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## Cheese in nutrition and health

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**Abstract** – Cheese has a long history in the human diet. In ancient times, cheese was primarily a concentrated form of milk with the benefit of a prolonged shelf life. The high content of fat and protein in cheese made it an energy-rich and nutritious food that was suitable for our hard-working ancestors. Recent advances in nutrition science have highlighted the contribution of cheese to nutrition and health. Cheese is a rich source of essential nutrients; in particular, proteins, bioactive peptides, amino acids, fat, fatty acids, vitamins and minerals. Ripened cheese is free of lactose and therefore suitable for the nutrition of lactose-intolerant individuals. There is evidence to suggest that two bioactive tripeptides, VPP and IPP, found in sour milk fermented with *Lactobacillus helveticus*, lower blood pressure. These peptides were also detected in specific cheese varieties in significant quantities. The high concentration of essential amino acids in cheese contributes to growth and development of the human body. Despite the presence of a notable amount of saturated and *trans* fatty acids, there is no clear evidence relating the consumption of cheese to any disease. Conjugated linoleic acid and sphingolipids present in cheese may have anti-carcinogenic properties. The high concentration of calcium in cheese is well known to contribute to the formation and maintenance of strong bones and teeth, but also shows a positive effect on blood pressure and helps in losing weight in combination with low-energy diets. Cheese is an important dairy product and an integral part of a healthful diet due to its substantial contribution to human health. In recent times, diet has been linked to various diseases such as diabetes, obesity, cardiovascular disease, osteoporosis and cancer, and the focus of nutrition research has shifted towards specific food ingredients contributing to nutrition and health.

### cheese / composition / nutrition / health

**摘要 – 干酪的营养和健康作用。** 在人类的饮食中干酪有着悠久的历史。远古时代,人类为了延长奶的保质期,将奶浓缩制成干酪。高含量的脂肪和蛋白质为我们勤劳的祖先提供了充足的能量和营养。营养学研究表明干酪是一种营养和健康食品。干酪富含人体必需的营养素,特别是蛋白质、生物活性肽、氨基酸、脂肪、脂肪酸、维生素和矿物质。成熟的干酪不含乳糖,因此特别适合乳糖不耐症人群。有资料显示,在以瑞士乳杆菌 (*Lactobacillus helveticus*) 发酵的酸乳中存在 2 种具有降血压功能的生物活性三肽 VPP 和 IPP,在某些特殊的干酪中也发现这两种活性肽的含量较高。干酪中高含量的必需氨基酸有助于人体的生长。尽管干酪中含有大量的饱和脂肪酸及反式脂肪酸,但是没有充分的证据证明干酪的消费与任何疾病有关。相反,干酪中的共轭亚油酸和鞘脂类具有抗癌的特性。众所周知,干酪中高浓度的钙离子有利于形成和维持强壮的骨骼和锋利的牙齿,而且还有助于保持正常的血压,与低能量食品结合可以起到瘦身的作用。由于干酪对人类的健康具有重要的作用,因此干酪是重要的乳制品,也是健康食品的重要配料。近年来,许多疾病的形成都与饮食直接相关,如糖尿病、肥胖、心血管疾病、骨质疏松症和癌症等,因此对营养的研究则更多是关注特定食物成分的营养和对健康的作用。

### 干酪 / 成分 / 营养 / 健康

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**Résumé – Fromage en nutrition et santé.** Le fromage a une longue tradition dans l'alimentation humaine. Autrefois, il s'agissait principalement d'une forme concentrée de lait qui avait l'avantage d'avoir une durée de conservation prolongée. Le taux élevé de lipides et de protéines dans le fromage en fait un aliment nutritif, riche en énergie, qui convenait bien à nos ancêtres travaillant durement. Des recherches récentes en nutrition ont mis en évidence la contribution du fromage dans l'alimentation et la santé. Le fromage est une source riche en nutriments essentiels, en particulier en protéines, en peptides bioactifs, en acides aminés, en lipides, en acides gras, en vitamines et en minéraux. Le fromage affiné ne contient plus de lactose et convient donc aux personnes intolérantes à ce composant. Par ailleurs, il y a tout lieu de penser que deux tripeptides bioactifs, les VPP et IPP, détectés dans le lait fermenté par *Lactobacillus helveticus*, abaissent la pression sanguine. Ces peptides ont aussi été détectés en quantités significatives dans divers types de fromage. La concentration élevée d'acides aminés essentiels dans le fromage contribue à la croissance et au développement du corps humain. Malgré la présence d'une quantité notable d'acides gras saturés et *trans*, il n'y a aucun élément de preuve mettant en relation la consommation de fromage et une quelconque maladie. Au contraire, il semble que les acides linoléiques conjugués et les sphingolipides présents dans le fromage possèdent des propriétés anti-cancérigènes. La concentration élevée de calcium dans le fromage est connue pour contribuer à la formation et au maintien d'une ossature et d'une dentition solides, mais exerce aussi un effet positif sur la pression sanguine et aide à perdre du poids en combinaison avec un régime hypocalorique. Le fromage est un produit laitier important et fait partie d'une alimentation équilibrée en raison de sa contribution substantielle à la santé humaine. Récemment, l'alimentation a été mise en relation avec diverses maladies comme le diabète, l'obésité, les maladies cardiovasculaires, l'ostéoporose et le cancer. En conséquence, l'accent a été mis, dans les recherches sur la nutrition, sur des ingrédients alimentaires spécifiques, contribuant à une alimentation saine et donc à la santé.

