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Review

Structured lipids: methods of production, commercial products and nutraceutical characteristics

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Summary. Structured lipids (SLs) are generally defined as triacylglycerols (TAGs) that have been modified to change the fatty acid composition and/or their positional distribution in glycerol molecules by chemical and/or enzymatic reactions and/or by genetic engineering processes. They are designed for obtaining TAGs with improved functional properties (i.e. fats with specific physical properties for food applications) and/or for medical and nutritional applications, especially to meet for the growing need for healthier foods and to prevent obesity, cancer and cardiovascular disease cardiovascular disease. Production methods of SLs and commercial products examples are discussed in this review. Moreover, nutritional and medical uses of SLs and their effect on human health are also reviewed in this paper.

Key words: Structured lipids, methods of production, commercial products and nutraceutical characteristics.

Introduction

Lipids have long been recognized for the richness they impart to foods as well as their satiety value in the diet. Lipid is an important component of the diet, because it provides both energy and essential fatty acids (EFAs). It is the most concentrated energy source in the diet, with an average energy value of 9 kcal/g compared to 4 kcal/g for carbohydrates and proteins. They serve several important biological functions including: 1) acting as structural components of all membranes; 2) serving as storage form and transport medium of metabolic fuel; 3) serving as a protective cover on the surface of several organisms; and 4) being involved as cell-surface components concerned with cell recognition, species specificity and tissue immunity (1, 2). The role of dietary lipids in health and disease -notably coronary heart disease, obesity, hyperlipidemia, diabeties and cancer- is one of the most active areas of research in modern food science, nutrition, and biochemistry (3, 4).

A high-fat diet poses at least two risks to one's health. First, fats produce a relatively large amount of energy when metabolized, nine calories per gram, compared with four calories per gram for carbohydrates and proteins (5). Second, saturated fats and trans fatty acids are believed to be responsible for an increase in LDL cholesterol levels and decrease of HDL cholesterol levels which, in turn, have been implicated with an increased risk for heart disease (6, 7).

The guidelines for a healthy diet issued in various countries recommend to lower the diet fat content to 20-35% of total energy content (5). A reduction of energy intake through a reduction of dietary fat intake is easier said than done because fat contributes strongly to the sensory characteristics of our food such as taste, appearance and texture. New developments in food technology now allow the partial replacement of dietary fat with substitutes called structured lipids (SLs), which combine unique characteristics of component fatty acids such as melting behavior, digestion, absorption, and metabolism to enhance their use as

functional lipids and as nutraceuticals of much lower energetic value and many health benefits.

Structured lipids are generally defined as triacylglycerols (TAGs) that have been modified by the incorporation of new fatty acids, restructured to change the positions of fatty acids, or synthesized to yield novel TAGs aiming at obtaining some desirable properties (Figure 1) (8, 9). Various fatty acids, including different classes of saturated, monounsaturated, and n-3 and n-6 polyunsaturated fatty acids (PUFAs) or their mixtures may be used in this process, depending on the desired metabolic effect (10). Lipids can be restructured to meet essential fatty acid requirements or to incorporate specific fatty acids of interest. SLs may offer the most efficient means of delivering target fatty acids for nutritive or therapeutic purposes as well as to alleviate specific disease and metabolic conditions. Structured lipids can also be produced to obtain TAG with modified physical and/or chemical features, including melting point, iodine and saponification values. They can be produced via inter-esterification reactions of fats, oils, or mixtures thereof, either chemically or enzymatically (11-14).

Much attention is being paid to SLs due to their potential biological functions and nutritional perspectives. The aim of this review is to focus on the component fatty acids, production strategies, medical and food applications and future prospects for research and development in this field.

Methods of SLs production

Chemical or enzymatic reactions. SLs can provide medium-chain fatty acids (MCFA) as a quick energy source and long-chain fatty acids (LCFA) as essential fatty acids to hospital patients (15). Basic strategies for developing structured lipids are essentially based on one of the following approaches:

- replacement of glycerol moiety of triacylglycerols with alternative alcohols such as carbohydrates, sugar alcohols or polyols such as sucrose fatty acid esters;
- replacement of long-chain fatty acids with alternative acids such as short-, medium and long-chain fatty acids esterified to glycerol.

To produce SLs, chemical or enzymatic reactions such as direct esterification, acidolysis, alcoholysis, or interesterification can be used depending on the types of substrates available.

Chemical interesterification is a random reaction conducted at relatively high temperature and producing complete randomization of the fatty acid moieties in the triacylglycerol backbones (16). Chemical interesterification seems to be attractive due to the low cost and large scale application. However, under the perspective of producing lipids with very specific compositions aiming at functional and medical applications, enzymatic interesterification is far more interesting (17). With this respect, the enzymatic interesterification has the advantage of allowing a greater control of the positional distribution of fatty acid moieties in the final product due to both selectivity and regiospecificity of lipases (16, 18).

Many factors can influence the synthesis of SLs such as the type of lipase and the lipase/substrate ratio (19), the reaction medium (19), substrate concentrations, content of water (20), temperature (19), and operational mode (21-23).

Lipases occur widely in nature and are active at oil/water interface in heterogenous reaction system. They catalyze the hydrolysis of triacylglycerols into monoacylglycerols, diacylglycerols, free fatty acids and glycerol, under macroaqueous conditions (24). In addition to acylglycerol ester hydrolysis, lipases can also catalyze a wide variety of esterification, transesterification, and polyesterification reactions (24). The set of transesterification reactions includes acidolysis, interesterification, and alcoholysis (24, 25).

