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Nutraceuticals with Animal Origin

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CHAPTER 4

Nutraceuticals with Animal Origin

Raghunandan Yendapally

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**Introduction**

This chapter outlines the nutraceuticals derived from animal origin. Nutraceuticals derived from animals include, but are not limited to, fish oils, conjugated linoleic acids (CLAs), choline, chitin and chitosan, glucosamine, chondroitin, and L-carnitine. Nutraceuticals that are obtained from animals have a gamut of applications. Typically, they have beneficial effects relating to cardiovascular diseases, inflammation, tumors, obesity, joint pains, diabetes, convulsions, and hypercholesterolemia. They are commonly formulated as soft-gel capsules, tablets, and powders.

**Omega-3 Fatty Acids from Fish**

**Typical Properties and Description**

Omega-3 fatty acids are the essential fatty acids, meaning the fatty acids that cannot be biosynthesized in the human body. Consequently, they must be obtained by supplementation in diet. Fish oils and cold-water fish such as tuna, salmon, catfish, sardines, and mackerel are great sources of omega-3 fatty acids. Omega-3 fatty acids from the fish primarily contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
Structural Formula

See Figures 4.1 and 4.2 for the structural formula.

Functional Category

Fatty acids are long-chain aliphatic carboxylic acid groups. These aliphatic systems are either saturated or unsaturated. Typically, fatty acids contain an even number of carbon atoms. Omega-3 fatty acids are unsaturated fatty acids, and the first carbon-carbon double bond (−C=C) is present on the third carbon from the terminal methyl group (−CH₃). The chain length in fish oils consist of either 20 carbons, as in EPA, or 22 carbons, as in DHA.

Applications in Nutraceuticals

Omega-3 fatty acids have a wide variety of applications in nutraceuticals. Omega-3 fatty acids are recommended by several scientific organizations, such as the American Heart Association and the European Society for Cardiology, to prevent or reduce the risk of cardiovascular diseases [Harris 2007]. In a study conducted by Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto-Prevenzione investigators, the supplementation of omega-3 fatty acids after myocardial infarction has led to the reduction in rate of death, nonfatal myocardial infarction and stroke [Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto-Prevenzione Investigators 1999]. Omacor, a drug composed of 85% of omega-3 fatty acid ethyl esters, when administered, has significantly lowered triglycerides, very-low-density lipoprotein (VLDL) cholesterol and increased high-density lipoprotein (HDL) cholesterol in people suffering from hypertriglyceridemia [Harris et al. 1997]. High doses of omega-3 fatty acids at 3 g/day have significantly reduced the blood pressure in older (> 45 years of age) and hypertensive patients [Geleijnse et al. 2002].

Maxepa, a drug composed of EPA (171 mg/capsule) and DHA (114 mg/capsule), when administered, has reduced the requirement of nonsteroidal anti-inflammatory
drugs (NSAIDs) for the treatment of rheumatoid arthritis (RA), indicating the potential application of omega-3 fatty acids in the treatment of RA. However, the maximum benefit was observed after 11 months, implying the need for long-term treatment [Lau, Morley, and Belch 1993].

**Stability and Storage Conditions**

Omega-3 fatty acids contain double bonds, which makes them unstable and prone to oxidation. The unique chemical structure causes rapid deterioration during handling and storage. A chemical quality study was conducted using the fish oils extracted from shad, horse mackerel, garfish, and golden mullet at different temperatures and time periods. All these oils had acceptable characteristics for 90 days when stored at 4°C. The acceptable characteristics for these oils (except shad oil) were increased from 90 to 150 days when the temperature was decreased from 4 to −18°C. However, the acceptable characteristics for the shad oil were found to be only 120 days when stored at −18°C [Borana, Karaçam, and Boran 2006].

**Interactions**

In a case study, it was observed that the international normalized ratio (INR) significantly increased when fish oil dose was doubled from 1 to 2 g/day during anticoagulation therapy with warfarin. This indicates that omega-3 fatty acids when administered along with warfarin may increase the risk of bleeding [Buckley, Goff, and Knapp 2004]. However, large clinical studies have to be conducted to critically examine the anticoagulant effect of omega-3 fatty acids and warfarin. Patients who are under warfarin therapy may be supplemented with safe doses of omega-3 fatty acids only under medical supervision.

**Method of Manufacture**

Omega-3 fatty acids obtained from fish have a strong odor and are unstable in the atmosphere. To overcome these problems, fish oils are usually manufactured by micro-encapsulation. Many of the fatty acids are marketed in the form of soft-shell capsules and oils.

**Safety**

Industrial contaminants and pesticide residues lead to contamination of dietary fish oil supplements. It has been reported that some of the fish oils that are used as dietary supplements contain high levels of organochlorine residues [Jacobs et al. 1998]. Therefore, during the usual manufacturing process, the chemical residual levels are checked before marketing these supplements. Cod liver contains high amounts of vitamins A and D apart from omega-3 fatty acids. Therefore, vitamins A and D should be consumed only in recommended doses during the concurrent supplementation of cod liver oil to avoid vitamin toxicities.
Handling Precautions

Because fish oils are prone to oxidation, special handling precautions are taken to minimize their exposure to atmosphere, and they are always stored under low temperatures. In fact, some of the fish products are incorporated with antioxidants.