#### fromage / composition / alimentation / santé

**Abbreviations:** ACE = angiotensin-converting enzyme, CLA = conjugated linoleic acid, IPP = isoleucyl-prolyl-proline, MUFA = monounsaturated fatty acid, PUFA = polyunsaturated fatty acid, SFA = saturated fatty acid, TFA = trans fatty acid, VPP = valyl-prolyl-proline.

## 1. INTRODUCTION

Cheese is one of the most ancient forms of manufactured food. It is thought that cheese-making could go as far back as 10 000 BC when sheep and goats were first domesticated in the Middle East and early herdsmen would have consumed milk. Due to contaminating bacteria, milk has a short shelf life, especially in warm climates. Therefore, it might have happened that sour milk naturally separated into curds and whey, the solid curd providing an edible and nourishing food [22]. It is likely that nomadic tribes, spread from the Middle East to Western Europe and South and Central Asia, found animal-skin bags a useful way to carry milk on animals' backs when on the move. Fermentation of the milk sugars would cause the milk to curdle and the swaying motion would break up the curd and provide solid curd and

drinkable whey. The curds would be removed, drained and lightly salted to provide a tasty and nourishing high protein food. The Romans then elevated this crude cheese-making to an early semblance of technology and spread it to various European regions. The basic reason for purposely processing milk into cheese is to preserve a perishable food and to convert it into a stable and storable product. It also expands the variety of food [105].

Cheese produced in Europe, where climates are cooler than in the Middle East, required less salting for preservation. With less salt and lower acidity, cheese was a suitable environment for a variety of beneficial microbes and molds, which give aged cheeses their pronounced and interesting flavors.

Nowadays, cheese consumption is widely spread throughout the world. However, the amount of cheese eaten is

**Table I.** Per capita cheese consumption in various countries, 2001 to 2006 [37, 38].

	2001	2002	2003	2004	2005	2006
	kg per capita					
Greece	26.6	27.5	28.7	28.7	28.9	28.9
France	25.8	25.0	24.8	24.5	24.5	23.9
Iceland	22.8	22.3	23.9	24.7	23.6	–
Germany	21.6	21.7	21.7	21.9	22.1	22.4
Italy	21.4	21.2	22.3	23.0	–	23.7
Austria	18.7	18.9	19.4	19.4	19.6	18.8
Switzerland	18.2	18.3	20.2	21.7	22.2	22.2
EU 25	17.5	17.6	17.8	18.0	18.3	18.4
Sweden	17.3	17.6	17.6	17.9	17.9	18.5
Finland	16.6	16.5	16.6	18.3	18.5	19.1
Norway	15.3	15.3	15.1	15.3	15.9	16.0
USA	15.1	15.3	15.3	15.7	15.7	16.0
Netherlands	14.7	14.7	14.7	14.7	14.7	20.4
Canada	14.1	13.9	14.0	14.3	14.4	–
Australia	11.6	12.3	12.4	11.7	11.9	–
Argentina	11.5	9.6	8.3	8.9	10.7	–
Poland	10.9	10.1	10.3	10.4	10.4	–
Ireland	10.3	10.3	10.5	10.5	10.5	10.5
Czech Republic	10.2	14.4	14.7	15.7	–	–
Portugal	10.0	10.1	10.2	10.3	–	–
UK	10.0	10.8	10.8	10.9	11.1	–
Hungary	8.7	8.9	8.8	9.0	10.0	–
Spain	8.7	9.1	9.5	9.5	9.6	–
New Zealand	7.3	7.1	7.1	7.1	7.1	–
Slovakia	6.3	9.1	9.3	8.2	9.3	–
Russia	5.3	5.5	5.6	5.7	6.2	–
Japan	1.9	1.8	1.9	2.0	–	–
Mexico	1.9	2.0	1.9	2.1	2.1	2.1
South Africa	1.0	1.0	0.8	0.6	–	–
Korea (Republic)	–	–	1.2	1.3	1.4	–

–: No values available.

very different from country to country. In Greece, France, Germany, Italy and Switzerland per capita consumption is more than 20 kg per year. At the other end of the scale, cheese consumption in

Mexico, Japan, Ukraine, South Africa and China is very low. Nevertheless, cheese consumption has risen continuously in recent years in most of the selected countries and also worldwide (Tab. I).