Most lipases have their substrate selectivity according to chain length, unsaturation, and positional distribution (26, 27). Many different types of lipases

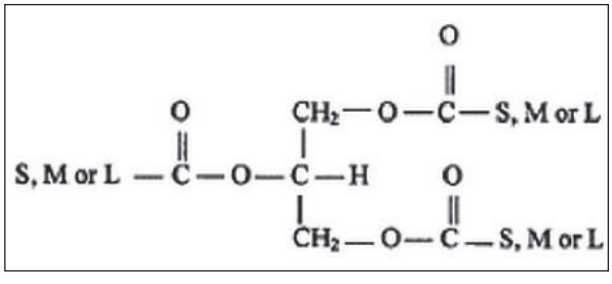

Figure 1. General structure of structured lipids.
S, M, and L is for short-chain, medium-chain, and long-chain fatty acids, respectively.

have been investigated for the enzymatic modification of oils and fats. Commercial lipases are available from microbial, plant, and animal sources. Among those, microbial lipases are the most attractive ones and their utilization has been described extensively (28). Lipases are enzymes that preferentially catalyze the hydrolysis and synthesis of esters and TAG. Some lipases exhibit substrate selectivity. Lipase from *Penicillium camembertii* U-150 can hydrolyze mono- and diacylglycerols but not TAG (29). TAG with lower molecular weight fatty acids were hydrolyzed more easily with lipase from *Penicillium caseicolum* than those with higher molecular weight fatty acids (30). Lipase from *Geotrichum candidum* has shown preference to the unsaturated substrates with a double bond at the 9-position (31). When cis- and trans- form of 18:1 in l-elaidate-2,3-dioleate were compared for lipolysis, lipase from *Geotrichum candidum* preferentially hydrolyzed the cis-form to free fatty acid (32).

Among the currently available methods for modifying lipids, lipase-catalyzed reactions are better than conventional chemical methods since lipases mimic natural pathways, which concern mild reaction conditions, high catalytic efficiency, and the inherent selectivity of natural biocatalysts (33, 34). Typical applications of lipase-catalyzed interesterification reactions include the production of cocoa butter substitutes, human milk fat substitutes, partial acylglycerols, modified fish oil products, margarines, structured lipids, and several lipid products (35, 36).

Genetic engineering. Genetic modification of oilseed crops to improve quality, pest and disease resistance and yield has expanded in recent years to include modification of the fatty acid composition of oils for food use.

The main method of fatty acid profile modification is the cloning and transfer of a gene from one plant species into another species to produce the desired levels of specific fatty acids. As well, naturally occurring enzymes can be modified or new ones can be introduced to modify the fatty acid profile of the oilseed (37). Genes from bacterial, animal and yeast sources have also been incorporated into oilseeds for fatty acid modification (38).

Genetic codes are available to introduce double bonds, elongate carbon chains, synthesize eicosapentaenate, and produce fatty acid isomers not normally found in common sources of edible oils. Plant engineers are now trying to incorporate the principles used in chemical and enzymatic synthesis of "tailor-made" structured lipids into their genetic engineering techniques.

Since oleic acid (18:1) appears to have a similar effect on cholesterol as linoleic acid (18:2 n-6) and is not as susceptible to oxidation, researchers increased the ratio of monounsaturated fatty acids (MUFAs) to PUFAs in soybean and canola oil by modifying the activity of a microsomal membrane-bound oleate desaturase (39). Trans fatty acids are produced during the hydrogenation process used by food companies and their presence become a major health concern for consumers. Several companies are actively pursuing the development of seed oils that contain levels of saturated fatty acids high enough to permit the elimination of the need for hydrogenation, and, subsequently, the production of trans fatty acids (40). Cloning and characterizing genes for a family of thioesterases was the 1st step toward the goal of incorporating MCFAs into oil seed crops that naturally do not contain such fatty acids. A gene from the California bay tree that produces MCFAs in its seeds was incorporated into canola plants. The transgenic canola now accumulates up to 65% more lauric acid in their seed TAGs (41). The sn-2 acyltransferase has a high degree of specificity for an unsaturated fatty acid; therefore, most of the oleic acid found in these TAGs is at the sn-2 position. This oil was marketed as Laurical® (Table 1).

Commercial products examples of structured lipids

Caprenin. Caprenin is a common name for caprocaprylobehenin, a structured lipid containing C8:0, C10:0, and C22:0 fatty acids esterified to glycerol moiety (Figure 2) (42). It is manufactured by Procter & Gamble's (Cincinnati, Ohio, U.S.A.) from coconut, palm kernel, and rapeseed oils by a chemical transesterification process. The MCFAs are obtained from the coconut oil and the LCFAs from rapeseed oil. Because behenic acid is only partially absorbed and capric and caprylic acids are more readily metabolized than other longer chain fatty acids, caprenin provides only 5 kcal/g (43, 44).

Procter & Gamble filed a Generally Recognized as Safe (GRAS) affirmation petition to the U.S. Food and Drug Administration (FDA) for use of caprenin in soft candies such as candy bars, and in confectionery coatings for nuts, fruits, cookies, and so on. Caprenin has a bland taste, is liquid or semisolid at room temperature, and is fairly stable to heat. It can be used as a cocoa butter substitute. Caprenin, in combination with polydextrose, was commercially available briefly in reduced-calorie and reduced- fat chocolate bars (45). Swift et al. (46) showed that Caprenin fed as an SL diet to male subjects for 6 days did not alter plasma cholesterol concentration but decreased HDL-chol by 14%. However, the medium chain triacylglycerol (MCT) diet raised plasma TAGs by 42% and reduced HDL-chol by 15%.

