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REVIEW ARTICLE……!!!

A REVIEW ARTICLE ON CASEIN

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KEYWORDS:

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ABSTRACT

In the recent years the usage of casein product is more because of the less Side effects and more beneficially to the experimental purposes. Casein contains phosphoproteins and these proteins are found in mammalian milk. It contains Structure of casein and its chemical properties, physiological characters. Also contains the method of preparation of casein product. And also therapeutic benefits of casein, evaluation studies of casein. Caseins and whey proteins contrast in their physiological and organic properties. Lately, numerous examinations have researched the helpful parts of milk proteins. Caseins and casein products proteins contrast in their physiological and organic properties. Lately, numerous examinations have researched the helpful parts of milk proteins. Cows' milk generally contains two types of β-casein, A1 and A2 types. Digestion of A1 type can yield the peptide β-casomorphin-7, which is implicated in adverse gastrointestinal effects of milk consumption, some of which resemble those in lactose intolerance. This study aimed to compare the effects of milk containing A1 β-casein with those of milk containing only A2 β-casein on inflammation, symptoms of post-dairy digestive discomfort (PD3), and cognitive processing in subjects with self-reported lactose intolerance. The casein is more beneficially using know a days.

INTRODUCTION:

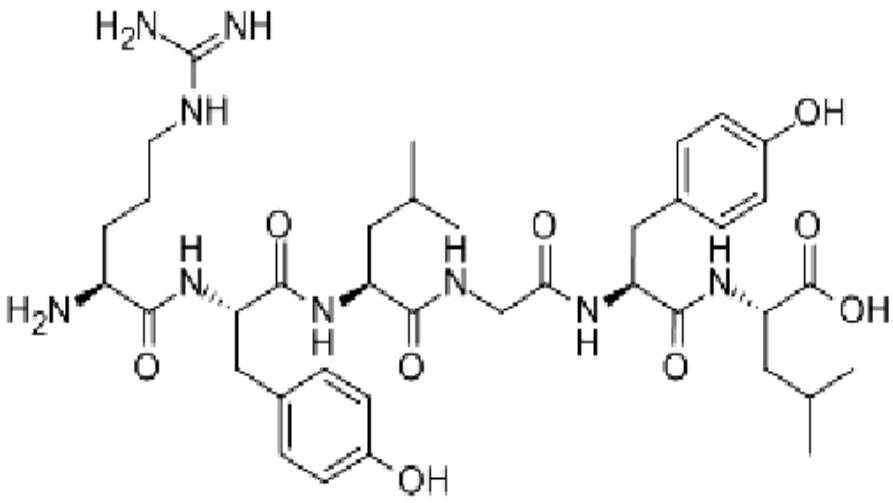
Casein is a family of related phosphoproteins (αS1, αS2, β, κ). These proteins are commonly found in mammalian milk, comprising c. 80% of the proteins in cow's milk and between 20% and 45% of the proteins in human milk. Sheep and buffalo milk have a higher casein content than other types of milk with human milk having a particularly low casein content. Casein has a wide variety of uses, from being a major component of cheese, to use as a food additive. The most common form of casein is sodium caseinate. As a food source, casein supplies amino acids, carbohydrates, and two essential elements, calcium and phosphorus.[1]

Casein contains a high amount of proline residues, which do not interact. There are also no disulfide bridges. As a result, it has moderately little tertiary structure. It is relatively hydrophobic, production it poorly soluble in water. It is found in milk as a suspension of particles, called casein micelles, which show only limited similarity with surfactant-type micelles in a sense that the hydrophilic parts reside at the surface and they are spherical. However, in sharp difference to surfactant micelles, the interior of a casein micelle is highly hydrated. The caseins in the micelles are held together by calcium ions and hydrophobic interactions. Any of several molecular models could account for the special conformation of casein in the micelles. It is used to form a type of organic adhesive. effect of calcium concentration, temperature, and pH on casein micelle stability in the presence of various concentrations of ethanol remains unknown.[2]