**Table II.** Average composition of fresh, soft, semi-hard, hard and extra-hard cheese [86].

	Water	Protein	Fat	Lactose	Minerals + Vitamins
	$\text{g}\cdot\text{kg}^{-1}$				
Fresh cheese	700	110	80	30	80
Soft cheese	520	200	220	0	60
Semi-hard cheese	400	250	270	0	80
Hard cheese	350	270	310	0	70
Extra-hard cheese	300	290	330	0	80

Today the main reason for the consumption of cheese is not the prevention of hunger but the supply of important and essential nutrients, its manifold uses in the kitchen, and its enjoyment. Technological progress has led to a multitude of different types of cheese on the market, varying in texture and flavor. Nowadays, a shift is observable from the optimum in product quality to the optimum for the consumer. So research is no longer based on the production of high quality cheese but more and more on the commercialization of cheese as a functional food. Technology is needed for gentle processing to retain or even accumulate desired nutrients and to remove undesired compounds. Since more and more individuals would like to control their health via custom-made food, the worldwide market for Functional Food is one of the fastest-growing markets in the world.

## 2. COMPOSITION OF CHEESE

The various cheese types can be classified according to the milk used (cow, sheep, goat, buffalo), their manufacture (rennet, sour milk cheese, ultrafiltration), consistency (extra-hard, hard, semi-hard, semi-soft, soft, fresh cheese), fat content (double cream, cream, full fat, three-quarters fat, half fat, quarter fat cheese), fermentation type (lactic acid, lactic and

propionic acid, butyric acid), surface (hard, soft, with smear, moulds) and interior (eyes, moulds). Additionally, they differ in flavor as well as some bioactive components, which are mainly created during the different stages of ripening when the main ingredients lactose, protein and fat are broken down by fermentation, proteolysis and lipolysis [58]. Thus, the varieties of cheese on the market are enormous, which is also reflected in the variability in the composition of the different types of cheese (Tab. II). In most of the countries with a high consumption of milk products the major part is produced from cow's milk. So we have concentrated on the composition of cow's milk. They mainly consist of fat, protein and water as well as vitamins, minerals and trace elements. Lactose is rarely present [87].

## 3. CHEESE AND NUTRITION

### 3.1. Lactose

At the beginning of the cheese ripening process, lactose is partly washed out with the whey: the rest is fermented into lactic acid and further into diacetyl, acetylaldehyde, acetic acid, ethanol and  $\text{CO}_2$  [47]. The fact that ripened cheese is free of lactose [86, 88, 96] is an advantage for most of the adult population. Approximately 70% of the global population cannot tolerate lactose in adulthood; consumption

of milk is followed by various unpleasant symptoms such as abdominal pain, diarrhea, nausea, flatulence, etc. [34]. Nevertheless, it is not necessary for these people to avoid dairy products. All types of cheese except fresh and, in a few cases, soft cheese, are free of lactose. Therefore, lactose-intolerant people can consume these cheeses, which contribute to a healthy diet with their indispensable ingredients such as calcium [89].

### 3.2. Protein

As already mentioned, cheese is an important source of proteins and amino acids. It is well documented that cheese provides all essential amino acids except methionine and cysteine in more than the recommended quantities for children or adults [101]. Not only the proteins and amino acids play an important role in human nutrition; during the last 30 years an intermediate product of proteolysis of proteins into amino acids has moved to the center of interest – bioactive peptides. These are special amino acid sequences within the proteins. As long as they are bound in the proteins they are biologically inactive. A wide range of biological activities have been described, including opioid, blood pressure-lowering, mineral-binding, antimicrobial, immunomodulating, cell-modulating, anti-carcinogenic, anti-cariogenic, anti-thrombotic, anti-inflammatory and cholesterol-lowering activities [4].