Regulatory Status

In 2004, the FDA approved soft-gel capsules of omacor for the treatment of elevated blood triglyceride levels. Typically, 1 g of omacor capsule contains approximately 465 mg of EPA ethyl ester and 375 mg of DHA ethyl ester [FDA 2004]. Recently, as per the FDA’s request in response to dispensing and prescribing errors attributable to close similarity in names between omacor and amicar (an antifibrinolytic), the reliant pharmaceuticals changed the name of omacar to lovaza (Reliant Pharmaceuticals Inc.).

Related Substances

Omega-3 fatty acids are also obtained from plants. For example, alpha-linoleic acid (ALA), an omega-3 fatty acid, is predominantly present in vegetable oils such as soybean and canola oil. Other sources of ALA include nuts, seeds, legumes, vegetables, fruits, and grains. Omega-3 fatty acids are related to other polyunsaturated systems such as omega-6 fatty acids, in which the first carbon-carbon double bond (−C=C−) is present on the sixth carbon from the terminal methyl group (−CH₃). Linoleic acid and arachidonic acid are the typical examples of omega-6 fatty acids.

CONJUGATED LINOLEIC ACIDS

Typical Properties and Description

CLAs were first identified by Pariza and Hargraves [1985] while investigating the extracts from ground beef. Other sources of CLAs include lamb and dairy products obtained from ruminants [Lin et al. 1995].

Structural Formula

See Figures 4.3 and 4.4 for the structural formula.

Figure 4.3  The structure of conjugated (9Z,11E)-linoleic acid.
CLAs are a group of naturally occurring stereoisomers and positional isomers of octadecadienoic acid, a polyunsaturated fatty acid. The term conjugated refers to the presence of alternating single and double bonds. These molecules exhibit cis or trans stereoisomerism based on the orientation of the functional groups attached to the double bonds. They also exhibit positional isomerism based on the location of the double bonds. In most of the CLAs, the double bonds are located at C8 and C10, C9 and C11, C10 and C12, or C11 and C13 [Bhattacharya et al. 2006]. However, the 9-cis, 11-trans CLA is the major isomer present in the food materials.

Applications in Nutraceuticals

CLAs have a wide array of beneficial effects on health [Bhattacharya et al. 2006]. The anticarcinogenic properties of CLAs were first discovered from fried ground beef extracts [Pariza and Hargraves 1985]. Although the individual CLA isomers were not tested for anticarcinogenic properties in humans, based on the data that were obtained from animals, there is a speculation that various isomers of CLA may regulate tumor growth by different mechanisms [Bhattacharya et al. 2006].

In a recent meta-analysis in humans, it was demonstrated that CLAs, when administered at 3.2 g/day, resulted in reduction of fat mass [Whigham, Watras, and Schoeller 2007]. CLAs have been shown to reduce the body weight by decreasing the body fat and increasing the lean mass in mice [Park et al. 1997]. Furthermore, it was also identified that 10-trans, 12-cis isomer is responsible for decreasing body fats [Navarro et al. 2006; Silveira et al. 2007] by inhibiting the functions of lipoprotein lipase and stearoyl-coenzyme A (CoA) desaturase and thereby resulting in reduction of deposition of lipids in adipocytes [Pariza, Park, and Cook 2001].

In a study on healthy humans, a dietary supplement of the CLA isomers 9-cis, 11-trans CLA and 10-trans, 12-cis CLA has been shown to reduce mitogen-induced T-cell lymphocyte activation [Albers et al. 2003]. However, these two isomers had no effect on lymphocyte subpopulations, cytokine production, or serum concentration of C-reactive protein [Albers et al. 2003]. In another study, administration of 3 g of soft-gel capsules of CLAs, 1:1 mixture of 9, 11 isomer and 10, 12 isomer, for 12 weeks resulted in decreased levels of the proinflammatory cytokines, TNF-α and IL-1β and increased the levels of anti-inflammatory cytokines, such as IL-10 [Song et al. 2005]. These results indicate that CLA may be useful in increasing the immunity in humans [Song et al. 2005].

CLAs reduce the levels of leptin, an adipose hormone that suppresses bone formation [Yamasaki et al. 2000]. Banu et al. [2006] have studied the effects of dietary supplementation of CLAs in BALB/c mice. It was shown that CLAs have a positive

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effect on bone mass in cancellous and cortical bones of the proximal tibial metaphysis, cortical bones of the tibia fibular junction.

Dietary supplementation of CLAs in combination with calcium during pregnancy has been shown to decrease pregnancy-induced hypertension [Herrera et al. 2005, 2006]. CLAs supplementation was shown to reduce hypertension and hyperinsulinemia in Zucker diabetic fatty [Nagao et al. 2003] rats, as well as primary hypertension in hypertensive rats [Inoue et al. 2004]. CLAs were also shown to exhibit antiatherogenic properties in rabbits [Kritchevsky et al. 2000]. CLAs, when administered as dietary supplements in rats, reduced the cardiac myocyte hypertrophy by activating peroxisome proliferator-activated receptors α and γ [Alibin, Kopilas, and Anderson 2008].

Stability and Storage Conditions

CLAs are prone to epoxidation when exposed to oxygen because of the double bonds. Many experiments were conducted to study the effect of conjugation in CLAs and auto oxidation. The free form CLAs and triacyl glycerols forms of CLAs are extremely unstable in air at 90°C, and the relative rate of oxidation is similar to DHA. However, CLAs are oxidized at a much faster rate than linoleic acid probably because of the conjugated double bonds [Zhang and Chen 1997].