The objectives of this study were to determine aggregation and dissociation of casein micelles (casein micelle mapping) as affected by ethanol concentration, calcium concentration, casein concentration, pH, and temperature in a buffer solution. Potential applications of ethanol-induced modifications of casein micelle include textural and stability enhancements of dairy products and the use of casein micelles in cosmetic, pharmaceutical, and biomedical applications.[3]

Structure of casein:

The Casein Micelle. Most, but not all, of the casein proteins exist in a colloidal particle known as the casein micelle. Its biological function is to carry large amounts of highly insoluble CaP to mammalian young in liquid form and to form a clot in the stomach for more efficient nutrition.



Milk is also a unique source of peptides with biological activity. Peptides derived from casein fractions and whey proteins, including opioid peptides, antihypertensive peptides, casein phosphor peptides (CPPs), glycomacro peptide (GMP), and lactorphins, possess various physiological roles, such as opioid-like features, immunostimulating activities, anti-hypertensive activities, antibacterial and antiviral impacts and also enhancement of calcium absorption.[4]

A) Milk proteins:

Casein and whey protein are the major proteins of milk. Casein constitutes approximately 80%(29.5 g/L) of the total protein in bovine milk, and whey protein accounts for about 20% . Casein is chiefly phosphate-conjugated and mainly consists of calcium phosphate- micelle complexes (20). It is a heterogeneous family of 4 major components including alpha- (αs1- and αs2-casein), beta-, gamma-, and kappa-casein .Whey protein is a collection of globular proteins with a high level of α-helix structure and the acidic-basic and hydrophobic-hydrophilic amino acids are distributed in a fairly balanced form (24). Alpha-Lactalbumin (α-LA) and beta-lactoglobulin (β-LG) are the predominant whey proteins and comprise about 70–80% of the total whey proteins. Among the other types of whey proteins, immunoglobulins (Igs), serum albumin, lactoferrin (LF), lactoperoxidase (LP), and protease-peptones must be mentioned (19, 24-26). Whey proteins have substantial levels of secondary, tertiary, and quaternary structures. They are heat-labile stabilizing their prtotein structure through intermolecular disulfide linkage.[5]

B) Therapeutic benefits

Caseins and whey proteins contrast in their physiological and organic properties. Lately, numerous examinations have researched the helpful parts of milk proteins.[6]