### 3.3. Fat

Another main component of cheese is fat. It varies between 20 and 35% of the dry mass. One portion (50 g) of full-fat cheese provides about two-thirds of the recommended daily intake of fat. Milk fat, and therefore also cheese fat (except

in mold cheese, fat does not change during ripening), has an average content of 600 g·kg<sup>-1</sup> fat of saturated fatty acids (SFA), 235 g·kg<sup>-1</sup> fat of monounsaturated fatty acids (MUFA) and 46 g·kg<sup>-1</sup> fat of polyunsaturated fatty acids (PUFA). The composition varies seasonally, and in summer saturated fatty acids are reduced in favor of the unsaturated fatty acids [86]. The most common saturated fatty acid is palmitic acid (16:0) with 260 g·kg<sup>-1</sup> fat, in second place myristic acid (14:0) with 98 g·kg<sup>-1</sup> fat and in third place stearic acid (18:0) with 80 g·kg<sup>-1</sup> fat. All other saturated fatty acids are present at between approximately 0.2 and 31 g·kg<sup>-1</sup> fat. The most common unsaturated fatty acid in milk fat is oleic acid (18:1 c9) with 165 g·kg<sup>-1</sup> fat. Milk fat also provides *trans* fatty acids. The seasonal variation is very large; in summer 73.5 g·kg<sup>-1</sup> fat, and in winter 38.3 g·kg<sup>-1</sup> fat.

*Trans* fatty acids, especially those of industrial origin, have been accused of enhancing the risk of coronary heart disease [110, 111]. Studies that investigated a possible similar effect of ruminant *trans* fatty acids did not support this hypothesis: in contrast, a neutral and even slightly negative correlation was observed both in men and women [13, 39]. A special *trans* fatty acid in milk fat is conjugated linoleic acid (CLA), which is typical of ruminant fat. In cheese, the content varies between 0.1 and 2.5 g·kg<sup>-1</sup> fat. Comparison of milk from the lowlands with milk from the highlands showed a threefold increase in concentration of CLA in the fat from the highlands [16]. These differences could be explained by breed and fodder. Several animal studies report various beneficial effects of CLA but only a few could also be demonstrated in humans [68] (see below).

Saturated fatty acids have a poor image because there is some evidence of a negative influence on blood lipids and therefore a possible promotion of coronary heart disease. However, in fact, individual saturated

fatty acids influence blood cholesterol level differently [30, 74, 81, 99]. In addition, some play an important role in cell regulation by protein modification (acetylation), in gene expression as well as in the modulation of genetic regulation, in the regulation of the bioavailability of PUFA, and in fat deposition [23, 72–74].

The knowledge of these physiological functions of SFA together with the results from new epidemiological studies indicate that we have to differentiate between individual saturated fatty acids and no longer treat them as a whole. If a reduction of the total SFA intake is sought it should not be done by reducing the consumption of dairy products (in Switzerland they represent 43% of total SFA intake) since they provide a series of nutritionally interesting fatty acids, as described above [20].

### 3.4. Vitamins and minerals

Milk and dairy products contain all vitamins and minerals in different quantities [86]. One of the most important minerals in dairy products and especially in cheese is calcium. Semi-hard and hard cheese contain about 6 to 11 g·kg<sup>-1</sup> cheese. The content in soft cheese is lower due to the acidification of the vat milk. One portion (50 g) of semi-hard or hard cheese supplies one-third to a half of the recommended daily intake of 1200 mg calcium. In Switzerland 71% of the daily calcium intake is consumed in the form of milk and dairy products and about 20% as semi-hard and hard cheese [20]. Besides calcium, cheese is also a good source of phosphorus and zinc, and magnesium is also worth mentioning. The relatively high content of salt has often been discussed in relation to hypertension. But other ingredients in cheese such as calcium and certain bioactive peptides have been shown to neutralize a possible negative effect (see below).

One portion of hard cheese contains 15% of the daily recommended intake of

vitamin A, over 10% of B<sub>2</sub>, over 20% of B<sub>6</sub> and almost 40% of the recommended value of B<sub>12</sub> with an energy content of only 10% of the daily diet [98].

## 4. CHEESE AND HEALTH ASPECTS

Cheese is a rich source of bioavailable calcium. The following discussion of the health aspect of cheese mainly focuses on the role played by this specific mineral, but at the same time, specific roles played by other ingredients such as protein, bioactive peptides, CLA and sphingolipids cannot be ignored.

### 4.1. Protective effect for dental caries

Dental caries has been shown to be due to the breakdown of tooth enamel by acids which are formed during the fermentation of sugars and starches by plaque bacteria. Despite an improvement in its incidence due to a better prophylaxis, caries is still the most prevalent dental disease. To avoid corrosion of tooth enamel good hygiene, on the one hand, and an adapted nutrition, on the other hand, are helpful. Even though milk contains sugar (lactose), animal and human studies showed that it is not cariogenic [18]. Milk even reduces caries in rats when added to their normal diet [71]. According to different studies the anti-cariogenic effect of cheese products is based on various components. On the one hand, calcium and phosphorus seem to minimize the drop in plaque pH, which means that acid production after dairy consumption is reduced [40]. Chewing a piece of cheese after a sugary food brings plaque pH rapidly back to neutrality [77]. Jensen et al. [42] realized that not all types of cheese are equally potent in inhibiting the drop in plaque pH. Aged cheese seems to protect better than young and fresh cheese.