The rate of oxidations is also different for different isomers. For example, it was found that rate of oxidation is much faster in 10-trans, 12-cis CLA isomer than in 9-cis, 11-trans CLA isomer [Minemoto et al. 2003]. Furthermore, the CLA isomers have different oxyradical scavenging capacity at different concentrations. For example, 10-trans, 12-cis CLA at 2–200 μM displays antioxidant properties, whereas 9-cis, 11-trans CLA at lower concentration (2 and 20 μM) exhibits antioxidant properties and at higher concentrations (200 μM) it demonstrates pro-oxidant properties [Leung and Liu 2000].

Interactions

A study conducted by the United States Department of Agriculture found that female mice, when fed with 10-trans, 12-cis isomer, reduced the concentrations of omega-3 fatty acids and omega-6 fatty acids in the liver by greater than 50% and reduced the concentrations of omega-3 fatty acids in the heart by 25%. It has also increased the concentrations of omega-3 fatty acids in the spleen by 700% [Kelley et al. 2006].

Method of Manufacture

CLAs are manufactured in the form of soft-gel capsules and tablets.

Safety

Maternal supplementation of CLAs has decreased milk fat and increased CLA milk concentrations in humans [Masters et al. 2002]. Therefore, it is recommended that CLAs should not be consumed by lactating women [Masters et al. 2002]. It was
also observed that supplementation of 10-trans, 12-cis CLA has induced the oxidative stress and increased very-low-density lipoprotein levels in men with metabolic syndrome [Riserus et al. 2002]. More detailed information on the safety of CLAs have been discussed in a review published previously [Pariza 2004].

**Handling Precautions**

Because CLAs are prone to oxidation, meticulous handling precautions are taken during the manufacturing and storage process to minimize their exposure to atmosphere.

**Regulatory Status**

In the United States, CLA has gained GRAS status. However, according to the French food authority, the Agence Française de Sécurité Sanitaire des Aliments, the addition of certain CLA isomers in the form of supplements or food ingredients are not justified.

**Related Substances**

Chemically, CLAs are related to other polyunsaturated systems. These systems are conjugated containing three conjugated double bonds or unconjugated as in omega-3 and omega-6 fatty acids.

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**L-CARNITINE**

**Typical Properties and Description**

Carnitine is biosynthesized mainly in the liver and kidneys from the two amino acids lysine and methionine [Rapport and Lockwood 2000]. Carnitine is also known as vitamin B7. However, it is not categorized as a true vitamin because it can be synthesized in the body. Carnitine and carnitine transporters primarily help in the transfer of fatty acids from the cytosol into mitochondrial matrix. In the mitochondrial matrix, the fatty acid oxidation takes place, which serves as the major source of energy during exercise [Wasserman and Whipp 1975]. Carnitine is present in good quantities in animal sources such as steak, beef, chicken, and eggs [Erfl, Fisher, and Sauer 1970; Rudman, Sewell, and Ansley 1977]. Apart from animal sources, carnitine is also present in plant products such as grains, fruits, and vegetables [Rudman, Sewell, and Ansley 1977].

**Functional Category**

Chemically, carnitine is β-hydroxy-γ-trimethylaminobutyric acid. Carnitine has one stereocenter and therefore exists as two enantiomers: D and L forms. However, the L form is the naturally occurring enantiomer and it has R-absolute configuration.
at the 3 position. The L form of carnitine is biologically and physiologically active. The D form of carnitine is physiologically inactive, inhibits the uptake of L-carnitine, and is toxic. Therefore, carnitine must be supplemented only in the L form.

**Structural Formula**

See Figure 4.5 for the structural formula.

**Applications in Nutraceuticals**

Adult diet from meat and dairy products provides about 75% of carnitine daily requirements [Rebouche 2004]. Therefore, carnitine supplementation may not be required under usual conditions. Even in people who follow strict vegetarianism, the carnitine levels are normal, indicating the effectiveness of carnitine biosynthesis and carnitine renal reabsorption [Rebouche 2004]. Carnitine supplementation has beneficial effects in people suffering from carnitine deficiency, which arises as a result of disorders of carnitine synthesis and carnitine transport across the mitochondrial membranes [Long, Amat di San Filippo, and Pasquali 2006]. Carnitine is supplemented under different forms, such as free carnitine, acetyl-L-carnitine, and propionyl-L-carnitine.

Acetyl-L-carnitine supplementation decreases the serum ammonia levels and enhances neurophysiological functions during the treatment of minimal hepatic encephalopathy [Malaguarnera et al. 2008]. Carnitine has a beneficial effect in the treatment of valproic acid, a broad-spectrum anticonvulsant, toxicity [Carcione et al. 1991] by reducing hyperammonemia caused by valproic acid poisoning [Chan, Tse, and Lau 2007].

Carnitine deficiency in hemodialysis patients is caused by the loss of carnitine during dialysis and insufficient carnitine synthesis [Bohmer, Bergrem, and Eiklid 1978]. In a study, it was demonstrated that intravenous administration of carnitine in subjects undergoing hemodialysis had a significant improvement in lipid metabolism, red blood cell count, antioxidant abilities, and protein nutrition [Vesela et al. 2001]. L-carnitine supplementation has shown to decrease the left ventricular hypertrophy [Sakurabayashi et al. 2008], an independent predictor of cardiac mortality in patients undergoing hemodialysis [Silberberg et al. 1989].

A review of clinical trials indicated that supplementation of carnitine did not improve the exercise capacity in healthy individuals; however, it is speculated that it may improve the exercise capacity in patients suffering from renal disease and peripheral arterial disease [Brass and Hiatt 1998]. It was also demonstrated that L-carnitine administration has hepatic and cardiovascular antioxidant properties in hypertensive rats [Gómez-Amores et al. 2007].