Salatrim/Benefat. Salatrim (an acronym derived from short and long acyl triglyceride molecule) is the generic name for a family of structured triglycerides comprised of a mixture containing at least one short chain fatty acid (primarily C2:0, C3:0, or C4:0 fatty acids) and at least one long chain fatty acid (predominantly C18:0, stearic acid) randomly attached to the glycerol backbone (Figure 3) (47).

Salatrim was developed by the Nabisco Foods Group (Hanover, N.J., U.S.A.) but now marketed as Benefat® by Cultor Food Science (Ardsley, N.Y., U.S.A.). Benefat is produced by base-catalyzed interesterification of highly hydrogenated vegetable oils with TAGs of acetic and/or propionic and/or butyric acids (48).

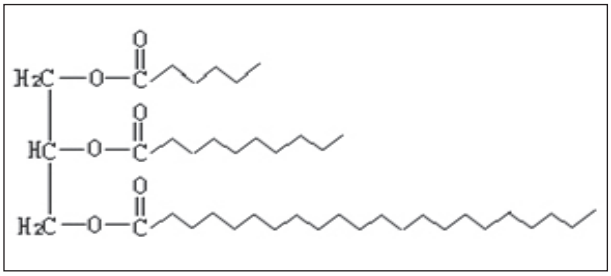

Figure 2. Caprenin chemical structure.

Benefat is a low-calorie fat like Caprenin, with a caloric availability of 5 kcal/ g. Stearic acid is poorly or only 50% absorbed (49), whereas acetyl and propionyl groups in Benefat are easily hydrolyzed by lipases in the stomach and upper intestine and readily converted to carbon dioxide (50). Nabisco filed a Generally Recognized as Safe (GRAS) affirmation petition to the U.S. Food and Drug Administration (FDA) in 1994 for use of Benefat in baking chips, chocolate-flavored coatings, baked and dairy products, dressings, dips,

Table 1. Commercial Sls containing polyunsaturated fatty acids and their applications.

Brand name	Fatty acid composition	Application
Betapol	C16:0 (45%)	Infant food formulation
Impact	Interesterification with high lauric acid oil and high linoleic acid oil	Pharmaceuticals for patients suffering from trauma or surgery, sepsis or cancer
Laurical	C12:0 (40%) and unsaturated fat (C18:1, C18:2 and C18:3)	Medical nutrition and confectionery coating, coffee whiteners, whipped toppings and filling fats
Neobee	C8:0, C10:0 and LCFA (n–6 and n–3)	Nutritional or medical beverages
Structolipid	LCT (63%) and MCT (37%) – caprylic (27%), capric (10%), palmitic (7%), oleic (13%), linoleic (33%) and α-linoleic acid (5%)	Intravenous fat emulsion as a rapid source of energy for patients and parenteral nutrition
Captex	C8:0, C10:0, C18:2	Captex diet resulted in increased heat production and altered energy metabolism in obese Zucker rats. It also improved absorption of 18:2 n-6 when administered to cystic fibrosis patients.

LCFA: Long chain fatty acid, LCT: Long chain triacylglycerol, MCT: Medium chain triacylglycerol.

and sauces, or as a cocoa butter substitute in foods. The consistency of Benefat varies from liquid to semisolid, depending on the fatty acid composition and the number of short chain fatty acids (SCFAs) attached to the glycerol molecule.

Olestra/Olean®. Olestra is an acylated sucrose polyester with six to eight fatty acids obtained from vegetable oil (e.g., soybean, corn, sunflower) as shown in figure 4. It is prepared by interesterifying sucrose and edible oil methyl esters in the presence of an alkali catalyst, at 100-140°C (51). Sucrose polyester (SPE) development dates back to the year 1880, when a derivative of sucrose was prepared by acetylation to sucrose octaacetate. In 1952 the concept of sucrose fatty acid polyester (SPE) production was initiated for use in detergents. The other concept was to come up with a fatlike molecule that would significantly reduce fat calories by preventing their hydrolysis and absorption. This led to the discovery of a non-digestible and non-absorbable fatlike molecule called sucrose fatty acid polyester, now known as olestra, by Mattson and Volpenhein while working on the absorption of fats by infants (52).

Olestra has the organoleptic, and thermal properties of fat. Is not hydrolyzed by gastric or pancreatic enzymes because the large size and number of the nonpolar fatty acids, thus it is nondigestible, hence noncaloric; it is also nontoxic, yet nutritional concerns potentially exist (53). Its functionality is dependent on the chain length and unsaturation of the esterified fats, as with normal lipids (54). Olestra made from highly unsaturated fatty acids is liquid at room temperature; olestra made from highly saturated fatty acids is solid (55). Because of its unique properties, olestra can serve as a zero-calorie replacement (up to 100%) for conventional fat in a variety of foods. It can be exchanged for fats in products such as ice cream, margarine, cheese, and baked goods, and it can be blended with vegetable oil (56). Olestra's configuration also makes it possible for the substance to be exposed to high temperatures, such as frying.