C) Hypocholesterolemic effects

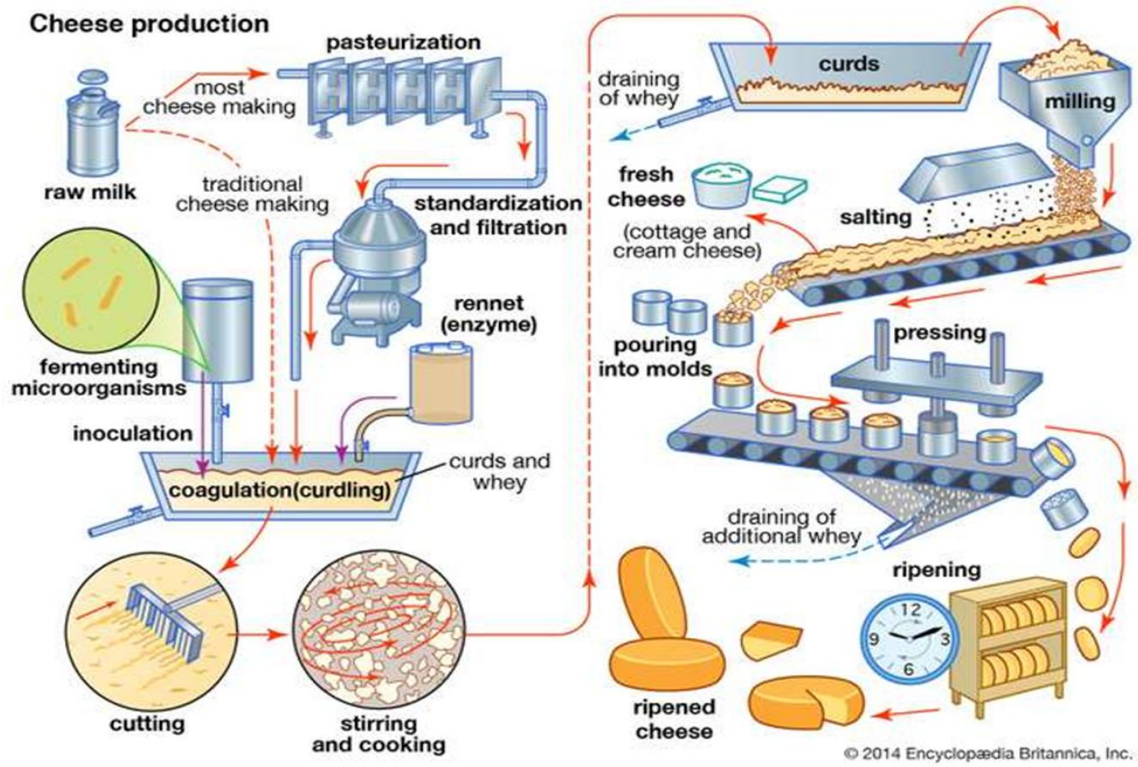
A few specialists have examined the impact of casein on blood cholesterol. In a hybrid report, 11 typical members got slims down giving 20% of calories from casein or soy protein. The mean of cholesterol admission was 500 mg/d. An underlying decrease in plasma cholesterol and low-thickness lipoprotein cholesterol (LDL-C) was seen in the two weight control plans (95). In another hybrid investigation, normolipidemic non obese sound men devoured 2 fluid recipe eats less carbs containing casein or soy protein. Following 30 days on each diet, the lipoprotein (a) fixation was diminished by roughly half with the casein diet compared to the soy-protein diet.[7]

D) Anticarcinogenic effects

Peptides got from the N-terminal area of LF have been researched so as to recognize successions with potential antitumor movement. detached 4 peptides from pepsin hydrolysates of lactoferrin with antiproliferative and apoptotic property. The arrangement comparing to buildups 17–38 of cow-like LF indicated the most elevated apoptotic action in human leukemia cells detailed that , exhibited cytotoxic action against Meth Afibrosarcoma, melanoma, and colon carcinoma cell lines, and altogether brought down the size of strong Meth A tumors. Additionally, Lfcin showed antitumor movement against MDA-MB-435 bosom malignancy cells by initiating apoptosis and cytotoxic action in-vitro and in-vivo against neuroblastoma cells by destabilization of the cytoplasmic and the mitochondria films.[8]

E) Antimicrobial and antiviral effects

Unblemished whey contains various one of a kind segments with expansive antimicrobial movement. A few examinations have shown the inhibitory action of whey proteins against Helicobacter pylori (H. pylori) in contaminated subjects.[9]



Method:

A) Casein is typically produced using skim milk (once in a while from buttermilk), by one of three techniques:

(1) normally soured casein turns sour when enough lactic corrosive creates frommaturation of milk sugar by the ever present bacterium Streptococcus lactisi;

(2) corrosive casein is accelerated by including weaken hydrochloric corrosive or sulfuric corrosive;

(3) for rennet casein, warm skim milk is set with rennet remove until the calcium paracaseinate clusters, after which the coagulation is sliced into little pieces to enable the whey to deplete. In each of the three strategies the whey is drawn off, the curd washed with water, depleted or squeezed, dried in warm air, ground, and stuffed available to be purchased. Rennet casein holds a significant part of the calcium phosphate from the milk.[10]

