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Review Article

Phosphatidylserine: A Well-Studied Cognitive Solution for Supplements and Functional Foods

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ABSTRACT

Phosphatidylserine is a structural component of cell membranes, which can be found in all biological membranes of plants, animals and other life forms. The human body contains about 30g of phosphatidylserine, close to half (~13 g) of which is found in the brain. Phosphatidylserine plays a vital role in several cellular processes, such as activation of cell-membrane bound enzymes, and is involved in neuronal signaling. Phosphatidylserine can also be found in human diet, though in the last decades it is estimated that average consumption levels have declined by approximately 50%. Phosphatidylserine has been extensively studied as a dietary supplement, mainly for cognitive health in various populations, from children with ADHD to elderly, healthy and diseased alike. Preclinical and clinical studies demonstrated that oral administration of phosphatidylserine is safe and well tolerated, and can improve cognitive functions, relieve daily stress, improve skin health, have benefits for those dealing with sports, and more. The physical traits of phosphatidylserine, such as the fact that it is an amphiphilic molecule or its lack of organoleptic problems, makes phosphatidylserine especially suitable for functional foods. Together with the growing consumer trend preferring functional foods over the traditional tablets and capsules, phosphatidylserine can be an interesting addition to foods for children, seniors, athletes and others.

Abbrevations

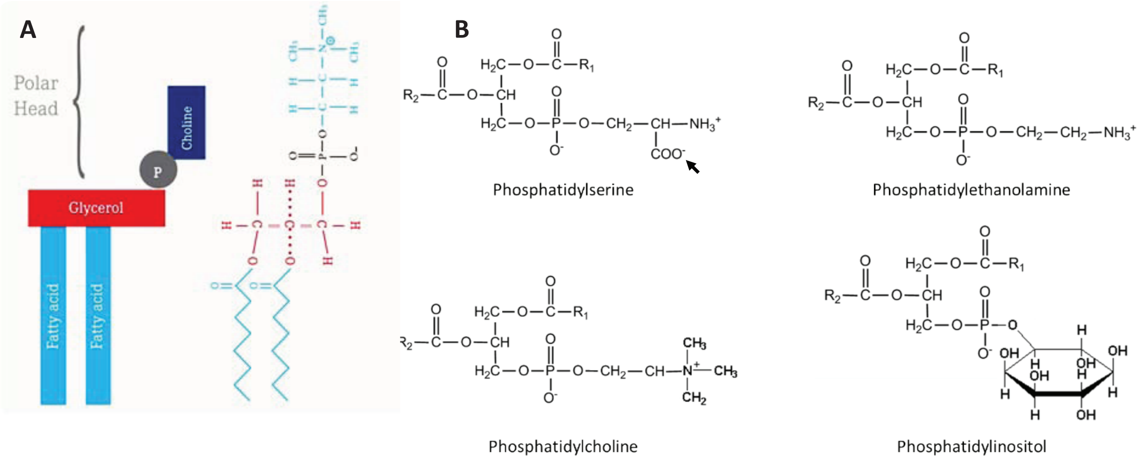
AAMI: Age Associated Memory Impairment; FA: Fatty Acid; ACTH: Adrenocorticotropic Hormone; PA: Phosphatidic Acid; ADHD: Attention Deficit Hyperactivity Disorder; PC: Phosphatidylcholine; ALA: Alpha Linolenic Acid; PE: Phosphatidylethanolamine; CK: Creatine Kinase; PKB: Protein Kinase B (Akt); CRH: Corticotropin-Releasing Hormone; PKC: Protein Kinase C; DAG: Diacylglycerol; PL: Phospholipids; DHA: Docosahexaenoic acid; PS: Phosphatidylserine; EPA: Eicosapentaenoic Acid

Introduction

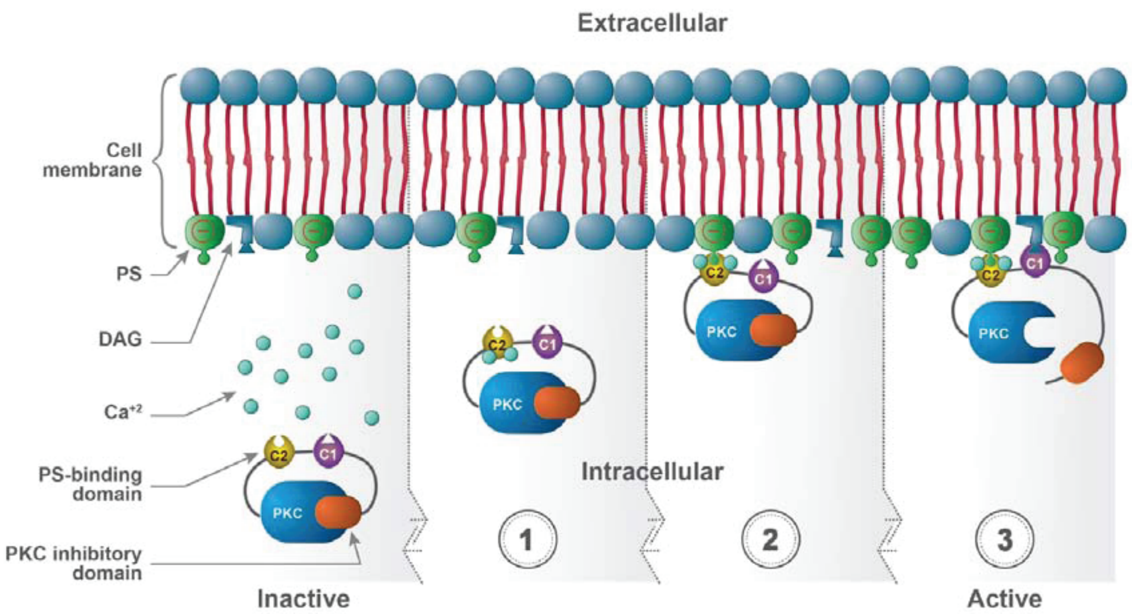
Phospholipids (PLs) are a family of important lipids composing the main building blocks of cell membranes. Each phospholipid consists of a glycerol backbone, which is bound to two fatty acids (FAs) and to a polar, water soluble, head group (Figure 1A). Due to the unique combination of hydrophobic FAs and hydrophilic head group, phospholipids are amphipathic molecules. This unique characteristic of phospholipids is what allows their function as building blocks of biological membranes. Of the primary PLs in the biological membrane, namely phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI) and phosphatidylserine (PS), phosphatidylserine is unique (along with PI) in that it carries a negative electric charge (Figure 1B), a charge which is responsible for many of the unique biological properties of PS (to be discussed next) [1]. Phospholipids, being part of the biological membrane, are also naturally found in foods. A human being first consumes PLs when it suckles from its mother, because human milk contains various PLs. Every natural food from a biological origin, animal and plant sources alike, contains PLs. Furthermore, due to the amphipathic nature of PLs, they are used in the food industry. For example, lecithin, made mainly of PC from various sources, is widely used as an emulsifier.