Neobee. Neobee is another caloric reduced fat, it is composed of capric and caprylic acids and produced by Stepan Company (Maywood, N.J., U.S.A.). This class of specialty lipids includes different products. For example, Neobee 1053 and Neobee M-5 contain both capric and caprylic acids, while Neobee 1095 is

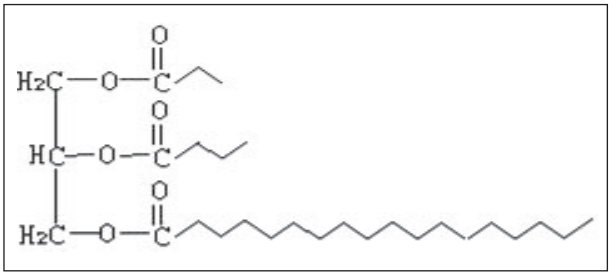

Figure 3. Salatrim chemical structure.

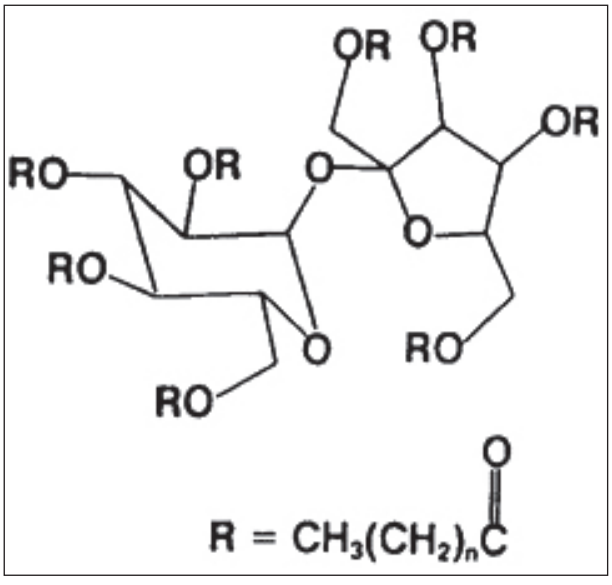

Figure 4. Olestra chemical structure.

made up of only capric acid (57). Neobee 1095 is a solid product. Therefore, this product may be suitable in certain applications which require solid fats. Neobee 1814 is an MCT derivative made by interesterification of MCT with butter oil (58); it contains half of the long-chain saturated fatty acids found in conventional butter oil and is suitable to replace butter oil in a variety of applications. Neobee 1814 may serve as a flavor carrier and functions as a textural component for low-fat food products (57).

Structured lipid containing polyunsaturated fatty acids (PUFA). Nowadays, the most familiar types of low-calorie lipids are triacylglycerols with short- and long-chain acyl residues (SLCTs), triacylglycerols with medium- and long-chain acyl residues (MLCTs) and diacylglycerols (DAGs) (59). To act as an ideal lipid substitute, the products should contain

unsaturated fatty acids, especially essential fatty acids, and have no harmful effects. SLs containing n–3 highly unsaturated fatty acids were produced with immobilized sn–1,3 specific and non-specific lipases as biocatalysts. Highly unsaturated fatty acids, such as eicosapentaenoic (EPA, 20:5 n–3), docosahexaenoic (DHA, 22:6 n–3), linolenic (18:3 n–3) and gamma linolenic (18:3 n–6) acids, are important in foods, nutrition, and pharmaceutical applications (60). SLs containing these fatty acids and medium-chain fatty acids may be desirable as 'nutraceuticals' for supplementation in infant formula or as food supplement for adults to enhance overall health (61).

For the most part, the position of the highly unsaturated fatty acid in the glycerol moiety is key to their functionality in foods and absorption when consumed. Perhaps, these designer lipids may replace conventional fats and oils in certain specialty applications because of their structure-health (nutraceutical or medical lipids) and structure-function (functional lipids) attributes. In most cases, insertion of the desired highly unsaturated fatty acid at the sn–2 position will provide maximum nutritional benefits (60). Specific structured lipids were designed with PUFA residues at the sn-2 position and MCFA residues at the sn-1,3 positions. In this form, the PUFA residues are protected against oxidation by the two saturated MCFA residues. Hamam et al. (62) showed that the presence of palmitate in the sn-2 position of the TAG, in infant formula instead of conventional fats, improved digestibility of the fat and absorption of other important nutrients such as calcium. In a study conducted by Decker (63), saturated fatty acids at the sn-2 position have been found to be beneficial in terms of providing increased caloric intake through infant formula and enteral supplements.

An SL made by reacting tripalmitin with unsaturated fatty acids using an sn-1,3 specific lipase closely mimicked the fatty acid distribution of human milk was commercially developed for application in infant formulas under the trade name Betapol (Loders Croklaan, Glen Ellyn, Ill., U.S.A.) (64).

Structured lipids (SL) enriched with omega 6 PUFA were synthesized from coconut oil triglycerides by employing enzymatic acidolysis with free fatty acids obtained from safflower oil (65).

Structured triacylglycerols (ST) enriched in eicosapentaenoic acid (EPA) in position 2 of the triacylglycerol (TAG) backbone were synthesized by acidolysis of a commercially available EPA-rich oil and caprylic acid, catalyzed by the 1,3-specific immobilized lipase lipozyme IM (66).

Table 1 summarize some commercial SLs containing polyunsaturated fatty acids and their food and medical applications (67).