B) Preparation of milk protein hydrolysates by in vitro enzymatic digestion: Aqueous dispersions of WPC-70 (1.4% w/v, Modern Dairies Ltd., Karnal, India.) and sodium caseinate (1% w/v) were prepared, and their protein content was determined. Hydrolysis of CP and WP was carried out by incubating their aqueous dispersions at constant *p* H and temperature in shaker water bath with pepsin (*p* H 2.0, 37°C) and pancreatin (*p* H 7.5, 40°C) separately at enzyme-substrate ratio (E:S) of 1:25 on

protein basis. Samples of WPs digested with pepsin were withdrawn after 60, 120 and 240 min and coded, respectively, as WP1, WP2 and WP3 and those of casein as CP1, CP2 and CP3, respectively. Similarly, samples were coded as WT1, WT2 and WT3, respectively, for WP hydrolysates prepared with pancreatin and those of casein as CT1, CT2 and CT3. In addition, to simulate gastrointestinal digestion, two-stage hydrolysis was carried out. For this, protein samples (WP and CP) were first hydrolyzed with pepsin (E:S 1:50; *p* H 2.0; temperature 37°C) for 60 min, followed by 60 min hydrolysis with pancreatin (E:S 1:50; *p* H 7.5; temperature 40°C) and coded as W2 and C2. Enzymes in all reactions were inactivated at the end of desired incubation period by heating samples at 90°C for 20 min. The hydrolysates were used immediately or stored at −80°C until further use. The extent of protein hydrolysis was determined in terms of per cent degree of hydrolysis (DH) by O-phthaldialdehyde (OPA) method. The hydrolysates were also analyzed with sodium dodecyl sulphate-polyacrylamide gel electrophoresis(SDS-PAGE)[11].

Arrangement of bioactive peptides with proteolytic Lactobacillus helveticus: Proteolytic lactobacilli L. helveticus NCDC 288 and L. helveticus NCDC 292 were secured from National Collection of Dairy Cultures (NCDC), NDRI, Karnal, and kept up in de Man, Rogosa and Sharpe (MRS) soup at 37°C for 16-18h. Pressure-controlled release has been achieved for the casein

For generation of bioactive peptides, reconstituted skim milk (11%) was autoclaved and inoculated with overnight grown culture of *L. helveticus* (10^6 cells/ml) followed by incubation at 37°C for 24 h. After 24 h, the curd was broken by vigorous shaking and centrifuged at 12,000 × g for 10 min. The supernatant was neutralized to PH 7.5 and filtered through 0.2 μm filter. The protein content of this supernatant was estimated and analyzed further for the expression of gut hormones. Proteolysis in fermented milk was measured using OPA method.[12]

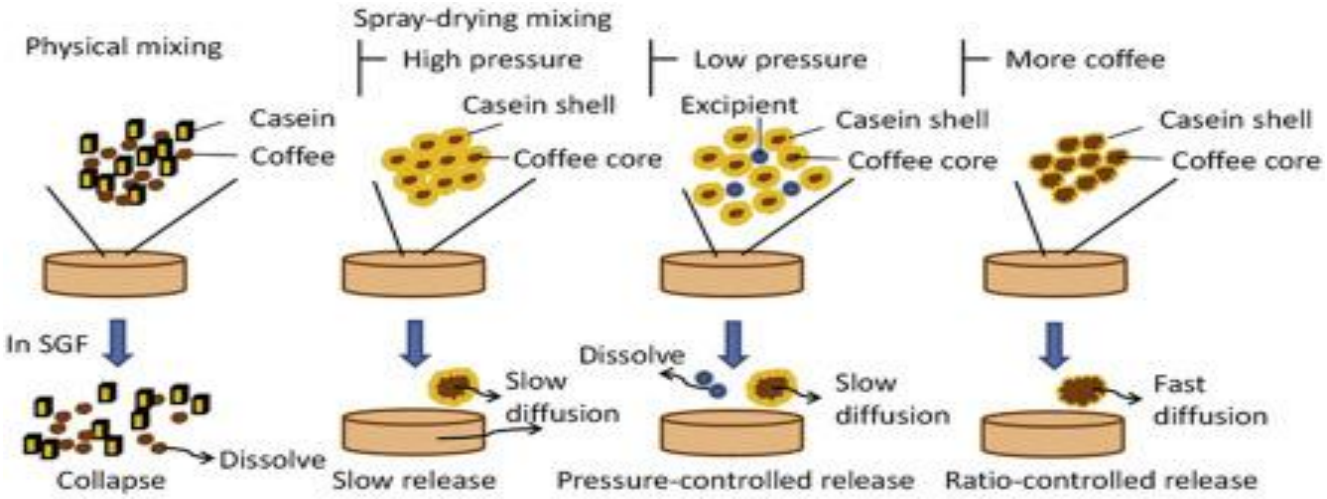
C) Cell lines and cultures Human prostate malignant growth cell lines, androgen-autonomous PC-3 and androgen-subordinate LNCaP cells (ATCC, Manassas), were kept up in a Roswell Park Memorial Institute (RPMI) 1640 medium (Invitrogen, Carlsbad, CA, USA) enhanced with 10% fetal ox-like serum (FBS), penicillin (100 U/mL), and streptomycin (100 mg/mL). Human A549 (ATCC, Manassas) lung malignant growth cells, SNU-484 (KCLB, Seoul, Korea) stomach disease cells, and HEK293 (ATCC, Rockville, MD, USA) human undeveloped kidney cells were kept up in a similar way. Human bosom disease cells (MCF7; ATCC, Rockville) were kept up in Dulbecco's changed Eagle's insignificant basic medium (Invitrogen) with the previously mentioned enhancements. Deified RWPE-1 (ATCC, Manassas) ordinary human prostate cells were developed in cow-like pituitary concentrates (50 μg/mL), keratinocyte, and epidermal development factor (5 ng/mL) under a similar hatching conditions.