One explanation for the protection could be a buffering effect by the stimulation of saliva flow by cheese. Saliva contains calcium and phosphate ions at super saturation which leads to a mineralization of the enamel in a neutral environment [3]. Moynihan et al. [60] measured the calcium concentration of the plaque after a meal containing cheese and a meal without cheese. The meal with cheese increased the calcium concentration of the plaque significantly more than the control meal. Jensen et al. [41] observed a remineralization of enamel when cheese or milk was used as a snack between meals. A similar result was found when the influence of milk and dairy product consumption and the progression of dental caries were studied [24]. Cheese was found to decrease the dental caries coefficient. Rat studies also showed an inhibitory effect of cheese on the metabolism or survival of cariogenic bacteria such as *Streptococcus mutans* [19]. Casein also plays an important role. Micellar casein selectively modifies the microbial composition of dental plaque [28]. Casein phosphopeptides react with high concentrations of calcium and phosphate to form calcium phosphate complexes. These complexes lead to remineralization of the enamel and today are incorporated in toothpaste, gels and chewing gum [9].

#### 4.2. Weight reduction or anti-obese effects

Obesity is an established health hazard, increasing the risk of coronary heart disease, hypertension, diabetes and some cancers, as well as other metabolic abnormalities [64, 69, 76]. The cost in Switzerland, due to obesity, adiposity and associated subsequent diseases, was calculated at CHF 2691 million in 2001 [82].

The main causes of this epidemic disease, i.e. poor nutrition, minimal physical activity, social and cultural or other

lifestyle factors as well as genetic predisposition are discussed. The recommended nutritional interventions for weight reduction vary among low-fat, low-carbohydrate and other models. When the low-fat approach is argued, milk, dairy products and especially (full-fat) cheese are usually condemned because of their high fat content. Therefore, dairy products are often omitted by people trying to lose weight.

Overweight women seem to benefit most from the intake of cheese: regular intake ( $\geq 1$  serving·d<sup>-1</sup>) of whole milk, sour milk or cheese was inversely associated with weight gain. No association was seen between a regular intake of less than 1 serving·d<sup>-1</sup> or an increase or decrease in the intake of dairy products. When adjusted for BMI, the findings remained significant for cheese and for whole milk and sour milk for normal-weight women only. Thus, Rosell et al. [75] concluded that the association between the intake of dairy products and weight change differed according to the type of dairy product and body mass status.

Calcium in food seems to play an important role in this relationship. Zemel et al. [115] found an unexpected side effect in a study in which they investigated the effect of calcium on blood pressure. Not only was there a significant decrease in blood pressure after increased calcium intake from 400 to 1000 mg, but there was also a significant reduction in body fat by 4.9 kg. These findings were confirmed in some further studies, but not in all [95, 103, 113]. Regardless of exercise group assignment, calcium (adjusted for energy intake) had a negative and vitamin A intake a positive correlation with the changes in total body weight and body fat over two years in young women aged 18 to 31. Thus, subjects with high calcium intake, corrected for total energy intake, and low vitamin A intake gained less weight and body fat over two years in this randomized exercise intervention trial [49].

The exact mechanism is still unclear, but it may be partly due to the formation of calcium and fatty acid complexes in the gut, preventing their absorption. Dietary calcium suppresses calcitriol, stimulates lipolysis and decreases adipocyte lipid accumulation [114]. Furthermore, milk and cheese are high in protein, which bestows them with a relatively high satiety value, helpful in a calorie-restricted diet [32, 95]. Additionally, total daily energy intake is significantly higher when high-carbohydrate, fat and protein foods are ingested as liquids rather than as solids [59]. Nevertheless, other bioactive compounds in dairy products such as CLA may also have an influence on weight control and body composition [15, 46, 107, 108]. However, the results in human studies are still not consistent [45, 61, 66, 91, 100].

Accumulation of abdominal body fat is associated with an even greater health risk than the same amount of fat deposited around the hips [5, 8, 44]. In an animal experiment the effects of Gouda-type cheese on biological markers of the metabolic syndrome were examined. The study revealed a significantly lower weight of mesenteric adipose tissue in cheese-fed rats on a 20% fat diet compared with rats fed a similar high-fat diet containing casein and butterfat. The amount of cholesterol in very low-density lipoprotein and the serum levels of low-density lipoprotein were lower in rats receiving the cheese diet. Thus, cheese consumption might have a beneficial suppressive effect on abdominal adipose accumulation, which is one of the known risk factors for the development of metabolic syndrome [35].