Despite the health benefits of SLs containing polyunsaturated fatty acids, they are highly prone to oxidative deterioration and thus require adequate protection to deter their oxidation (68). Some studies have shown that the rate of autoxidation and melting properties of TAGs can be affected by the position of unsaturated fatty acids on the glycerol molecule (69). TAGs having unsaturated fatty acids at the 2-position of glycerol are more stable toward oxidation than those linked at the 1- and 3-positions (70).

Further research are conducted in order to optimise the SLs' stabilisation and storage by use of appropriate antioxidants and packaging technologies.

In Nagachinta and Akoh study (71), Maillard reaction products, obtained from heated whey protein isolates and corn syrup solids solution, were used as encapsulants for microencapsulation of 2 enzymatically synthesized SLs for infant formula applications. The encapsulated SL powders had low peroxide and thiobarbituric acid-reactive substances values.

Nutraceutical characteristics of SLs

Functional SLs

The interesterification and genetic engineering processes have been used in the production of structured lipids with specific physical properties such as having a desired melting point, slow rancidification, and also for the production of functional structured lipids possessing specific compositions and nutritional properties. Table 2 summarize the potential uses of functional structured lipids.

Margarine fats. Chemical and enzymatic interesterification has been specially employed in the formulation of margarines and shortenings with no trans FAs while still maintaining physical properties, taste

and stability. The vegetable oils including corn, palm, peanut, cottonseed, canola, and sunflower oils can be randomly interesterified with fully hydrogenated soybean oil or fully hydrogenated cottonseed hard fats to produce desirable fat compositions for margarines and shortenings (72).

Cocoa butter equivalents. Due to high cost and fluctuations in the supply and demand of cocoa butter, cocoa butter equivalent (CBE) with a TAGs composition similar to cocoa butter is used as an alternative source. Recently, vegetable oils such as Mahua, Kokum and mango fats, palm oil, tea seed oil, and olive oil have been used to prepare CBE through enzymatic catalyzed interesterification until a similar composition of cocoa butter is obtained. The triacylglycerol composition of oils was redesigned so that properties such as the melting point, solid fat content and fat crystal network microstructures of the structured oil and cocoa butter were very much similar (73).

Frying oils. Genetic engineering process had been used for the production of modified oils that have a lot of benefits which include high oxidative stability, zero trans-fat and low saturated FAs, non-hydrogenated, high oleic content, liquid at room temperature, and excellent taste and flavor (74). Recently, genetically modified soybean oil has been introduced that eliminates the need for hydrogenation to be used in bakery goods and for frying. The oil also has a healthier FA composition. High-oleic sunflower oil having better oxidative stability in deep frying applications and extended shelf life compared to traditional sunflower oil has been developed using selective breeding and mutagenesis (75). Other example includes canola oil seed mutants with low linolenic/high oleic acid content (76).

Breast milk fat substitute. Lipids are the major source of energy in human milk or infant formulas. Hence, modification of fats and oils for infant formulas in order to obtain not only the correct fatty acid (FA) composition but also the same positional distribution as in human milk fat (HMF) via interesterification had been widely investigated. Christensen and Holmer (77) prepared a HMF analogue using a Rhizomucor miehei lipase-catalyzed modification of butter oil. Unilever produced a milk fat substitute named Betapol for infant formulas (64). Also, Yang et al. (78) modified lard by lipase to produce HMF substitutes.

Health benefits of SLs

One of the earliest uses of SL was in enteral and parenteral nutrition followed by its application in a range of clinical settings including prevention of thrombosis, improved nitrogen balance, and enhanced

Table 2. Potential uses of functional structured lipids.

Potential uses	SL related to food application	References
Margarine, butter, spreads, shortening, dressings, dips, and sauces	Benefat, Neobee and Olestra	48, 56, 58
Cocoa butter equivalents	Caprenin and Benefat	45, 50
Confectioneries and soft candies	Caprenin and Laurical	41, 45
Baking chips, baked goods	Benefat and Olestra	48, 56
Snack foods	Caprenin, Captex	45
Low caloric food	Caprenin, Benefat, Neobee	43, 49, 57
Frying oil	Genetically modified soybean oil, high-oleic sunflower oil and canola oil seed mutants with low linolenic/high oleic acid content.	75, 76
Infant food formulas	SLs containing EFAs and MCFAs such as Betapol	61, 64
Dairy products	Benefat	50

immune function (Table 3). Low-calorie structured lipids (SLs) are mainly designed for special nutritional applications, especially to meet the growing need for healthier foods and to prevent obesity (79, 80).

Data from several short-term investigations suggest that SLs are well tolerated and rapidly oxidized and cleared from the plasma (81-83).

Enteral and parenteral nutrition. The advantages of enterally fed SLs may well relate to differences in absorption and processing. Structure TAGs that contain MCFA may provide a vehicle for rapid hydrolysis and absorption, due to their smaller molecular size and greater water solubility in comparison to long-chain TAGs (84).

The TAGs in total parenteral nutrition (TPN) are normally administered as an emulsion. These emulsions are suspected of suppressing the immune function because pneumonia and wound infection often occur in patients treated with TPN. Kruimel et al. (85) attempted to explain this phenomenon, the results indicated that physical mixtures caused higher peak levels and faster production of oxygen radicals, compared to SLs. Chambrier et al. (86) conducted a similar study comparing the effect of physical mixtures and SL on postoperative patients. They did not see the hepatic function disturbances in patients given the SL, which are often observed with TPN.