Biological role of PS within the brain

Phosphatidylcholine is the most abundant PL in all cell types, followed by PE. Compared to most tissues, the brain is enriched with another member of the phospholipid family, namely PS, which



Figures 1: A representation of a phospholipid (A, PC is represented) and chemical composition of the main phospholipids (B). Note the extra negative charge on PS (marked by a black arrow), thought to be responsible for many of its cellular functions.



Figures 2: PKC activation is PS dependent. PKC activation requires the following steps: 1. Ions of calcium released from internal repositories in response to external stimuli, bind to PKC, charging it with a positive charge and opening a cleft for PS binding; 2. The now positively charged PKC is attracted to the negatively charged PS. When PS binds to PKC, it anchors it to the membrane; 3. PS-dependent membrane anchoring leads to binding of another lipid member, diacylglycerol (DAG), which leads to release of an inhibitory domain of PKC, making it active [12].

is up to 6 times more concentrated in the brain relative to other tissues [2]. This intriguing fact, identified in the 1940's by Spanish researcher Jordi Folch Pi [3,4], brought researchers to wonder about the requirement and function of this excessive concentration of PS, and led to many years of research.

As mentioned before, unlike most other phospholipids, PS is a negatively charged molecule (Figure 1B), and many of the mechanisms by which PS is involved in cellular and neurological functions are based on that fact [1]. PS was shown to participate in key signaling pathways in the neuronal system, and to bind positively charged proteins within the cytosol, thus directing them to the membrane where they are required [5]. For example, studies have shown that in neuronal cells and tissues, translocation of protein kinase B (PKB, also known as Akt) to the membrane, resulting in its activation, is PS-dependent [6], and its activation was shown to promote the survival of neurons. PS was also shown to be involved in activation of other cellular enzymes, such as protein kinase C

(PKC) [5], activation of which is known to be essential for cognitive processes such as memory and learning [7]. The dependence of PKC activation on PS is schematically presented in Figure 2. PKC is known to phosphorylate several proteins, such as MARCKS, GAP-43 [8], and the NMDA receptor [9], all of which are known to be involved in information storage processes. In a pre-clinical study, PKC activity within the brain was found to diminish with age [10], parallel to age associated deterioration in cognitive abilities. A pre-clinical study demonstrated that intake of PS increases PKC levels and activity in the brain [11], which may partly explain the positive effects of PS on memory and cognition.

Phosphatidylserine as a dietary ingredient

A human being will consume PS for the first time when he or she suckles from the mother, as human milk contains PS [13]. The existence of PS in human breast milk may be linked to cognitive development of the infant, as consumption of PS at an early stage was shown, in animal studies, to promote cognition at adulthood [14,15]. Later in life, as a component of biological membranes, PS is ingested regularly as part of normal human diet. In principle, all foods of biological origin must contain at least some PS. The foods most rich in PS are certain fish as well as animal innards. In the last few decades human diet went through profound changes, and Western diet may now be the most prominent diet globally, at the expense of more traditional diets. One of the outcome of these changes is that consumption of PS through regular diet has declined from an average of 250 mg per day during the 1980's, to less than 130 mg/day today [16]. Today, most people get their PS through supplementation.

Clinically proven benefits of PS ingestion

Approximately 60 clinical studies tested the effects of PS consumption in humans. Studies were performed on healthy people as well as on diseased populations with various illnesses leading to cognitive decline (i.e. Alzheimer's disease). These studies mainly tested the benefit of PS consumption on the cognitive capabilities of the tested subjects, but also on mood and stress. Additional studies were conducted on young people using models of sports, and yet others tested effects of PS consumption on skin parameters. The effects of PS as exemplified in these studies are presented in detail later on. The significant effect of PS on cognition and on brain health has led some to name it "brain nutrient" [17].

Phosphatidylserine in functional foods

Phosphatidylserine has characteristics making it suitable for many foods, but not all. For example, due to its amphipathic nature PS is mainly suitable for foods which are water and oil emulsions, such as dairy products or chocolates. On the other hand, PS is not water soluble and as such cannot be easily used in beverages. As with any ingredient of biological origin, stability can be an issue. Phosphatidylserine heat-stability is limited to low-heat foods (exact heat stability depends on the food matrix) and to those were heat exposure is relatively short. Nonetheless, PS is stable in pasteurization processes [exposure up to 100 degrees Celsius for 30 minutes led to less than 10% degradation when PS was added to milk (internal data)]. Furthermore, its acid-base stability is significant, from pH=3 to pH=11 (internal data). Phosphatidylserine is thus suitable for dairy products such as yogurts, fresh milk and dairy-based powders.

Phosphatidylserine as a Dietary Supplement

Origins of PS as a dietary supplement

Phosphatidylserine has been available for human consumption since the 1980s [18,19]. Historically, PS was extracted from bovine cortex, and many of the early studies using PS were conducted using this form of PS [18-22]. in this form, PS was developed as a drug, not dietary supplement, and studies were conducted in patients with Alzheimer's disease, senile dementia and other neurodegenerative diseases [18,19,22-24]. However, with the outbreak of the Bovine Spongiform Encephalopathy disease (BSE or "mad cow disease"), bovine cortex PS became unavailable.