The cells were refined at 37o C in a humidified air under 5% CO2 in air. The cells were plated first in 10% FBS; the development medium was evacuated following 24 hours and supplanted with a without serum medium enhanced with NaOH, αcasein, and casein from cow-like milk at convergences of 0.1 or 1 mg/mL for 72 hours. The cells were weakened in a fitting medium before each trial. 2. Casein and test conditions α-Casein and entire casein from cow-like milk were obtained from Sigma-Aldrich (St. Louis, MO, USA). Every cell line (PC-3, LNCaP, MCF7, SNU484, A549, RWPE-1, or HEK293) was seeded in 12-well plates at a thickness of 1×105 cells/well under sans serum conditions. Every cell was treated with NaOH, α-casein, or casein from cow-like milk at convergences of 0.1 or 1 mg/mL on the primary day as it were. Following 3 days, expansions of every cell line development were estimated by utilizing a 3-(4,5-Dimethyl-thiazol-2-yl)- 2,5-diphenyl tetrazolium bromide (MTT) measure. Before the foundation of the previously mentioned test conditions, every cell line was refined under different conditions. The quantity of medicines (first day just versus regular), length of analyses (2∼7 days), conditions with or without serum supplement, and convergence of casein (α-casein) were tried. Since serum is additionally a supplement like casein, we picked a without serum condition as the last exploratory condition. To find out the outcomes, tests were rehashed in any event multiple times. 3. Estimation of cell expansion and morphological change After treatment, cell feasibility was evaluated by hatching cells with 0.5 mg/mL of MTT for an additional 4 hours. Formazan delivered by suitable cells was set up in dimethyl sulfoxide. Colorimetric examination was performed at 570 nm in a Multiskan catalyst connected immunosorbent measure ((ELISA) peruser (Thermo, Vantaa, Finland). Cell practicality was displayed as an overall level of control. In addition, cells were photographed using light microscopy[13,14].