Structured lipids synthesized from fish oil and MCFA were administered to patients undergoing surgery for upper gastrointestinal malignancies. This diet was compared to a control diet that differed only in its fat source. The SL diet was tolerated significantly better, led to improved hepatic and renal function, and reduced the number of infections per patient (87).

In a recent study, a novel SL was designed and synthesized based on lipase-catalyzed interesterification of camellia oil fatty acid methyl esters and triacetin. The SL product contains relatively high amounts of unsaturated fatty acids and has a lower risk of safety problems (88). Triacetin was found to be metabolically beneficial in hypermetabolic states, it improves protein utilization and structural components of the small and large bowel and reduces the development of intestinal mucosal atrophy associated with conventional parenteral nutrition in burn injury (89).

The use of fish oil emulsions in patients undergoing stent implantation resulted in lower incidences of atrial fibrillation and the length of intensive therapy unit ITU and hospital stay is reduced, compared to the therapy with soybean oil-based emulsions (90).

SLs containing MCFAs and n-3 PUFAs could be a therapeutic or medical lipid source, and may be useful in enteral and parenteral nutrition. These SLs provided an efficient way to supplement n-3 PUFAs and to provide energy from the MCFAs, which were the preferred substrate for oxidative metabolism (91). No signs of central nervous system toxicity were noted in patients given the SL, and there was no tendency to ketosis (92). Additionally, SLs were safe and efficient when provided to patients on home parental nutrition on a long-term basis because they may be associated with possible reduction in liver dysfunction (93).

Immune function. The essential constituents of structured lipids in terms of their effects on the immune system are fatty acids, which are composed of the hydrocarbon chain of various lengths. Fatty acids used in structured lipids can affect the immune system via several mechanisms. The first mechanism involves incorporation of lipids into the structure of the cell membranes and thus affecting their fluidity, permeability of ion channels and functions of membranous receptors. The second mechanism is associated with penetration of fatty acids to the cell where they can affect the production of eicosanoids, resolvins, cytokines, pathways responsible for signal transduction into the cell, and expression of genes. Moreover, fatty acids can alter cell apoptosis and production of reactive oxygen species (94).

Table 3. The main applications of SLs in human health

The main application of SLs in human health	References
Lipids in enteral and parenteral nutrition	79-88
Enhanced immune function	89-95
Improved nitrogen balance	96-100
Prevention of thrombosis	101-104
Reduced cholesterol and triacylglycerols	60, 105-107
Decreased cancer risk	98, 108-113
Reduced-calorie triacylglycerols	114-120
Absorption of structured lipids	121, 122

Studies reporting on novel emulsions based on olive and fish oils, structured lipids or mixed-type emulsions in which various lipid species replace conventional long-chain triglycerides indicate that these lipids are generally well tolerated. While long-chain triglycerides may promote inflammation due to conversion of n-6 polyunsaturated fatty acids into arachidonic acid-derived eicosanoids, structured lipids and olive oil emulsions appear more immune-neutral (95, 96). The structured lipid diet named Impact, containing low levels of linoleic acid, resulted in decreased length of hospital stay compared to other enteral formulae. Bower et al (97) also demonstrated a decrease length of hospital stay and infection rate when using diets with low level of linoleic acid an added fish oil.

Fish oil-based emulsions contain mainly long-chain n-3 polyunsaturated fatty acids. They have inhibitory effects on signal transduction and expression of genes involved in the inflammation, they also modify significantly the cytokine profile and increase the EPA levels in serum (98). Moreover, its use was demonstrated to enhance the production of DHA and EPA metabolites without affecting the production of AA, whose products show pro-inflammatory effects (99). Importantly, recent investigations indicate beneficial effects of parenteral fish oil on relevant clinical outcome measures.

Leukocyte-activating effects of medium-chain triglycerides in experimental studies await further characterization in vivo, although the recent data indicate that MCTs are not indifferent to the functioning of the immune system (100).

Nitrogen balance. Patients with sepsis and trauma are characterized by hyper-metabolism, insulin resistance and protein catabolism. Fat emulsions containing medium chain triglycerides have been suggested to be beneficial for these patients since medium chain fatty acids are a more readily available source of energy when compared to long chain fatty acids. Lindgren et al. (101) show a better nitrogen balance by the infusion of a structured lipid emulsion comprising medium chain fatty acids (MCFA) and long chain fatty acids (LCFA) compared to a pure long chain triglyceride (LCT) emulsion during short term infusion over three days in ICU patients. The amelioration in nitrogen balance in the SLs group was despite the lack of effect on respiratory quotient or energy expenditure. The mechanism behind the improved n-balance by infusion of a structured triglyceride comprising MCFA, compared both to pure LCT emulsions and to physical mixtures of MCT and LCT, is not obvious. It has been suggested that this occurs as a result of a more favorable energy metabolism.

In the study of Teo et al. (102), the effects of enteral feeding with SL composed of MCT and fish oil were compared with sunflower oil on energy metabolism in burned rats. A decrease in total energy expenditure (7%) and improved nitrogen balance were obtained in the SL group, suggesting that SL reduced the net protein catabolic effects of burn injury. A similar study by Mendez et al. (103) compared the effects of a structured lipid (made from fish oil and MCFAs) with a physical mix of fish oil and MCTs and found that the SL resulted in improved nitrogen balance in animals, probably because of the modified absorption rates of SL.