Sources of PS

Since the 1990s [25,26], PS from various alternative sources, mainly from soy but also from sunflower, fish, krill, and squid, became available. These PS sources are synthesized, not extracted, by enzymatic transphosphatidylation of PC from source lecithin with the amino acid L-Serine. The various sources of PS differ from one another by the FA composition. For example, fish PS is enriched with the fatty acid DHA, an omega-3 FA, while krill PS contains EPA, another type of omega-3 FA. Plant sources of PS, namely soy PS and sunflower PS, contain the essential FA plant omega-3, alpha-linolenic acid (ALA) (internal data).

Phosphatidylserine from krill was developed as a medical food (as defined in the USA) for children with ADHD. Consumption of krill PS was shown to lead to improvement in the children attention as well as hyperactivity [27,28]. Krill PS was also found to be effective in adolescents suffering from ADHD (in press). Fish PS is the source of PS most similar to bovine-cortex PS, in that it also has DHA bound to the glycerol backbone. Fish PS was developed for elderly suffering from Mild Cognitive Impairment (MCI) [29-31]. For use in functional foods, however, mainly PS from plant sources is suitable, due to its almost neutral organoleptic properties. PS from animal sources has, due to the omega-3 content, organoleptic issues making it less suitable for food applications. Thus, the next section will discuss mainly findings from clinical studies conducted on plant PS.

Health benefits of PS consumption

The effects of PS consumption on the human body, especially on the brain, were investigated in a large number of clinical and pre-clinical studies. Clinical studies were conducted in various populations, from children with ADHD, through young adults and all the way to elderly. The main outcomes of these studies show that ingestion of PS has beneficial effect on the brain, leading to improved memory and cognitive capabilities. Ingestion of PS was also shown to reduce stress and to improve mood, to improve skin health and to improve various aspects of sport outcomes. Following, some of the findings from the many studies testing effects of PS consumption will be described.

Consumption of PS leads to improved cognitive capabilities

Gindin et al. [26] were the first to report the cognitive effects of soy PS in a clinical study. In their randomized, double blind, placebo controlled study, 57 elders aged 60-80 with complaints of memory decline (defined as Age Associated Memory Impairment or AAMI) were given 300 mg soy PS per day or placebo for a period of 3 months.

The main findings of the study were that both memory (using the Wechsler test) and mood (using the List of Depression Symptoms score) were significantly improved following administration of soy PS.

Another randomized, double-blind, placebo control study, was conducted in 79 Japanese elders with memory complaints (MCI). The efficacy of soy PS (100 mg/day or 300 mg/day) was evaluated over 6 month's supplementation, followed by 3 months of non-supplemented follow-up period. PS was found to be safe and no adverse events were reported. In subjects with relatively low cognitive score at baseline, the memory scores following PS treatment were significantly increased compared to baseline, while memory scores of the placebo group remained unchanged. The memory improvements in the soy PS-treated groups were mostly attributed to the increase in delayed verbal recall and memory abilities [32]. A dose of 100 mg/day was found to be sufficient for the noted improvement in memory. Interestingly, 3 months after termination of the supplementation period, the improvement in memory of those taking PS was maintained, demonstrating that the effects of PS are sustained (Figure 3).

The benefits of soy PS for cognition are not unique to the elderly. A dose of 100 mg/day soy PS was also demonstrated to improve cognitive performance in 120 students aged 17-18 who were randomized to receive either 250 ml milk supplemented with 100 mg PS (milk and other dairy products, an emulsion of oil in water, are especially suitable for inclusion of PS) or 250ml un-supplemented milk (placebo) for 40 days. Cognition was assessed by clinical memory scale with computerized tests. Various aspects of memory and learning were improved in the PS supplementation group. Improved domains included directed memory, associative learning, free memory of images, recognition of meaningless figures and portrait features-linked memory [33]. This study demonstrated that PS beneficial effect is not limited to the elderly population but may also lead to improved cognitive performance and, possibly, academic achievements in young populations as well. This study is an example that the inclusion of PS in milk-based products retains the effectiveness of PS and its beneficial properties.

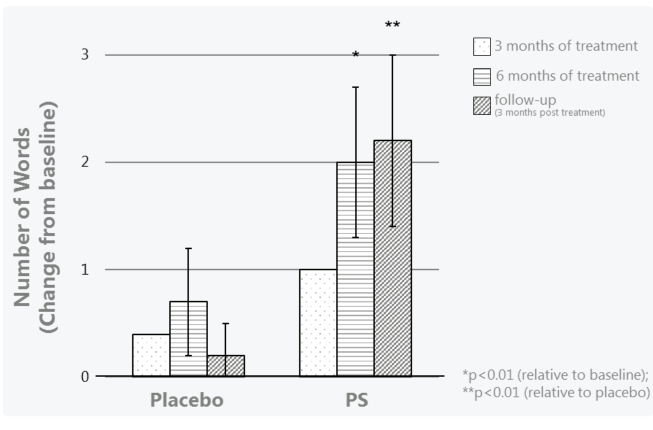
Consumption of PS blunts the increase in stress-related hormones

Stress can be caused by either mental or physical factors. Whether transient or chronic, stress can have detrimental effects on the human body [34-36]. The body reacts to stress by activation of the hypothalamic–pituitary–adrenal axis, a series of hormonal response, each affecting the next, aimed to strictly regulate the body's reaction to stress [37]. The key players in this hormonal cascade are the corticotropin-releasing hormone (CRH), produced and secreted by the hypothalamus; release of CRH leads to the release of adrenocorticotropic hormone (ACTH), produced by the pituitary gland; release of ACTH into the blood stream leads to release of cortisol, produced by the adrenal gland (in the kidneys). As part of a regulatory feedback mechanism, increase in ACTH blocks further production of CRH, while increased production of cortisol blocks further production of ACTH [37]. Cortisol, the terminal product of the cascade, is a glucocorticoid hormone which alleviates stress by several functions, among which are increase of blood sugar, suppression of the immune system, and aid in fat, protein and carbohydrate metabolism [38,39]. Prolonged increase in cortisol can also have deleterious effects, among them is proteolysis and muscle wasting, and decreased bone formation [38,39].