### 4.3. Anti-hypertensive property

In western countries hypertension is a major risk factor for both coronary heart disease and stroke. In several studies dairy products have shown a beneficial effect on

blood pressure, especially in mildly hypertensive subjects. Two main components seem to be relevant in this situation: calcium and bioactive peptides.

The inverse relationship between calcium intake and blood pressure was first suggested by several epidemiological surveys in the early 1980s, because populations with low calcium intake often had an increased prevalence of hypertension. Subsequent laboratory and clinical investigations provided further evidence for the association between calcium and blood pressure, but the results of these studies were often inconsistent [83, 92, 102].

A meta-analysis of 28 studies accomplished by Allender et al. [1] showed a significant decrease in systolic blood pressure with calcium supplementation, both for hypertensive individuals and for the overall sample. However, according to these authors, the effect is too small to designate the use of calcium supplementation for preventing or treating hypertension. The same conclusion was drawn [10] in a similar analysis of 33 studies between 1966 and 1994. On the other hand, a diet with (low-fat) dairy products seems to reduce the incidence of hypertension with a significant effect on primary prevention of cardiovascular diseases [53]. Besides calcium, potassium and magnesium also seem to have a beneficial effect on blood pressure. This is another reason why dairy products, as a good source of all three minerals, are recommended to reach the recommended daily allowance (RDA) of calcium [33, 50].

The randomized, controlled, clinical study “Dietary Approaches to Stop Hypertension Study” (“DASH”-Study) carried out between 1994 and 1996 demonstrated a dramatic blood pressure-lowering effect of a diet rich in dairy products, fruits and vegetables [2, 79]. Miller et al. [56] summarized in their survey that the consumption of dairy products, at the currently recommended level by expert panels, optimizes blood pressure

regulation in humans. Furthermore, failure to ingest adequate amounts of dairy products increases the risk of hypertensive heart disease. They draw their conclusions on the meta-analysis of observational studies as well as on randomized controlled trials, metabolic investigations, experimental studies of laboratory models of hypertension and basic research to identify biologically relevant mechanisms of how dairy product intake might optimize arterial pressure control. Recently published studies confirm the above-mentioned findings and show a beneficial effect of various dairy products on blood pressure [95]. Some results suggest an additional inverse association of dairy products and prevalent hypertension independent of dietary calcium [17, 78, 95].

Cheese is a rich source of bioactive peptides. Among these peptides, one of the most interesting and investigated biological functions is the angiotensin-converting enzyme (ACE)-inhibitory effect. ACE is a key enzyme in the regulation of blood pressure, because it enables the conversion of angiotensin I into the highly potent vasoconstrictor angiotensin II and inactivates the depressing action of bradykinin. By inhibiting the effect of ACE, these peptides have a positive influence on hypertension, although their effect is less pronounced than what has been observed with drugs based on the same principle. ACE-inhibiting peptides have been found in several food proteins [48]. Meisel et al. [54] list over 200 amino acid sequences derived from milk, animal (non-milk), plant and miscellaneous protein sources with an ACE-inhibitory effect. The chain length varies from 2 to 20 amino acids and the potency of these peptides is also extremely different. In cheese, these peptides are produced during secondary proteolysis through the action of proteinases and peptidases. Several studies have shown ACE-inhibitory activity in various cheese varieties with different bioac-

tive peptides being responsible for that effect (Tab. III) [27, 80, 94, 97]. Among these different ACE-inhibiting peptides, the tripeptides valyl-prolyl-proline (VPP) and isoleucyl-prolyl-proline (IPP) belong to the most potent ACE-inhibiting peptide group. They are easily absorbed by the intestine and it has been shown that peptides containing a C-terminal Pro-Pro sequence are rather resistant to further degradation by digestive proteases and peptidases [21]. VPP and IPP are encrypted in the  $\beta$ -casein of milk. Proteinases from the lactic acid bacteria *L. helveticus* have the potential to release these two peptides in fermented milk. Various in vivo experiments showed a hypotensive effect in spontaneous hypertensive rats fed with sour milk fermented with special strains of *L. helveticus* [51, 63, 67, 93], as well as in humans [29, 57, 62, 84, 104].