![Figure 4.5 The structure of L-carnitine.](image-url)
L-carnitine, when administered as a continuous infusion, significantly improved the insulin resistance in type II diabetic patients, implying the potential application of L-carnitine in the treatment of diabetes [Mingrone et al. 1999].

**Stability and Storage Conditions**

Carnitine is stable at room temperature and should be stored away from light to avoid any chemical degradation.

**Incompatibilities Known**

L-carnitine levels were significantly reduced during the treatment of convulsions with phenobarbital, valproic acid, phenytoin, and carbamazepine [Hug et al. 1991].

**Method of Manufacture**

L-carnitine is obtained by chemical synthesis coupled with stereochemical biotransformation using bacterial culture and is sold under the trademarked name L-Carnipure [Held and Siebrecht 2003]. L-carnitine and its acetyl and propionyl derivatives are manufactured in the form of tablets, capsules, or powders.

**Safety**

In general, L-carnitine and its derivatives are considered to be safe supplements. According to the observed safe level (OSL) risk assessment method, L-carnitine is deemed safe at an intake of up to 2000 mg/day for chronic supplementation [Hathcock and Shao 2006]. However, appropriate care has to be taken in patients with low levels of thyroid because it has been reported that L-carnitine inhibits thyroid hormone nuclear uptake [Benvenga, Lakshmanan, and Trimarchi 2000]. Acetyl-L-carnitine may cause gastrointestinal disturbances and should be used under medical supervision in patients suffering from seizure disorders.

**Handling Precautions**

Carnitine does not need any special handling precautions because of its excellent stability. In fact, carnitine is heat stable up to 120°C, and, even in baking trials, it has minimal degradation. Therefore, carnitine can be added to a variety of food products, including but not limited to bars, cereals, chocolates, bread, and biscuits [Held 2004].

**Regulatory Status**

In the United States, the two forms of carnitine, L-carnitine crystalline and L-carnitine L-tartrate, hold GRAS status when used at prescribed levels [Held and Siebrecht 2003]. Carnitine was approved by the FDA as an orphan drug for the treatment of pediatric rare and serious diseases.
CHONDROITIN

Typical Properties and Description

Chondroitin is an integral component that is biosynthesized by specialized cells referred to as chondrocytes. Chondroitin provides the cushioning effect to the joints. Despite that chondroitin is synthesized in normal individuals, supplementation of chondroitin is necessary in deficient individuals. Chondroitin deficiency can be caused by external injury, age, or arthritis. Externally, chondroitin is usually obtained from bovine cartilage, bovine trachea, and shark cartilage.

Structural Formula

See Figure 4.6 for the structural formula.

Functional Category

Chondroitin is composed of heteropolysaccharides, known as glycosaminoglycans (GAGs). GAGs are polymers composed of repeated disaccharide units. Chondroitin chain typically contains 60 disaccharides, which is made up of alternating N-acetylgalactosamine and D-glucuronic acid. Chondroitin is often supplemented in the sulfate form, and these sulfate groups are located at either the 4 position or the 6 position in the cyclic ring system. The carboxylic acid and the sulfate groups present in chondroitin impart negative charge to the molecule.

Applications in Nutraceuticals

Osteoarthritis is typically characterized by excruciating pain and inflammation in joints caused by the wearing of cartilage. Pharmacological intervention for osteoarthritis typically consists of analgesics and NSAIDs [Tamblyn et al. 1997]. However, these drugs typically alleviate the symptoms but do not replenish the cartilage, which is the underlying problem. As a result, several studies were conducted by

![Figure 4.6](image-url)  
**Figure 4.6** The structure of chondroitin 4-sulfate.
supplementing chondroitin externally. However, the interpretations of these results vary greatly. In a series of clinical studies, chondroitin was widely interpreted as a very useful agent for the treatment of osteoarthritis [Bourgeois et al. 1998; Bucsi and Poor 1998; Uebelhart et al. 1998]. The efficacy of glucosamine and chondroitin was reviewed for the treatment of osteoarthritis, and it was concluded that these agents may have some degree of efficacy; however, previous publications might have exaggerated their effects [McAlindon et al. 2000]. In a recent systematic review and meta-analysis of available randomized, controlled studies, it was observed that the benefit attributable to supplementation of chondroitin is minimal or nonexistent, and therefore it has been suggested that the usage of chondroitin should be discouraged [Reichenbach et al. 2007]. However, the methodology of this review was further questioned [Goldberg, Avins, and Bent 2007]. In conclusion, based on the several published studies, chondroitin may be beneficial to a certain extent in osteoarthritis. Additional concrete studies are absolutely necessary to unequivocally claim the beneficial effects of chondroitin for the treatment of osteoarthritis.

Stability and Storage Conditions

Chondroitin and glucosamine tablets, when manufactured and stored at 25°C and modest humidity (15%), were found to retain full potency and quality for a period of two years after the packing. This indicates that these compounds are quite stable [Kennedy et al. 2006].

Interactions

Chondroitin may interact with warfarin and may potentiate the effect of warfarin [Rozenfeld, Crain, and Callahan 2004]. This effect is monitored by increased INR or increased bleeding or bruising [Knudsen and Sokol 2008]. Therefore, patients are required to inform their healthcare provider if they are using these medications in combination.

Method of Manufacture

Chondroitin is manufactured in the form of tablets, capsules, or powders.