Already during the early 1990s, Monteleone et al published a series of studies demonstrating that consumption of bovine-cortex PS is effective for the relief of stress. In the published studies, Monteleone first tested various lipids for their ability to relieve stress induced by physical exercise [40], and then, once PS was identified as the most effective component tested, described the mechanism by which PS attenuated the reaction to stress [41]. The mechanism described by Monteleone was the blunting of the increase in blood levels of the stress-related hormones ACTH and cortisol. Since the publication of these preliminary findings, others have also looked at the anti-stress effects of soy PS, in models describing mental (such as job interview [42] or mathematical exam [43]) or physical (following moderately intense exercise [44]) stress.

In a double blind, placebo controlled study, a mock job interview was used to cause mental stress. Eighty subjects were given a complex of soy PS + PA (phosphatidic acid, an impurity often left during production of PS, with no known effect, as a single ingredient, on markers of stress) at a dose-response from 200 mg/day up to 800 mg/day (amount of PS alone), vs. placebo, for a period of 4 weeks. Samples of blood and saliva were taken before the interview, after interview completion and at intervals of 10-15 minutes up to 1 hour after the interview. Levels of ACTH (in the blood) and cortisol (blood and saliva) were monitored. The results show that both ACTH and cortisol levels were significantly reduced compared to the placebo [42].

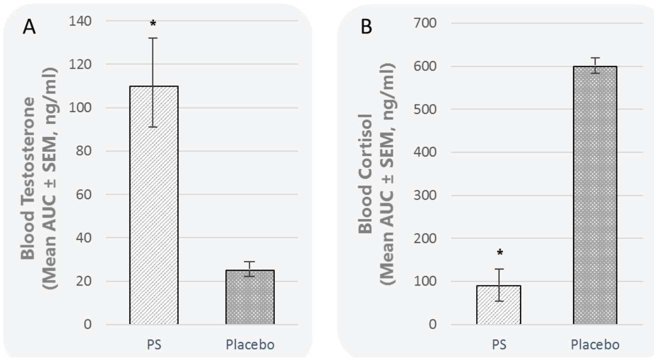
Stress can also be increased by physical activity. In fact, due to the detrimental effects of stress and cortisol on muscles and bones, many of those dealing with sports are actively seeking ways to control their cortisol levels, and PS ingestion may very well offer a solution. In a double-blind, placebo-controlled, crossover clinical study, 10 healthy male subjects were assigned for 10 days' ingestion of 600 mg per day soy PS or placebo. Blood samples were taken at rest, after a 15-minute moderate intensity exercise protocol on a cycle ergometer, and during a 65-minute passive recovery. Plasma samples were tested for cortisol as well as other hormones and factors. Results of the study



Figures 3: Effects of soy PS supplementation on memory of elderly participants with MCI was tested over 6 months with 3 months follow-up. Ingestion of 100 mg/day soy PS was shown to be effective even 3 months after termination of the study (grey bars). Cognitive test: Delayed Word Recall of the revised version of Hasegawa's Dementia Scale [32].

demonstrate that cortisol levels were significantly reduced in those taking PS (Figure 4B) [44]. Interestingly, in the same study PS was shown to affect another hormone, testosterone, which was increased significantly in those taking PS (Figure 4A). This latter fact may suggest that intake of PS can affect other hormones as well, though a more thorough investigation of this effect is necessary.

Another study shows that adding soy PS to food is effective (we have already seen that adding PS to milk was effective). In this double blind, placebo controlled study, effects of soy PS ingestion on golf performance were tested. Twenty healthy adults (mean age ~32) received daily supply of nutrition bar containing 200 mg soy PS, or a placebo bar, for 42 days. The measures were perceived stress, heart rate and quality of ball flight. The perception of stress improved in the PS group though this result did not reach statistical significance (p=0.074). The number of good ball flights was significantly increased in the PS group, but not in the placebo group, an improvement which was attributed to the reduction in stress felt by the golfers. Heart rate was not affected by consumption of the PS-containing bar [45].

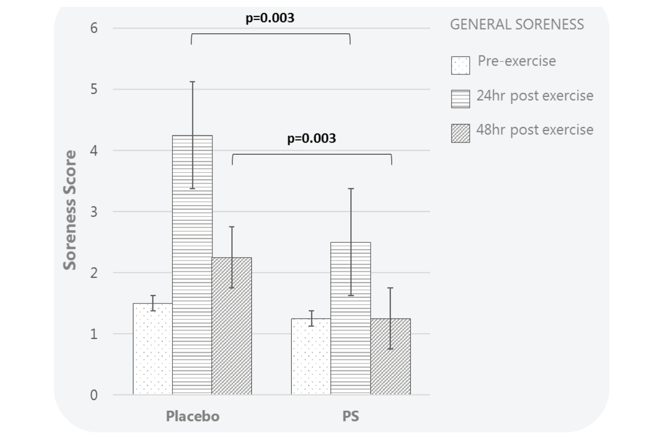


Figures 4: Ingestion of soy PS affects blood levels of hormones. Levels of one hormone, testosterone, were increased (left figure), while those of another, cortisol, were reduced (right figure) following intake of PS. Shown is Area Under the Curve (AUC) of testosterone and cortisol levels, measured in a serial venous blood samples taken at rest, after a 15 minute moderate intensity exercise protocol on a cycle ergometer and during a 65 minute passive recovery [44].

Consumption of PS is beneficial for those dealing with sports

Sports nutrition may be one of the best examples for a functional food industry, as almost all sports nutrition products, either powders, bars, shakes or others, may be considered functional, pertaining to assist in muscle buildup, to give energy, to allow trainers better performance, better recovery and more. As we've seen above, soy PS was shown to affect levels of two hormones, cortisol and testosterone, both with relevance to sports: testosterone is the main androgen in the male body, thus an increase in this hormone is linked to increased muscle size and muscle strength, and to increase in lean body mass [46]; The testosterone to cortisol ratio is considered a marker for muscle recovery [44]. As ingestion of PS led to a reduction of cortisol, concurrent to an increase in testosterone, the testosterone to cortisol ratio increased quite significantly, indicating PS ingestion can be useful for this muscle recovery. A study published in 2013 in *Nature* may suggest a mechanism by which PS can affect muscle recovery. In said study, a cell-surface receptor for PS, called BAI1, was shown to be involved in promotion of myoblast fusion, with important implications for muscle development and repair [47]. While this study was not an intervention study, it may suggest a mechanism of action by which PS may assist in muscle recovery.