The fact that *L. helveticus* is a common strain used in cheese-making, and that during ripening intense proteolysis takes place, led to the assumption that cheese may also show ACE-inhibiting activity due to the formation of VPP and IPP. However, the quantitative determination of these two peptides in cheese was a problem. This problem has now been solved by the development of a method based on liquid chromatography with subsequent triple mass spectrometry (LC-MS<sup>3</sup>). The application of this method to the analysis of 44 traditional cheese varieties (Swiss and non-Swiss cheeses) showed that the concentrations of VPP and IPP varied widely from 0–224 mg·kg<sup>-1</sup> and 0–95 mg·kg<sup>-1</sup>, respectively. There was an increasing trend from low concentrations in soft cheese, average concentrations in semi-hard and hard cheeses and high concentrations in extra-hard cheeses [12]. A second study investigated the occurrence of the ACE-inhibiting tripeptides VPP and IPP in 11 cheese varieties of Swiss origin [11]. In individual samples, the total concentration of VPP and IPP

**Table III.** ACE-inhibiting di-, tri-, tetra- and pentapeptides found in different cheeses.

Peptide	Amino acids <sup>1</sup>	Cheese variety	Literature
Di-	QP, PP, FP, RI/RL	Spanish origin	[27]
Tri-	VPP, IPP	Swiss origin	[11, 12]
	FPE, IPY, PFP, PQL, AWY, PSE, EEL/EEL, RPK, MPI/MPL, REL, RPK	Spanish origin	[25, 27]
Tetra-	VRYL, HPIK, HQGL, NINE, ERYL, ENLL, EVLN, VRGP, GVPK, VRGP, GVPK, EVVR, GPIH, PEVP	Cheese-like system of caprine milk	[90]
	YQEP	Spanish origin	[26, 27]
Penta-	DKIHP, RPKHP, EIVPK, PQEVL, NENLL, NLLRF, VVVPP, TDVEK, PGPIH, PVEPF	Cheese-like system of ovine milk	[90]
		Spanish origin	[27]

<sup>1</sup> One-letter abbreviation of amino acids.

varied from 1.6 to 424.5 mg·kg<sup>-1</sup>, indicating that some cheese varieties contain VPP and IPP concentrations similar to fermented milk products with blood pressure-lowering capacities of commercial products sold nowadays. The results also indicate that different factors such as milk pretreatment and cultures, as well as scalding and ripening times, contribute to the concentration of VPP and IPP in cheese. Further studies are needed to determine the main influencing factor(s) to develop a cheese with constantly high concentrations of the two described bioactive peptides. In order to demonstrate the hypotensive effect of cheese containing significant amounts of VPP and IPP, it will be necessary to carry out *in vivo* studies in spontaneous hypertensive rats and/or hypertensive patients similar to those carried out with fermented milk products.

#### 4.4. Beneficial effect on bone health

The role of calcium in bone health is well documented and recognized [31]. As discussed above, cheese can provide a significant amount of calcium, especially in the diet of lactose-intolerant individuals.

Female adolescents, limiting the intake of dairy products because of self-perceived milk intolerance, have a significantly lower intake of calcium as well as a significantly lower spinal bone mineral content than female adolescents without perceived milk intolerance [52]. Kato et al. [43] could even show, in their experiments with rats, that milk calcium taken with cheese is even better absorbed than milk calcium taken without cheese. And as a consequence, the bone mineral density of the rats fed milk calcium with cheese was significantly higher than in the control group. Cheng et al. [14] supported the results of Kato et al. [43] in their study with 10- to 12-year-old children. Calcium supplementation with cheese resulted in a higher change in cortical thickness of the tibia than the placebo, or treatment with calcium supplementation in the form of pills with or without vitamin D. Cheese was significantly better than placebo treatment with respect to whole-body bone mineral density.

Besides calcium other cheese compounds such as magnesium and vitamin D also play an important role in building up bone mineral density and reducing

bone loss. However, phosphorus has a hypocalciuric effect, so that the consumption of cheese with its remarkable amount of phosphorus might have a negative effect on bone mineral density. Bizik et al. [7] could not confirm this hypothesis with their study, in which they doubled the consumption of phosphorus in healthy young men by the addition of cheese and milk. High phosphorus intake does not promote bone resorption if the calcium to phosphorus ratio is  $< 1:1.5$ , which is the case in cheese.

Besides calcium other cheese compounds such as magnesium and vitamin D and even some bioactive peptides also play an important role in building up bone mineral density and reducing bone loss. Recent clinical studies suggest that several anti-hypertensive drugs, especially ACE-inhibitors, reduced bone fractures, because angiotensin II, a potent vasoconstrictor, also affects bone by activating osteoblasts [85]. VPP, a small peptide, formed during fermentation of milk with *L. helveticus*, has been shown to possess ACE-inhibitory activity (see above).