Safety

According to the OSL risk assessment method, chondroitin is considered safe at an intake of up to 1200 mg/day [Hathcock and Shao 2007]. It is also suggested that there may be a link between chondroitin and glucosamine supplements and asthma exacerbations [Tallia and Cardone 2002]. Therefore, the patients suffering from asthma should seek medical advice before taking these medications. On March 19, 2008, the FDA identified that heparin, a blood-thinning drug, was being contaminated with an over-sulfated chondroitin sulfate, which is responsible for serious
adverse reactions [Food and Drug Administration 2008]. However, chondroitin sulfate (natural origin) should not be mistaken with over-sulfated chondroitin sulfate (synthetic origin).

**Regulatory Status**

In the United States, chondroitin is available as a dietary supplement and regulated by the Dietary Supplement Health and Education Act of 1994. Recently, the bovine-based OptaFlex™ Chondroitin, manufactured by Cargill, holds a self-affirmed GRAS status [Cargill Health and Food Technologies 2004]. In Europe, chondroitin is approved for the treatment of symptomatic slow-acting drug for osteoarthritis (SYSADOA).

**Related Substances**

Hyaluronate is the other major heteropolysaccharide containing GAGs. It is an essential component of cartilage and ligaments providing strength and elasticity. In addition, it serves as a lubricant in the synovial fluid joints. Like chondroitin, hyaluronate is composed of D-glucouronic acid and N-acetylglucosamine. However, it differs from chondroitin by the presence of about 50,000 disaccharide units per chain.

**GLUCOSAMINE**

**Typical Properties and Description**

Glucosamine is found naturally in the body, especially in cartilage, tendons, and ligament tissues. Glucosamine supplements are usually obtained from the shells of shrimps, crabs, and other crustacean exoskeleton. In addition, glucosamine is derived from the fungus [Cargill Health and Food Technologies 2007].

**Structural Formula**

See Figure 4.7 for the structural formula.

**Functional Category**

Glucosamine is a monosaccharide and hexose derivative containing an amino group at C-2 position. Glucosamine-6-phosphate is biosynthesized from fructose-6-phosphate and amino acid glutamine. Glucosamine is a precursor for the biosynthesis of GAGs and proteoglycans. All the nitrogen-containing sugars obtain nitrogen atom from glucosamine-6-phosphate [Ghosh et al. 1960]. Several scientists believe that glucosamine is the most important substance in the formation of cartilage [Andersen 1998a].

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Applications in Nutraceuticals

In a long-term, randomized, placebo-controlled, double-blind clinical trial study, supplementation of glucosamine sulfate has delayed the advancement of knee osteoarthritis in terms of joints structure changes and symptoms [Reginster et al. 2001]. Another study, involving 202 patients, demonstrated that oral administration of glucosamine sulfate, at 1,500 mg once a day, significantly retarded the progression of knee osteoarthritis, possibly by disease modification [Pavelka et al. 2002]. However, in a recent randomized trial for a period of 18 months, it was found that supplementation of glucosamine for the treatment of osteoarthritis combined with exercise did not have any significant additive effect when compared with the exercise itself [Kawasaki et al. 2008].

Combination of chondroitin and glucosamine sulfate demonstrated a beneficial effect in osteoarthritis pathophysiology by decreasing pro-resorptive properties of human osteoarthritis subchondral bone structural changes [Tate et al. 2007]. A recent review suggested that chondroitin and glucosamine sulfate may have symptomatic efficacy in moderate arthritis, probably by interfering with the disease progression [Bruyere and Reginster 2007]. In a study involving 1,583 patients, it was suggested that glucosamine and chondroitin sulfate in combination may be effective in a subgroup of patients with moderate to severe knee pain. However, it did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee [Clegg et al. 2006].

Interactions

Similar to chondroitin, glucosamine may interact with warfarin and may potentiate the effect of warfarin [Knudsen and Sokol 2008]. Therefore, the patients are required to inform the healthcare provider if they are using these medications in combination.

Method of Manufacture

Glucosamine is manufactured in the form of tablets, capsules, or powders. Glucosamine is often sold in combination with chondroitin. Glucosamine is supplemented in various forms, such as glucosamine sulfate (stabilized with sodium chloride or potassium chloride), N-acetyl glucosamine, and glucosamine hydrochloride [Andersen 1998b]. Special formulations of glucosamine are also used for other purposes. For example, glucosamine-carrying temperature- and pH-sensitive microgels may be useful in targeted drug delivery to tumors [Teng et al. 2008].

Safety

According to the OSL risk assessment method, glucosamine is considered as safe at intake of up to 2,000 mg/day [Hathcock and Shao 2007]. Patients suffering from asthma should seek medical advice before taking these medications. It is indicated
that glucosamine may worsen insulin resistance in patients with underlying poorer insulin sensitivity [Pham et al. 2007]. Therefore, diabetic patients should take medical advice before using glucosamine.

**Regulatory Status**

In the United States, the animal form of glucosamine does not hold GRAS status. However, GRAS has recently recognized the fungus-derived glucosamine as safe. In Europe, glucosamine is used for the treatment of SYSADOA.

**Related Substances**

Glucosamine is structurally related to other hexose amino sugars such as galactosamine and mannosamine. Glucosamine is also the precursor for the biosynthesis of $N$-acetylmuramic acid, which is an integral component of bacterial cell wall.

**CHITIN AND CHITOSAN**

**Typical Properties and Description**

Chitin is obtained from the hard exoskeleton of shrimps, crabs, lobsters, and insects. Unlike glucosamine, chitin is not biosynthesized in the human body and cannot be digested by vertebrates.

**Structural Formula**

See Figure 4.8 for the structural formula.