Phosphatidylserine ingestion leads to reduced muscle soreness: Muscle recovery can be measured by assessing muscle soreness. Muscle soreness was tested in subjects undergoing a training session involving intermittent running, a model aimed to mimic a game of soccer. Following 10 days' supplementation with 750 mg/day soy PS or placebo, subjects were asked to fill questionnaires asking about soreness in various muscles, over 48 hours' time. Those in the PS group felt reduced soreness in the quadriceps and hamstring, as well as in general soreness, relative to those in the placebo group, both 24 hours and 48 hours after training (Figure 5) [48].

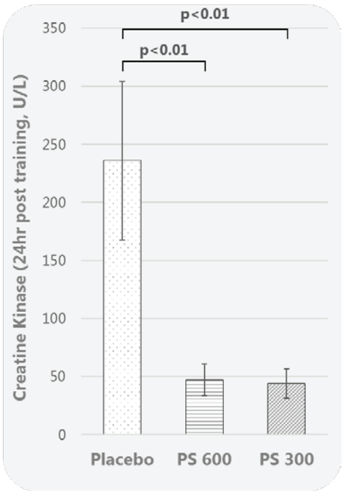


Figures 5: Soy PS intake reduces perception of muscle soreness, both 24 and 48 hours after training, as was found in a clinical study mimicking a model of soccer. Shown is the score for General Soreness [48].

Phosphatidylserine ingestion leads to reduced muscle damage following training : Creatine kinase (CK) is an important enzyme in tissues requiring high energy consumption, such as the brain, spermatozoa and muscles. When found in the blood, however, high levels of CK are indicative of damage in CK-rich tissues, especially muscle damage. The muscle-protective properties of soy PS consumption were demonstrated in a small clinical study which was part of an academic dissertation. In that double blind, placebo controlled, crossover study, participant consumed high level of soy PS (600 mg/day), low levels of soy PS (300 mg/day) or placebo, for a period of 15 days. Following 90-minute run blood samples were taken and CK levels measured. The findings of the study clearly point to a significant (about 66% reduction, p<0.01) reduction in CK levels following intake of PS (Figure 6) [49].

As we see, ingestion of soy PS may have a muscle protecting effect and may lead to improved recovery. Interestingly, however, the benefits of soy PS ingestion for those dealing with sports go beyond those of muscle protection.

Phosphatidylserine ingestion leads to increased time to exhaustion: A study conducted by a UK-based group tested the effects of soy PS ingestion on endurance. In this double blind, placebo controlled study, 14 healthy and trained males received either 750 mg soy PS per day or placebo for 10 days. Subjects underwent a cycling exercise prior to and following the supplementation period. Endurance was measured using a cycle ergometer at an escalating



Figures 6: Soy PS intake, either 300 mg/day or 600 mg/day, leads to reduction in blood levels of Creatine Kinase (CK), indicating a possible reduction in muscle damage [49].

intensity ending in a bout of 85% $VO_{2\ max}$. The main finding of this study was that following soy PS supplementation, time to exhaustion at 85% $VO_{2\ max}$ increased by 25%, while in the placebo group there was no such change [50]. In another double blind, placebo controlled study, 16 male soccer players received either 750 mg soy PS per day or placebo for 10 days. Subjects underwent an exercise of intermittent running, a model aimed to mimic an actual soccer game . Time to exhaustion increased 4.2% in the soy PS group compared to 3.7% reduction in the placebo group. The difference did not reach statistical significance (p=0.084), but the trend was strong [48].

To summarize this part, consumption of soy PS is shown to have many benefits for those dealing with sports. These benefits include physical and mental effects and allow users to enjoy both aspects. Furthermore, the hormonal regulating aspects of PS consumption, reducing cortisol and increasing testosterone (explained in detail above) may have direct benefits for athletes.

Consumption of PS has skin-protective properties

Healthy aging may inherently be accompanied by changes in skin structure and appearance, changes which may be accentuated by environmental factors such as smoking, air pollution and UV exposure. Prolonged exposure of the skin to UV irradiation results in depletion of collagen, an important structural protein crucial for proper structure of the skin. Depletion of collagen, formation of wrinkles, reduced moisture and formation of spots and discolorations are collectively termed photodamage. These effects are the result of not only external events but also of changes occurring within the skin, some as part of the natural protection mechanisms of the skin and others as a result of aging. Internal effects include breakdown of collagen, thickening of the epidermal layer and a decrease in skin hydration level.

Several studies, using *in vitro*, pre-clinical and clinical settings, studied the effects of soy PS, applied topically or ingested, on skin health. These studies demonstrated that the main effect of soy PS ingestion is in decrease of skin damages following UV exposure. PS was found to affect skin cells and live skin in a number of ways, such as decreasing the expression of collagen degrading enzyme MMP-1 and increasing the production of procollagen; preventing thickening of the epidermis; and decreasing pro-inflammatory biomarkers [51-53].

The effect of oral administration of soy PS was tested in a double blinded, placebo-controlled trial which included 63 healthy subjects aged 40-60 supplemented with 300 mg/day soy PS or placebo for 12 weeks [52]. Following 6 and 12 weeks of treatment the participants were evaluated for skin moisture, wrinkle number and wrinkle depth. A global photodamage score was used to assess the skin damage of the participants. The study showed that the photodamage score was improved only in subjects who received PS, with a trend effect after 6 weeks (p=0.084) and significant improvement after 12 weeks (p=0.001). Skin roughness and skin moisture were also significantly improved [52].

The benefits of soy PS consumption on skin health make it suitable for a growing trend of "beauty from within", orally ingested ingredients and foods with a cosmetic effect. In some cases, this is done through "beauty drinks", and PS can be considered as an addition to this form of consumption.

