Dairy nutrients and their effect on inflammatory profile in molecular studies. 2015;59(7):1249-63.

[105] Piccolomini A, Iskandar M, Lands L, Kubow SJF, Research N. High hydrostatic pressure pre-treatment of whey proteins enhances whey protein hydrolysate inhibition of oxidative stress and IL-8 secretion in intestinal epithelial cells. 2012;56(1):17549.

[106] Terakura D, Shimizu M, Iwasa J, Baba A, Kochi T, Ohno T, et al. Preventive effects of branched-chain amino acid supplementation on the spontaneous development of hepatic preneoplastic lesions in C57BL/KsJ-db/db obese mice. 2012;33(12):2499-506.

[107] Xiao X, Wu Z-C, Chou K-CJPo. A multi-label classifier for predicting the subcellular localization of gram-negative bacterial proteins with both single and multiple sites. 2011;6(6):e20592.

[108] Malinowski J, Klempt M, Clawin-Rädecker I, Lorenzen PC, Meisel HJFc. Identification of a NFκB inhibitory peptide from tryptic β-casein hydrolysate. 2014;165:129-33.

[109] van Meijl LE, Popeijus HE, Mensink RPJMn, research f. Amino acids stimulate Akt phosphorylation, and reduce IL-8 production and NF-κB activity in HepG2 liver cells. 2010;54(11):1568-73.

[110] Kumar A, Takada Y, Boriek AM, Aggarwal BBJJomm. Nuclear factor-κB: its role in health and disease. 2004;82(7):434-48.

[111] Lee J, Giordano S, Zhang JJBJ. Autophagy, mitochondria and oxidative stress: cross-talk and redox signalling. 2012;441(2):523-40.

[112] Da Silva MS, Bigo C, Barbier O, Rudkowska IJNR. Whey protein hydrolysate and branched-chain amino acids downregulate inflammation-related genes in vascular endothelial cells. 2017;38:43-51.

[113] Wang L, Wang Y, Song Z, Chu J, Qu XJJoI, Research C. Deficiency of interferon-gamma or its receptor promotes colorectal cancer development. 2015;35(4):273-80.

[114] Osawa E, Nakajima A, Fujisawa T, Kawamura YI, Toyama-Sorimachi N, Nakagama H, et al. Predominant T helper type 2-inflammatory responses promote murine colon cancers. 2006;118(9):2232-6.

[115] Ito R, Shin-Ya M, Kishida T, Urano A, Takada R, Sakagami J, et al. Interferon-gamma is causatively involved in experimental inflammatory bowel disease in mice. 2006;146(2):330-8.

[116] Saltanat H, Li H, Xu Y, Wang J, Liu F, Geng XJXbyfzmyxzzCjoc, et al. The influences of camel milk on the immune response of chronic hepatitis B patients. 2009;25(5):431-3.

[117] Rubie C, Frick VO, Pfeil S, Wagner M, Kollmar O, Kopp B, et al. Correlation of IL-8 with induction, progression and metastatic potential of colorectal cancer. 2007;13(37):4996.

[118] Ustunol Z, Wong CJJods. Effect of nonfat dry milk and major whey components on interleukin-6 and interleukin-8 production in human intestinal epithelial-like Caco-2 cells. 2010;93(6):2311-4.

[119] Becker C, Fantini MC, Schramm C, Lehr HA, Wirtz S, Nikolaev A, et al. TGF-β suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. 2004;21(4):491-501.