D) Statistical analysis:

A two-route investigation of change (ANOVA) test was utilized to contrast the test gatherings and the benchmark group, while results when medications were looked at utilizing Tukey's correlation test. Measurable hugeness was resolved at $p < 0.05$. Every factual count were figured utilizing PASW Statistics. expansion of 1 mg/mL of casein upgraded the development to 166% ($p < 0.05$) and 142% ($p < 0.05$) multiplication in the PC-3 and LNCaP cells, separately. Be that as it may, there was no critical change in the development of different cells under the equivalent trial conditions. Fig. 2 shows the adjustments in the expansion of every cell following 72 hours of sans serum culture. Treatment with α-casein initiated checked portion subordinate increments in cell multiplication in the PC-3 and LNCaP cells.[15]

E) The controlled release of caffeine from the casein gel tablets has been achieved over release periods lasting from a few minutes to over a few days. A novel casein gel has been acidified at pH of 1.0 as the insoluble controlled-release matrix and spray-dried with coffee for microencapsulation. The optimal inlet temperature of spray drying for the casein-coffee mixtures has been found to be 150 °C. The elastic casein-coffee tablets have been engineered without denaturing the components (as indicated by DSC and coffee tablets prepared by compression at 8 (with lactose excipient), 80 and 160 MPa. The corresponding releases of over 80% caffeine are about 24, 12 and 3–6 h, respectively. By changing the coffee/casein ratio from 10 to 100%, the release time of 80% caffeine can be controlled from 24 to 0.5 h. The spray-dried casein-coffee particles shown in the SEM images are similar in size (about 10 μm) and shape (raisin-like). No significant interactions between the casein and coffee components have been observed by FTIR analysis.[16]



Evaluation studies:

1) Ultrafiltration: The milk protein hydrolysates (fermented milk and *in vitro* digested protein hydrolysates) were centrifuged at 12,000 × g for 20 min at 4°C and supernatant thus obtained was filtered through 0.2 μm filter. The filtered samples were ultra-filtered through 10, 3 and 1 kDa MWCO membranes, sequentially using stirred cell assembly (Amicon, USA) and OMEGA MWCO membrane discs (dia. 62 mm, Pall Life Sciences, USA) under nitrogen pressure (50 psi) at 4°C. Permeate of each (10, 3 and 1 kDa) was collected and analyzed for GLP-1 secretion[17].

2) Characterization of 1 kDa filtrate: The selected 1 kDa permeates were assessed for amino acid content and by Fourier transform infrared (FTIR) spectroscopy analysis. Amino acid analysis of 1 kDa fraction was performed according to the method of Heinrikson & Meredith. The IR spectra were recorded on FT-IR RX-1 spectrometer (Perkin Elmer, USA) in the 200-4000/cm range[18].

3) Reversed phase chromatography (RPC) for purification of active molecule: The 1 kDa permeates of selected hydrolysates were further purified by RPC (AKTA purifier, GE Healthcare, India). The hydrolysates were resolved using SOURCE 15RPC column (6.4 mm × 100 mm, particle size 15 μm, GE Healthcare) with mobile phase consisting of water added with 0.1 per cent TFA (A) and 70 per cent acetonitrile with 0.01 per cent TFA (B). For separation of analysts, a gradient programed (0-100% B for 20 column volumes) was used with flow rate of 1 ml/min. The absorbance of the eluent was monitored at 214 nm. The fractions were collected manually and concentrated using lyophilizer. Protein content in individual fractions was estimated and each fraction (25 μg/ml) was analyzed for the GLP-1 secretion. Active fractions for GLP-1 secretion were further analyzed for their effect on expression of gut hormones. Mass of the active fractions obtained from RPC was determined using electrospray ionization-mass spectrometry (ESI) on micro mass Quattro II triple quadrupole mass spectrometer (Agilent 4000 QTRAP, USA).