Usage of PS in Functional Foods

The food industry is diverse and varied from segment to segment. As such, there is little in common between production of dairy products and production of bakery products, for example. Thus, careful consideration is required when considering to add PS to a specific food product. The characteristics of PS make it attractive for food fortification. For example, it is organoleptically inert, and does not affect taste, smell or mouth feel. Stability of PS in foods is limited for low-heat products (up to 100 degrees Celsius), but not to acid products as its acid-base stability is quite good over a wider range of pH levels (~3-11, internal data). Being a lecithin-like ingredient, PS can bind both water and oil, but is soluble in neither. As a lecithin, oil in water emulsions are especially suitable for inclusion of PS, while 100% water or 100% oil products are less fitting. PS has been successfully introduced to dairy products, both liquid-based and powder-based, and for chocolates. On the other hand, adding PS to bakery products can be challenging, as PS is not stable in the heating used when baking. In these kinds of products PS can be added post-baking, avoiding the heat issue.

In some of the many clinical studies where PS was tested, it was given to subjects as part of a food item. These food items include milk [33], nutritional bar [45,54] and candies [55]. In all of these studies PS was found to be effective, attesting to the stability of PS in these food items and exemplifying that adding PS to foods is indeed an effective and easy way to supplement this unique ingredient.

Discussion

The many benefits of PS ingestion, along with the possibility of adding it to many types of foods, makes it an excellent ingredient to be included in functional foods, for the general population as well as for specific sub populations such as elderly, children, athletes, students, women and more. Globally, PS is known mainly for its cognitive enhancing properties, which are backed by significant clinical database and pre-clinical studies. Numerous dietary supplements contain PS, with claims pertaining to improve cognition, memory and brain health. Today, however, more and more brands are also using PS in foods, making these foods functional.

Changes in the nutrition habits over the last few decades have led to significant reduction in the nutritional content of human diets all over the world. These nutrients range from vitamins, through healthy lipids (such as omega-3 fatty acids) and to many other nutrients. The same developments in food production that led to reduction in consumption of omega-3 fatty acids [56] also led to a dramatic reduction in consumption of PS through the diet. Being an omnipresent phospholipid in cell membranes, PS is consumed naturally in human diet. Nonetheless, the inclusion of plant oils, instead of animal fat sources previously used, the process which is considered as the number one reason for reduction in consumption of omega-3 fatty acids, also led to a significant reduction in consumption of PS. If during the 1980's each person used to consume, on average, 250 mg per day of PS through regular diet, today it is estimated that PS consumption has reduced by about half, to 130 mg/day, and in some populations, mainly vegans, vegetarians and children, this estimate is even much lower [16]. To most people, the only way to enrich their diet with PS is through supplementation with dietary supplements or functional foods.

Due to consumer trends, as well as economic and cultural habits, many people across the world do not consume dietary supplements. In some countries the phenomena of "pill fatigue", due to consumption of large number of pills (supplements and drugs alike), is taking root and consumers are actively seeking alternatives to supplementing their diet with various nutrients. Other countries, most noticeably in South-East Asia, due to cultural, habitual and economic reasons, consume some dietary nutrients only when included in foods. Moreover, most supplements are not suitable for children, or not appealing to their parents. Thus, many children, whose modern diet is poor in many nutrients important to their physical and mental development, are getting these nutrients only through fortified or functional foods.

Inclusion of PS in functional foods may have many benefits for consumers, from improved cognition [26,32,33], reduction of stress [40-42], improved mood [8,57], benefits for skin health [also known as "beauty from within", [52]] and benefits for those dealing with sports [44,45,48-50]. In some of the many clinical studies where PS effects were tested, PS was supplemented through various foods fortified with PS. Types of foods included in these studies include milk [33], candies [55,58] and nutritional bars [45]. The effectiveness of ingesting PS, as shown in these studies, attest to the effectiveness of adding PS to foods.

From the clinical database it is clear that PS is safe and effective ingredient. Phosphatidylserine effects are accumulating, as it is effective when consumed over at least 40 days, and the longer it is consumed the more evident are the effects. After sufficient consumption, however, the effects are sustained for at least three months [32], and by that PS is different than other cognitive ingredients which can be found in the market. Consumption of PS is considered to be very safe, at least up to consumption of 800 mg/day [59]. In the many studies were soy PS was ingested, only 1.2% of subjects reported any side effects, all related to GI discomfort and all passing within a day. For comparison, for two of the most commonly used dietary supplements, omega-3 fatty acids and vitamin E, GI problems are reported in 6.3% and 3.3% of subjects, respectively [60]. Many of the studies testing effects of PS were conducted in diseased population, thus many of the participants were taking additional drugs related to their illness. In all these studies no drug-drug interactions were reported, and no contraindications issued. At least one pilot study actually suggests that intake of PS in combination with drugs may enhance the effectiveness of certain drugs. In that study, a formula, containing PS blended with omega-3, was given to patients with Major Depressive Disorder, treated with anti-depressant drugs but not reacting to them for at least 6 months. The PS-containing formula was given on top of the medication. Many of the study participants showed significant improvement after taking the formula [57]. Whether this effect is due to consumption of PS, of omega-3 or their combination, requires further research.

To conclude, consumption of PS has been shown to be safe and to benefit many aspects of human health, first and foremost cognitive health. Adding PS to foods to make them functional may have significant benefits for consumers whose current daily diet is low in this important nutrient, and who cannot, or will not, consume PS through regular diet or through supplementation of the regular diet with dietary supplements. The properties of plant PS, such as lack of taste or smell as well as emulsifying properties, along with the many benefits for consumers, make PS an attractive ingredient for functional foods.

Conflict of Interest

Itay Shafat is an Employee of Frutarom Health, a global supplier of Phosphatidylserine.