In an animal study with ovariectomized rats, the group fed with *L. helveticus*-fermented milk significantly prevented bone loss by decreasing bone turnover and increasing bone mineral density [65]. VPP in water could not prevent bone loss and the authors concluded that this might be due to the poor bioavailability of the bioactive peptide in water. It is not clear whether the preventive effect of the fermented milk is due to VPP. Because VPP is known to have a lowering effect on blood pressure, these results show an interesting connection to a study by Metz et al. [55]. They investigated the relationship between blood pressure, dietary calcium and bone mass. The findings show that blood pressure was negatively related to bone mineral density and bone mineral content independent of age, BMI and calcium intake. The observational nature of the study precluded causal-

ity, which is supported by experimental data associating hypertension with calcium metabolism. Therefore, it is hypothesized that hypertension may be related to the risk of osteoporosis. At any rate, in females with primary hypertension, bone strength, although fitting for chronological age and body height, was lower than expected for body weight [70].

#### 4.5. Anti-carcinogenic effects

The World Cancer Research Fund and the American Institute for Cancer Research [112] have recently examined the literature on food and cancer. Cheese consumption was related to colorectal and prostate cancer. Eleven cohort studies and 25 case-control studies exist, showing a correlation between colorectal cancer and cheese. Due to inconsistency of the results, they declared that the evidence for cheese consumption as a cause for colorectal cancer was limited. Prostate cancer was discussed because of numerous associations between dairy product and calcium (dietary and supplemental) consumption in epidemiological studies. The report mentioned above evaluated 9 cohort studies, 12 case-control studies and 2 ecological studies for the relation between dietary calcium and prostate cancer. A dose-response relationship was apparent from cohort but not case-control data. However, a coherence of prostate cancer and calcium only correlates with diets very high in calcium ( $1.5 \text{ g}\cdot\text{d}^{-1}$  or more). Diets high in calcium are a probable cause of prostate cancer. According to the panel there is, however, limited evidence that high consumption of milk and dairy products is a cause of prostate cancer.

These findings could be explained by the presence of anti-carcinogenic compounds such as CLA and sphingolipids in cheese. Almost 20 years ago an initial study suggested an anti-mutagenic

activity of CLA. Since then considerable in vitro experiments and animal trials have been carried out concerning CLA inhibition of carcinogenesis. It is assumed that CLA is involved in various steps in all three stages of carcinogenesis, exerting its effect by modulation of cell proliferation and apoptosis, regulation of gene expression, influence on eicosanoid synthesis and metabolism, and anti-oxidative mechanisms [6]. Further studies will have to provide information on possible anti-carcinogenic effects in humans. Experiments have shown that the CLA concentration in blood can be enhanced by the consumption of CLA-rich cheese [36].

Another interesting group of lipids relating to the prevention of cancer are the sphingolipids. There are no human trials or epidemiological studies evaluating a protective effect on the development and progression of colon cancer. Based on the fact that sphingolipids reduce markers of colon cancer in animal trials and that their metabolites induce spontaneous cell death in human cancer cells, it is highly probable that sphingolipids also have anti-carcinogenic properties in humans [106]. Besides soybeans ( $189 \text{ mg}\cdot\text{kg}^{-1}$ ), the best sources of these lipids are milk, full cream, butter and cheese, containing 115, 490, 710 and  $995 \text{ mg}\cdot\text{kg}^{-1}$ , respectively. They provide about one-third of the total intake in countries with high dairy product consumption, such as Switzerland. Because of their amphiphile character and their distribution in the milk fat globule membrane, quantitative determination in milk products is very difficult [106, 109].

## 5. CONCLUSIONS

Cheese has a long history in the human diet to which it contributes a substantial amount of important nutrients; in particular, proteins, bioactive peptides,

amino acids, fat, fatty acids, vitamins and minerals. Research today is concentrated more and more on the influence of nutrition on human health. Calcium, which is present in large quantities in cheese, has been shown to have a positive effect on various disorders (hypertension, osteoporosis, obesity and dental caries). Besides calcium, other constituents with potentially positive effects on health are found, e.g. bioactive peptides, which also decrease hypertension. In humans, the possible anti-carcinogenic effects of specific lipids (CLA, sphingolipids) have not yet been investigated but animal studies suggest a certain potential. Cheese still has a negative image because of its fatty acid composition. However, research has uncovered ever more details, whereby these old convictions have started to waver. Further studies are needed both to confirm earlier results and clarify their mechanism as well as to discover further interesting cheese constituents and their effects. Besides all this scientific research, the inseparable tradition and enjoyment of cheese should not be forgotten. Cheese is more than the sum of its constituents.

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