**Functional Category**

Chitin is a homopolysaccharide containing several units of $N$-acetylglucosamine units in $\beta$ linkage. Chitosan is chemically derived from chitin by $N$-deacetylation reaction. Therefore, chitosan is also referred to as deacetylated chitin.

![Figure 4.8](image)

**Figure 4.8** The structures of chitin and chitosan.
Applications in Nutraceuticals

Several studies indicate that chitosan has a beneficial effect in weight reduction and cholesterol management [Shields et al. 2003]. Because chitosan has an amino group at C-2, it is ionized into positive charge at gastrointestinal pH, and these cationic groups are believed to interact with the anionic groups of lipids and bile, preventing their absorption and storage by the body [Shields et al. 2003].

In a randomized, double-blind, placebo-controlled dietary intervention study, involving 134 overweight adults, it was found that the chitosan treatment group lost more weight than the placebo and control groups. In this study, chitosan also facilitated the depletion of excess body fat under free-living conditions with minimal loss of fat-free or lean body mass [Kaats, Michalek, and Preuss 2006].

In a multicenter, placebo-controlled, randomized study, eligible patients were treated with HEP-40 low-molecular-weight chitosan at daily doses of 1,200, 1,600, or 2,400 mg or placebo for 12 weeks. LDL cholesterol concentrations were reduced to some extent in patients treated with chitosan, suggesting that chitosan may be beneficial in patients with low to moderate hypercholesterolemia [Jaffer and Sampalis 2007]. However, chitosan was not as effective as statins, the class of drugs commonly used in lowering cholesterol levels [Jaffer and Sampalis 2007].

Chitosan sulfate has strong anticoagulant properties [Bourin and Lindahl 1993]. However, chitosan as such does not have any anticoagulant activity. It was reported that chitosan sulfate prolongs the activated partial thromboplastin time and thrombin time, the two assays involved in measuring the effectiveness of coagulation cascade [Hirano et al. 1985].

Stability and Storage Conditions

Chitin is a highly stable molecule at room temperature. Chitin by itself serves as a protective layer in animals and insects and shields them against pressure variations and changes in external environment. Therefore, chitin does not need any special storage conditions, except it should be stored away from chemicals.

Interactions Known

It was reported recently that chitosan potentiated the warfarin anticoagulant effect probably by binding to the lipids of the intestine and decreasing the absorption of vitamin K.

Method of Manufacture

Chitin and chitosan are manufactured in the form of tablets, capsules, or powders. Chitin and chitosan are also manufactured for other applications attributable to their disintegrant, dissolution, adhesive, and mechanical properties [Schneider et al. 2007].
Safety

Chitin, when given to mice, induces the tissue accumulation of IL-4, eosinophils, and basophils, a characteristic feature of allergic and parasitic immunity [Reese et al. 2007]. This indicates that chitin and chitosan should be used with caution in patients suffering from asthma and other allergic diseases.

Regulatory Status

The FDA has recently approved Celox, a proprietary product of chitosan, sold in the form of free granules or granules in soluble bag. It is used as a hemostat in emergencies for the temporary control of severe topical bleeding [Food and Drug Administration 2007].

Related Substances

Chitin has close structural similarity to cellulose, the most abundant polysaccharide in nature. However, it differs from cellulose by the presence of acetamide functionality instead of hydroxyl group at the C-2 position.

CHOLINE

Typical Properties and Description

Choline is biosynthesized in the human body by sequential phosphatidylethanolamine methylation pathway [Bremer and Greenberg 1961]. There are many studies that indicate choline as an essential nutrient in humans. Choline and its derivatives are an important source of methyl groups, essential in the synthesis of acetylcholine (cholinergic neurotransmitter) and membrane phospholipids [Zeisel and Blusztajn 1994]. Choline and its derivatives are present in rich quantities in egg yolks, chicken, beef, pork, turkey, veal, and lamb legumes [Zeisel et al. 2003].

Structural Formula

See Figure 4.9 for the structural formula.

![Figure 4.9](image)

The structure of choline.
Functional Category

Choline is a saturated quaternary trimethyl ammonium compound. Choline is used as a precursor for the synthesis of phosphatidylcholine, a class of phospholipids.

Applications in Nutraceuticals

Alzheimer’s disease (AD) is typically characterized by the low levels of acetylcholine. Therefore, scientists have studied the effects of supplementation choline on AD. In a multicenter, double-blind, randomized, placebo-controlled trial, it was found that the group receiving choline alfoscerate (glycerylphosphorylcholine), 400 mg capsules three times a day, had a cognitive improvement in mild-to-moderate AD when compared with the group receiving placebo [De Jesus Moreno Moreno 2003]. However, a Cochrane review of 12 randomized trials found that supplementation of lecithin, a major dietary source of choline, did not support its use in the treatment of dementia [Higgins and Flicker 2003].

In an open study, it was indicated that supplementation of choline may serve as a beneficial adjunct in the treatment of human complex partial seizures [McNamara et al. 1980].

In trained athletes, it was found that, after a marathon, the choline levels have dropped significantly [Conlay, Sabounjian, and Wurtman 1992]. This lead to the speculation that supplementation of choline may improve the performance of the athletes. However, in a double-blind crossover study, it was demonstrated that supplementation of choline did not improve physical or cognitive performance [Deuster et al. 2002].

Stability and Storage Conditions

Choline is stable at room temperature and should be stored away from light and atmosphere.

Interactions Known

No interactions have been reported.

Method of Manufacture

Choline is available at the market in the form of powders and tablets.