References

1. Yeung, T., Gilbert, GE., Shi, J., Silvius, J., Kapus, A., Grinstein S. (2008) Membrane phosphatidylserine regulates surface charge and protein localization. Science, 319(5860): 210-213.
2. Svennerholm, L. (1968) Distribution and fatty acid composition of phosphoglycerides in normal human brain. J Lipid Res, 9(5): 570-579.
3. Folch, J. (1948) The chemical structure of phospatidyl serine. J Biol Chem, 174(2): 439-450.
4. Folch, J. (1949) Complete fractionation of brain cephalin; isolation from it of phosphatidyl serine, phosphatidyl ethanolamine, and diphosphoinositide. J Biol Chem, 177(2): 497-504.
5. Newton, AC. (1995) Protein kinase C: structure, function, and regulation. J Biol Chem, 270(48): p. 28495-28498.
6. Akbar, M., Calderon, F., Wen, Z., Kim, HY (2005) Docosahexaenoic acid: a positive modulator of Akt signaling in neuronal survival. Proc Natl Acad Sci U S A, 102(31): 10858-10863.
7. Sun, MK., Alkon, DL. (2010) Pharmacology of protein kinase C activators: cognition-enhancing and antidementic therapeutics. Pharmacol Ther, 127(1): 66-77.
8. Gianotti, C., Porta, A., De Graan, PN., Oestreicher, AB., Nunzi, MG. (1993) B-50/GAP-43 phosphorylation in hippocampal slices from aged rats: effects of phosphatidylserine administration. Neurobiol Aging, 14(5): 401-416.
9. Borghese, CM., Gomez, RA., Ramirez, OA. (1993) Phosphatidylserine increases hippocampal synaptic efficacy. Brain Res Bull, 31(6): 697-700.
10. Sharma, D., Sethi, P., Hussain, E., Singh, R. (2009) Curcumin counteracts the aluminium-induced ageing-related alterations in oxidative stress, Na+, K+ ATPase and protein kinase C in adult and old rat brain regions. Biogerontology, 10(4): 489-502.
11. Lee, MH., Bell, RM. (1992) Supplementation of the phosphatidyl-L-serine requirement of protein kinase C with nonactivating phospholipids. Biochemistry, 31(22): 5176-5182.

12. Bell, RM., Burns, DJ. (1991) Lipid activation of protein kinase C. J Biol Chem, 266(8): 4661-4664.

13. Bitman, J., Wood, DL., Mehta, NR., Hamosh, P., Hamosh, M. (1984) Comparison of the phospholipid composition of breast milk from mothers of term and preterm infants during lactation. Am J Clin Nutr, 40(5): 1103-1119.

14. Ammassari-Teule, M., Fagioli, S., Maritati, M., Populin, R., Pavone, F. (1990) Chronic administration of phosphatidylserine during ontogeny enhances subject-environment interactions and radial maze performance in C57BL/6 mice. Physiol Behav, 47(4): 755-760.

15. Fagioli, S., Castellano, C., Oliverio, A., Pavone, F., Populin, R., Toffano, G. (1989) Phosphatidylserine administration during postnatal development improves memory in adult mice. Neurosci Lett, 101(2): 229-233.

16. Hamm, M. (2002) Nutritional-scientific statement on the change of nutritive provision with phosphatidylserine.

17. McDaniel, MA., Maier SF., Einstein, GO. (2003) “Brain-specific” nutrients: a memory cure? Nutrition, 19(11-12): 957-975.

18. Palmieri, G. (1987) Double blind controlled trial of phosphatidylserine in patients with senile mental deterioration. Clinical Trials Journal, 24(1): 73-83.

19. Villardita, C. (1987) Multicentre clinical trial of brain phosphatidylserine in elderly patients with intellectual deterioration. Clinical Trials Journal, 24(1): 84-93.

20. Cenacchi, T., Baggio, C., Palin, E. (1987) Human tolerability of oral phosphatidylserine assessed through laboratory examinations. Clin trials J, 24: 125-130.

21. Crook, TH., Feher, EP., Larrabee, GJ. (1992) Assessment of memory complaint in age-associated memory impairment: the MAC-Q. Int Psychogeriatr, 4(2): 165-176.

22. Crook, TH., Tinklenberg, J., Yesavage, J., Petrie, W., Nunzi, MG., Massari, DC. (1991) Effects of phosphatidylserine in age-associated memory impairment. Neurology, 41(5): 644-649.

23. Cenacchi, T., Bertoldin, T., Farina, C., Fiori, MG., Crepaldi, G. (1993) Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. Aging (Milano), 5(2): 123-133.

24. Crook, T., Petrie, W., Wells, C., Massari, DC. (1992) Effects of phosphatidylserine in Alzheimer’s disease. Psychopharmacol Bull, 28(1): 61-66.

25. Crook, T. (1998) Treatment of age-related decline in cognitive capacities: The effects of phosphatidylserine, in Anti-Aging Medical Therapeutics,, Katz, RM, and Goldman, Editors. 20-28.

26. Gindin, J. (1995) Effect of soy lecithin phosphatidylserine (ps) complex on memory impairment and mood in the functioning elderly Unpublished Report. Lipogen, Ltd.; Israel.

27. Manor, I., Magen, A., Keidar, D., Rosen, S., Tasker, H., Cohen, T., et al. (2013) Safety of phosphatidylserine containing omega3 fatty acids in ADHD children: a double-blind placebo-controlled trial followed by an open-label extension. Eur Psychiatry, 28(6): 386-391.

28. Manor, I., Magen, A., Keidar, D., Rosen, S., Tasker, H., Cohen, T., et al. (2012) The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: A double-blind placebo-controlled trial, followed by an open-label extension. Eur Psychiatry, 27(5): 335-342.

29. Vakhapova, V., Cohen, T., Richter, Y., Herzog, Y., Kam, Y., Korczyn, AD. (2014) Phosphatidylserine containing omega-3 Fatty acids may improve memory abilities in nondemented elderly individuals with memory complaints: results from an open-label extension study. Dement Geriatr Cogn Disord, 38(1-2): 39-45.

30. Vakhapova, V., Richter, Y., Cohen, T., Herzog, Y., Korczyn, AD. (2011) Safety of phosphatidylserine containing omega-3 fatty acids in non-demented elderly: a double-blind placebo-controlled trial followed by an open-label extension. BMC Neurol, 11: 79.

31. Vakhapova, V., Cohen, T., Richter, Y., Herzog, Y., Korczyn, AD. (2010) Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in non-demented elderly with memory complaints: a double-blind placebo-controlled trial. Dement Geriatr Cogn Disord, 29(5): 467-474.

32. Kato-Kataoka, A., Sakai, M., Ebina, R., Nonaka, C., Asano, T., Miyamori, T. (2010) Soybean-derived phosphatidylserine improves memory function of the elderly Japanese subjects with memory complaints. J Clin Biochem Nutr, 47(3): 246-255.