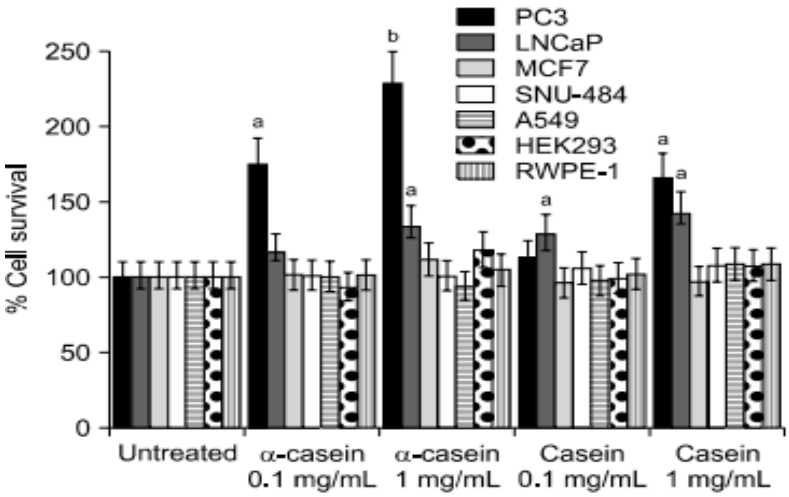
The samples were dissolved in water and introduced into the ESI source through a syringe pump at the rate of 10 ml/min. During this whole process, ESI capillary was set at 3.5 KV and the cone voltage[19].

4)* Statistical analysis:* Statistical analysis was carried out with ANOVA followed by Newman–Keuls multiple range post hoc test. All data for mRNA expression are presented as relative fold change obtained using REST software from three independent experiments[20].

5) **Purification and characterization***:* The 1 kDa fractions which elicited higher GLP-1 secretion (3.07-, 2.71-, 1.78- and 1.27-fold by *L. helveticus* NCDC 288, *L. helveticus* NCDC 292, WP3 and CP1, respectively, relative to control; (Figure)for fermented milk as well as *in vitro* digested milk protein hydrolysates were characterized for FTIR and amino acid content[21].

Result:[22-25]

Casein can promote proliferation of prostate cancer cells. Prostate cancer cells (PC-3 and LNCaP) proliferated at an increased rate with α-casein supplementation under serum-free conditions. However, other cancer cells did not show any differences as compared to an untreated group. a $p < 0.05$, b 0.001 versus control responses.



Casein cannot be absorbed directly from the digestive system. However, casein and α-casein have been detected in various conditions and tissues, even serum. No obvious mechanism of how casein might be transported from the intestines to the body tissues or cancer cells has yet been identified. Although casein promoted the growth of cancer cells under serum-free conditions in this study, it is not clear whether dietary casein could have an effect on prostate cancer cells in vivo. Further experiments on the molecular mechanisms of casein induced proliferation in prostate cancer cells and in vivo studies should be conducted.

Representative morphological changes in each cell after exposure to α-casein and casein (0.1 and 1mg/mL) for 72 hours. Under control conditions (NaOH alone), PC-3 cells appeared to have a typical phenotype, with round nuclei and homogeneous cytoplasm. PC-3 cells treated with casein or α-casein showed distinct morphological changes, increases in cell volume, cellular adhesion, and cell numbers. Likewise, LNCaP cells treated with casein or α-casein showed increased cellular adhesion. MCF7, SNU-484, and A549 cells treated with casein or α-casein showed no morphological changes compared with the untreated cells. RWPE-1 and HEK293 cells treated with casein or α-casein also showed an increase in cellular adhesion without any changes in cell volume or numbers.

Conclusion:

Milk is the oldest and one of the most widely consumed nutritious foods worldwide. It is highlighted as a source of high-quality proteins and one of the most important sources of bioactive peptides. Milk proteins have high nutritive value and remarkable medicinal properties. They are known as potential ingredients of health-promoting functional foods, and the dairy industry has already commercialized many milk proteins and peptide-based products which can be consumed as part of a regular daily diet. They are consumed by infants, the elderly, and immune-compromised people. They are also consumed

to maintain good health status and prevent diet-related chronic diseases such as obesity, cardiovascular disease, and cancer. Milk-derived peptides are commonly ingested both in functional foods and drugs. They exhibit various well-defined pharmacological effects, for example, in the treatment of diarrhea (casomorphins), hypertension (casokinins), thrombosis (casoplatelins), dental diseases, mineral malabsorption (CPPs), and immunodeficiency (immunopeptides). These findings introduce new perspectives in the nutritional and technological evaluation of milk products and encourage utilization of these substances for production of food and new health promoting products.

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