Safety

The Food and Nutrition Board of the Institute of Medicine recommends choline intake of 550 mg/day for men and 425 mg/day for women [United States Department of Agriculture 2008]. The tolerable upper intake level of choline for adults is 3.5 g/day. Excess consumption of choline may result in a strong fishy odor and nausea and may trigger existing epilepsy.
Regulatory Status

The FDA under the Food and Drug Administration Modernization Act has authorized that food or dietary supplemented products containing choline may provide nutrient claims on their labels. In Europe and Japan, CDP-choline has been approved to treat stroke, head injuries, and other neurological disorders [D’Orlando and Sandage 1995].

COENZYME Q₁₀

Typical Properties and Description

Coenzyme Q₁₀ (CoQ₁₀) is a vitamin-like substance that is present in the majority of human cells. CoQ₁₀ is biosynthesized in the human body from tyrosine or phenylalanine and mevalonate [Schultz and Clarke 1999]. CoQ₁₀ transports electrons in the oxidation-reduction reaction that drives the adenosine triphosphate (ATP) synthesis in mitochondria. In addition, CoQ₁₀ provides stability, fluidity, and regulates apoptosis in cell membranes [Lenaz et al. 1999; López-Lluch et al. 1999]. Despite that CoQ₁₀ is synthesized in humans, supplementation of CoQ₁₀ may be necessary in populations having CoQ₁₀ deficiency. The deficiency of CoQ₁₀ is linked to aging, certain type of diseases, genetic mutations, and 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors [Crane 2001]. CoQ₁₀ is present in common dietary consumptions of meat, fish, vegetables, and fruits [Lester and Crane 1959; Weber, Bysted, and Holmer 1997].

Structural Formula

See Figure 4.10 for the structural formula.

Functional Category

CoQ₁₀ is benzoquinone with a long isoprenoid side chain (10 units). This side chain makes the molecule highly lipophilic, which is readily diffusible across the

![Figure 4.10 The structure of CoQ₁₀.](TAF-82213_PATHAK-09-0501-C004.indd)
membranes. During the electron transport, CoQ₁₀ is reduced to ubisemiquinone and ubiquinol by accepting one and two electrons, respectively.

**Applications in Nutraceuticals**

In a randomized, double-blind study, 22 aerobically trained and 19 untrained human subjects were supplemented with placebo or CoQ₁₀ supplement. The results from this study suggest that acute (single dose) and/or chronic (14 days) supplementation of CoQ₁₀ may enhance the exercise performance in both the trained and untrained subjects [Cooke et al. 2008].

In an 11.5-year-old patient suffering from mitochondrial myopathy, it was observed that CoQ₁₀ concentration in the skeletal muscle decreased to 46% of normal average [Lalani et al. 2005]. The supplementation of CoQ₁₀ resulted in complete recovery of myopathy. Furthermore, muscle biopsy specimens of 82 children showed CoQ₁₀ deficiency to be the best indicator for electron transport chain abnormality. Therefore, the early identification of CoQ₁₀ deficiencies in children and supplementation of this agent may cure certain mitochondrial disorders [Miles et al. 2008].

In a randomized, double-blind, placebo-controlled trial involving 42 patients, it was observed that supplementation of CoQ₁₀ (three times at 100 mg/day) reduced headache frequency and nausea [Sandor et al. 2005]. In another study, Hershey et al. [2007] assessed CoQ₁₀ levels in patients suffering from severe headaches. About 32.9% of 1,550 patients were below the reference range of CoQ₁₀ levels. The CoQ₁₀-deficient patients were suggested to intake 1–3 mg/kg/day CoQ₁₀. In a subset of patients, supplementation with CoQ₁₀ has resulted in improved CoQ₁₀ levels, decreased headache frequency and disability, implying the potential application of CoQ₁₀ for migraine.

In a multicenter, randomized, parallel-group, placebo-controlled, double-blind study, patients with Parkinson’s disease were supplemented with placebo or CoQ₁₀ at 300, 600, or 1200 mg/day. In this study, it was observed that CoQ₁₀ supplementation is safe even at 1,200 mg/d, and the beneficial effects were observed in a dose-dependent manner [Shults et al. 2002].

It is observed that dietary supplementation of 0.07–0.7% CoQ₁₀ for 26 weeks in a rat model of metabolic syndrome had a beneficial effect on increased oxidative and nitritative stress markers and inflammatory markers. In addition, CoQ₁₀ has reduced elevated blood pressure and serum levels, implying that CoQ₁₀ may have a beneficial effect in cardiovascular diseases in metabolic syndrome [Kunitomo et al. 2008].

**Stability and Storage Conditions**

CoQ₁₀ should be stored at room temperature under atmosphere-, light-, and moisture-free conditions.

**Interactions**

HMG-CoA reductase inhibitors or statins are primarily used to treat hypercholesterolemia. It is evident that HMG-CoA reductase inhibitor reduces blood
CoQ<sub>10</sub> concentrations. This is probably because CoQ<sub>10</sub> and cholesterol share a similar biosynthetic pathway. In a mice model, it was shown that supplementation of CoQ<sub>10</sub> during statin therapy reduces the oxidative stress caused by statin administration [Kettawan et al. 2007]. However, at this point in time, the coadministration of CoQ<sub>10</sub> and statin to prevent myotoxicity remains questionable [Levy and Kohlhaas 2006].