33. Yong, T., Qianyong, Z., Mantian, M., Gang, H., Jing, W. (2011) Research on human memory enhancement by phosphatidylserine fortified milk. Chongqing Medicine, 40(30): 3022-3023.

34. APA. Impact of Stress. 2012; Available from: http://www.apa.org/news/press/releases/stress/2012/impact.aspx.

35. Lovallo, WR., Pincomb, GA., Edward,s GL., Brackett, DJ., Wilson, MF. (1986) Work pressure and the type A behavior pattern exam stress in male medical students. Psychosom Med, 48(1-2): 125-133.

36. Savendahl, L. (2012) The effect of acute and chronic stress on growth. Sci Signal, 5(247): pt9.

37. Miller, GE., Chen, E., Zhou, ES. (2007) If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol Bull, 133(1): 25-45.

38. Heshmati, HM., Riggs, BL., Burritt, MF., McAlister, CA., Wollan, PC., Khosla, S. (1998) Effects of the circadian variation in serum cortisol on markers of bone turnover and calcium homeostasis in normal postmenopausal women. J Clin Endocrinol Metab, 83(3): 751-756.

39. Simmons, PS., Miles, JM., Gerich, JE., Haymond, MW. (1984) Increased proteolysis. An effect of increases in plasma cortisol within the physiologic range. J Clin Invest, 73(2): 412-420.

40. Monteleone, P., Beinat, L., Tanzillo, C., Maj, M., Kemali, D. (1990) Effects of phosphatidylserine on the neuroendocrine response to physical stress in humans. Neuroendocrinology, 52(3): 243-248.

41. Monteleone, P., Maj, M., Beinat, L., Natale, M., Kemali, D. (1992) Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo-pituitary-adrenal axis in healthy men. Eur J Clin Pharmacol, 41(4): 385-388.

42. Hellhammer, J., Fries, E., Buss, C., Engert, V., Tuch, A., Rutenberg, D., et al. (2004) Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress. Stress, 7(2): 119-126.

43. Benton, D., Donohoe, RT., Sillance, B., Nabb, S. (2001) The influence of phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor. Nutr Neurosci, 4(3): 169-178.

44. Starks, MA., Starks, SL., Michael K., Martin, P., Ralf, J. (2008) The effects of phosphatidylserine on endocrine response to moderate intensity exercise. J Int Soc Sports Nutr, 5: 11.

45. Ralf, J., Martin, P., Kurt-Reiner, G., Michael, W., Jochen, B., Francesco, A., et al. (2007) The effect of phosphatidylserine on golf performance. J Int Soc Sports Nutr, 4: 23.

46. Mooradian, A.D., Morley, JE., Korenman, SG. (1987) Biological Actions of Androgens. Endocrine Reviews, 8(1): 1-28.

47. Hochreiter-Hufford, AE., Lee, CS., Kinchen, JM., Sokolowski, JD., Arandjelovic, S., Call, JA., et al. (2013) Phosphatidylserine receptor BAI1 and apoptotic cells as new promoters of myoblast fusion. Nature, 497(7448): 263-267.
48. Kingsley, MI., Wadsworth, D., Kilduff, LP., McEneny, J., Benton, D. (2005) Effects of phosphatidylserine on oxidative stress following intermittent running. Med Sci Sports Exerc, 37(8): 1300-1306.
49. Fernholz, KM., (1997) The Effects Of Phosphatldylserine On Markers Of Muscular Stress In Endurance Runners. St. Cloud State University.
50. Kingsley, MI., Miller, M., Kilduff, LP., McEneny, J., Benton, D., (2006) Effects of phosphatidylserine on exercise capacity during cycling in active males. Med Sci Sports Exerc, 38(1): 64-71.
51. Cho, S., Kim, HH., Lee, MJ., Lee, S., Park, CS., Nam, SJ., et al. (2008) Phosphatidylserine prevents UV-induced decrease of type I procollagen and increase of MMP-1 in dermal fibroblasts and human skin in vivo. J Lipid Res, 49(6): 1235-1245.
52. Choi, H.D., Jeong, JH., JI-Hee, Y., Sang-Hong, L., Yun-Suk, K., Guk-Hoon, C., et al. (2013) Effect of Soy Phosphatidylserine Supplemented Diet on Skin Wrinkle and Moisture in Vivo and Clinical Trial. J Korean Soc Appl Biol Chem, 56: 227-235.
53. Sang Hoon, L., Ji-Hee, Y., Yong-Kon, P., Jeong-Jun, H., Guk-Hoon, C., Dae-hyun, H., et al. (2013) Protective effect and mechanism of phosphatidylserine in UVB-induced human dermal fibroblasts. European Journal of Lipid Science and Technology, 115(7): 783-790.
54. Baumeister, J., Barthel, T., Geiss, KR., Weiss, M. (2008) Influence of phosphatidylserine on cognitive performance and cortical activity after induced stress. Nutr Neurosci, 11(3): 103-110.
55. Hirayama, S., Terasawa, K., Rabeler R., Hirayama, T., Inoue, T., Tatsumi, Y., et al. (2013) The effect of phosphatidylserine administration on memory and symptoms of attention-deficit hyperactivity disorder: a randomised, double-blind, placebo-controlled clinical trial. J Hum Nutr Diet, 2: 284-291.
56. Simopoulos, AP. (2002) The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed Pharmacother, 56(8): 365-379.
57. Komori, T. (2015) The Effects of Phosphatidylserine and Omega-3 Fatty Acid-Containing Supplement on Late Life Depression. Ment Illn, 7(1): 5647.
58. Wells, AJ., Hoffman, JR., Gonzalez, AM., Stout, JR., Fragala, MS., Mangine, GT., et al. (2013) Phosphatidylserine and caffeine attenuate postexercise mood disturbance and perception of fatigue in humans. Nutr Res, 33(6): 464-472.
59. Fahey, TD., Pearl, MS. (1998) The Hormonal and Perceptive effects of phosphatidylserine administrtion during tow weeks of resistive exercise induced overtraining. Biology of sport, 15(3): 136-144.
60. Kris-Etherton, PM., Harris, WS., Appel, LJ. (2002) American Heart Association. Nutrition Committee. et al., Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation, 106(21): 2747-2757.