More studies in humans and animals indicate that the use of SLs in catabolic subjects improves nitrogen balance and preserves the function of the hepatic reticuloendothelial system (104, 105).

Thrombosis. Thrombosis is the formation of blood clots. Blood clotting involves the clumping together of platelets into large aggregates and is triggered when endothelial cells lining the artery walls are damaged. If the platelet membranes are rich in long-chain n-3 PUFAs, formation of certain eicosanoids such as prostacyclin I3 and thromboxane A3 is promoted. These do not trigger platelet aggregation as much as the corresponding eicosanoids, prostacyclin I2 and thromboxane A2, that are formed from n-6 PUFA. Therefore, long-chain n-3 PUFAs may help to reduce the tendency for blood to clot (106).

Mori et al. (107) suggested that n-3 fatty acid intake from fish consumption in conjunction with a low-fat diet was most beneficial in terms of reducing cardiovascular disease. Studies indicate that the n-3 fatty acids, especially EPA and DHA, may be effective in reducing the clinical risk of cardiovascular disease by favorably altering lipid and hemostatic factors such as bleeding time and platelet aggregation (108). EPA incorporating into the atheromatous plaque decreases the number of foam cells and T lymphocytes, reduces

the inflammatory process and increases the stability of platelets (109).

Cholesterol and triacylglycerols concentrations. Long-term feeding studies with an SL containing MCFAs and fish oil fatty acids showed that SL modified plasma fatty acid composition, reflecting dietary intake and induced systemic metabolic changes that persisted after the diet was discontinued (110). When SL (emulsion of MCT + fish oil composed of 50% MCT, 40% fish oil, and 10% canola oil) and soybean oil were provided to rats enterally, TAG and cholesterol levels in liver were lowered in the SL group (111).

Rats were fed a diet containing coconut oil, coconut oil-sunflower oil blend (1:0.7 w/ w) or structured lipid enriched with omega 6 PUFA at 10% levels for a period of 60 days. The SL lowered serum cholesterol levels by 10.3 and 10.5% respectively in comparison with those fed coconut oil and blended oil. Similarly the liver cholesterol levels were also decreased by 35.9 and 26.6% respectively in animals fed structured lipids when compared to those fed on coconut oil or the blended oil. Most of the decrease observed in serum cholesterol levels of animals fed structured lipids was found in LDL fraction. The triglyceride levels in serum showed a decrease by 17.5 and 17.4% while in the liver it was reduced by 45.8 and 23.5% in the structured lipids fed animals as compared to those fed coconut oil or blended oil respectively (65).

SL containing caprylic and n-3 polyunsaturated fatty acids was synthesized and this enzymatically produced SL vs soybean oil (20% of diet weight) were fed to female mice for 21 days. The result showed that the concentration of total cholesterol, LDL cholesterol, and triacylglycerol were significantly decreased in SL-fed group (112).

Tumor and cancer risk.

In contrast to the tumor promoting effects of diets high in fat, some FAs of chain length 8-C or higher have been found to have cytolytic activity, which can be directed against tumor cells in some situations, and represent a novel type of antitumor agent. In a study by Burton (113), caprylic acid showed oncolytic effects in liver of mice and rats.

Many studies have shown that n-3 fatty acids can decrease the number and size of tumors and increase the time elapsed before the appearance of tumors (114). Reddy and Maruyama (115) showed that diets containing high levels of fish oils were effective in destroying some cancer cells, but it is not known whether such results are reproducible with humans, or what potential side effects exist (116).

Medium chain fatty acids possess a nutritional advantages compared with other fatty acids in that they are non-tumor-producing forms of fat (117). Ling et al. (118) demonstrated that tumor growth in mice was decreased when they were fed with a SL made from fish oil and MCTs.

Diet and calorie intake. Salatrim, Neobee and Caprenin are widely known as the low-calorie fats, whereas Olestra is known as a zero calorie fat. Reduced calorie SLs are designed by taking advantage of either limited absorption of long-chain saturates or the low caloric value of SCFAs. In humans, SCFAs contribute to 3% of total energy expenditure and these are more easily absorbed in the stomach and provide fewer calories than MCFAs and LCFAs (119). Thus, acetic, propionic, and butyric acids have caloric values of 3.5, 5.0, and 6.0 kcal/g, respectively.

Despite containing saturated fatty acids, MCT are utilized by the human body more readily than triacylglycerols containing other fatty acids. Their digestion process omits the lymphatic system and they enrich the cardiovascular system without hydrolysis or re-esterification. Therefore, MCT do not accumulate in the fatty tissue and do not form a reserve fat and, unlike other triacylglycerols, they have lower caloric values. Thus, MCT are used as a source of easily available energy and a low-calorie product (120).

Although MCTs provide fewer calories than absorbable long chain triacylglycerols (LCTs), MCTs need to be used with LCTs to provide a balanced nutrition in enteral and parenteral products (121, 122). In many medical foods, a mixture of MCTs and LCTs is used to provide both rapidly metabolized and slowly metabolized fuel as well as EFAs. Clinical nutritionists have taken advantage of the simpler digestion of MCTs to nourish individuals who cannot utilize LCTs owing to fat malabsorption. Thus, patients with certain diseases (Crohn's disease, cystic fibrosis, colitis, enteri-

tis, etc.) have shown improvement when MCTs are included in their diet (123).