There is an increasing amount of evidence showing that CoQ<sub>10</sub> affects warfarin metabolism [Landbo and Almdal 1998]. Structurally CoQ<sub>10</sub> is similar to vitamin K, which may explain its interaction with warfarin [Landbo and Almdal 1998]. It is speculated that concurrent administration of CoQ<sub>10</sub> (100 mg) and warfarin would increase the total clearance of S-warfarin and R-warfarin by 32 and 17%, respectively [Zhou, Zhou, and Chan 2005]. Therefore, patients using this combination of medication must be kept under close medical supervision.

**Method of Manufacture**

CoQ<sub>10</sub> is available in the market in the form of soft-gel capsules, tablets, and powder.

**Safety**

According to the OSL risk assessment method, CoQ<sub>10</sub> is considered to be safe at intake of up to 1,200 mg/day. In fact, much higher levels of CoQ<sub>10</sub> have been tested, but the data are not sufficient enough to provide a reasonable assurance of safety [Hathcock and Shao 2006].

**Handling Precautions**

CoQ<sub>10</sub> should be handled at room temperature under inert conditions, away from light.

**Regulatory Status**

In the United States, CoQ<sub>10</sub> holds GRAS status and is regulated as a dietary supplement. In the United Kingdom, CoQ<sub>10</sub> is regulated as a dietary or food supplement. Japan approved CoQ<sub>10</sub> in 1974 as a prescription drug for the treatment of congestive heart failure [Tran et al. 2001].

**Related Substances**

Coenzyme Q is closely related to other quinones such as vitamin K, plastoquinone (present only in plants), and menaquinone (present only in bacteria). Plastoquinone and menaquinone play the equivalent role of ubiquinone, i.e., they transport electrons in oxidation-reduction reactions.
CONCLUSION

See Table 4.1 for details and an overview of what this chapter has discussed regarding nutraceuticals obtained from animal origin.

Table 4.1 Nomenclature, Chemical Abstracts Service (CAS) Number, and Empirical Formula or Molecular Formula of Nutraceuticals Obtained from Animal Origin

<table>
<thead>
<tr>
<th>Category</th>
<th>Synonyms</th>
<th>Chemical Name</th>
<th>CAS no.</th>
<th>Empirical Formula or Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 fatty acids from fish</td>
<td>EPA; timnodonic acid DHA</td>
<td>cis-5, 8, 11, 14, 17-EPA, cis-4, 7, 10, 13, 16, 19-DHA</td>
<td>10417-94-4, 6217-54-5</td>
<td>C_{20}H_{30}O_{2}</td>
</tr>
<tr>
<td>Conjugated linoleic acids</td>
<td>9-cis, 11-trans-Octadecadienoic acid solution; 9Z,11E-CLA; bovinic acid; conjugated linoleic acid (9Z,11E)-(10E,12Z)-10,12-Octadecadienoic acid; 10E,Z12-CLA; linoleic acid (10-trans, 12-cis)</td>
<td>Conjugated (9Z,11E)-linoleic acid solution</td>
<td>2540-56-9</td>
<td>C_{18}H_{32}O_{2}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conjugated (10E,12Z)-linoleic acid solution</td>
<td>2420-56-6</td>
<td>C_{18}H_{32}O_{2}</td>
</tr>
<tr>
<td>L-Carnitine</td>
<td>(-)-(R)-3-Hydroxy-4-(trimethylammonio)butyrate; vitamin B_{t}</td>
<td>L-Carnitine inner salt</td>
<td>541-15-1</td>
<td>(CH_{3})<em>{3}N\cdot CH</em>{2}CH(OH)CH_{2}COO</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>Chondroitin sulfate A sodium salt; CSA</td>
<td>Chondroitin 4-sulfate sodium salt from bovine trachea</td>
<td>39455-18-0</td>
<td>C_{6}H_{13}NO_{5}•HCl</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>2-Deoxy-2-sulfamino-D-glucopyranose; 2-amino-2-deoxy-D-glucose hydrochloride; chitosamine hydrochloride</td>
<td>D-Glucosamine 2-sulfate sodium salt</td>
<td>38899-05-7</td>
<td>C_{6}H_{12}NO_{8}•SNa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D-(+)-Glucosamine hydrochloride</td>
<td>66-84-2</td>
<td>C_{6}H_{12}NO_{5}•HCl</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Chitosan from crab shells; deacetylated chitin; poly(D-glucosamine)</td>
<td>Chitosan low molecular weight</td>
<td>9012-76-4</td>
<td>Chitosan from crab shells; deacetylated chitin; poly(D-glucosamine)</td>
</tr>
<tr>
<td></td>
<td>Poly(N-acetyl-1,4-β-D-glucopyranosamine)</td>
<td>Chitin from crab shells</td>
<td>1398-61-4</td>
<td>Poly(N-acetyl-1,4-β-D-glucopyranosamine)</td>
</tr>
</tbody>
</table>

(Continued)
Table 4.1 (Continued)

<table>
<thead>
<tr>
<th>Category</th>
<th>Synonyms</th>
<th>Chemical Name</th>
<th>CAS no.</th>
<th>Empirical Formula or Molecular Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline</td>
<td>(2-Hydroxyethyl)trimethyl ammonium hydroxide; choline solution</td>
<td>Choline base solution</td>
<td>123-41-1</td>
<td>HOCH₂CH₂N(CH₃)₃OH</td>
</tr>
<tr>
<td>Coenzyme Q₁₀</td>
<td>Q-10; ubiquinone-50; ubiquinone-10</td>
<td>Coenzyme Q₁₀</td>
<td>303-98-0</td>
<td>C₉₅H₉₀O₄</td>
</tr>
</tbody>
</table>

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