For example, Akoh and Yee (124) interesterified tristearin with tricaprin (C10:0) or tricaprylin (C8:0) with sn-1,3-specific immobilized lipase to produce a low calorie SL.

Another group of researchers synthesized an SL from natural vegetable oils so it would contain EFAs and natural antioxidants (125). The synthesized product delivered 5.36 kcal/g and had an improved plastic nature, which increases the potential food applications for such a product, especially since it is a trans-free solid fat. After producing the SL, it was fed to rats and compared to a control group fed sunflower oil. No differences were observed in the amount of food consumed, which indicates that the palatability and taste of the SL was very similar to the native sunflower oil (125).

Absorption of structured lipids. In the absence or deficiency of pancreatic lipase, previous studies have indicated that a large fraction of MCT can be absorbed as triacylglycerol, whereas LCT are not absorbed. However, structured triacylglycerols containing LCFAs in the sn-2 position and MCFAs in the primary positions have improved metabolic benefits and have potential advantages for providing polyunsaturated fatty acids. The presence of MCFAs in dietary fatty acid as well as the triacylglycerol structure may influence the absorption and lymphatic transport of fatty acids (126). Swails et al. (127) demonstrated that diets containing an SL composed of MCFAs and linoleic acid led to improved absorption of EFAs in patients with cystic fibrosis.

Finally, the differences in the health effects of structured lipids are largely dependent on the composition of lipid mixtures, particularly the content of MUFA, n-6 or n-3 PUFA. Table 4 gives the suggested levels of some of these fatty acids in SLs intended for clinical applications (123).

Critics attribute a variety of gastrointestinal complaints to the consumption of olestra. Symptoms cited include bloating, diarrhea, cramps, loose stools, and urgency of defecation (38, 48). In addition, olestra is lipophilic, non-digestible and non-absorbable, so it has the potential to interfere with the absorption of other components of the diet, especially lipophilic ones, eaten at the same time as olestra. Among these biochemicals are fat-soluble vitamins (A, D, E, and K) and carotenoids, such as beta-carotene, lycopene, lutein, and zeaxanthin (128, 129). However, the effects can be offset by adding specified amounts of the vitamins to olestra foods.

The concentration of vitamins A, D, E, and K required for supplementation in olestra-containing foods are 0.34 X RDA (Recommended Dietary Allowance) for vitamin A/10g olestra, 0.3 X RDA for vitamin D/10g olestra, 0.94 X RDA for vitamin E/10g olestra, and 1.0 X RDA for vitamin K/10g olestra (130).

As a result, the Food and Drug Administration (FDA) requires that food containing olestra be labeled with the statement: "This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added".

Conclusion

Public concerns about obesity, cancer and cardiovascular disease have increased our interest in minimizing the consumption of saturated fats and trans fats. These concerns have been a driving force in the lipid industry to develop fat-based ingredients that retain the physical, functional and sensory features of traditional lipids and provide specific nutritional properties and health benefits.

Food chemists have developed a number of synthetic fats using new processing technologies, along with the creative use of newly discovered functional properties of triglycerides. Chemical and enzymatic interesterification lead to the development of structured lipids which can be useful for diabetics, people who are trying to lose weight, and others concerned about maintaining a healthy diet. At the same time, this is not to ignore that while FDA had approved the use of different SLs, EFSA (European Food Safety Authority) restricted the use of some SLs such as Olestra because of the potential health risks for some people who may be allergic to such products and may develop other health problems by using them.

Research on structured lipids remains an interesting area that holds great promise for the future and has certainly not come to an end. Food chemists will continue to search for new products with which to aug-

Table 4. levels and function of different fatty acids in SLs intended for clinical applications

Fatty acid	Levels and function	References
n-3	2–5% to enhance immune function, reduce blood clotting, lower serum triacylglycerols, and reduce risk of coronary heart disease.	93, 102, 103, 107
n-6	3–4% to satisfy essential fatty acid requirement in the diet.	118
n-9	monounsaturated fatty acid (18:1n-9) for the balance of long chain fatty acid.	118
SCFA and MCFA	30–65% for quick energy and rapid absorption, especially for immature neonates, hospitalized patients, and individuals with lipid malabsorption disorders. SCFAs affect gastrointestinal function by stimulating pancreatic enzyme secretion and increasing sodium and water absorption in the gut. The TAGs, containing MCFA, are applied in the nutrition of infants as well as in the clinical nutrition of patients with digestion or nutrient absorption disorders, since their digestion requires negligible amounts of bile salts and pancreatic lipase.	106, 108, 114
LCFA	They are mixed with bile salts and lecithin to form micelles, which are absorbed through the wall of the intestine. They are very slowly oxidized to release energy. LCFAs need to be used with MCFAs to provide a balanced nutrition in enteral and parenteral products. In many medical foods, a mixture of MCFAs and LCFAs is used to provide both rapidly metabolized and slowly metabolized fuel as well as EFAs.	116,117

SCFA: Short chain fatty acid, MCFA: Medium chain fatty acid, LCFA: Long chain fatty acid, TAGs: Triacylglycerols.

ment and improve peoples' diets. Designing SLs with specific fatty acids at specific locations of the TAG for use in medicine needs more studies. For example, it may be desirable to develop a SL for patients with cystic fibrosis that contains PUFA (e.g., EPA or DHA) at the sn-2 position, and MCFA at the sn-1, 3 positions.

Further research is also needed to stabilize the modified fats containing PUFAs during storage by incorporation of appropriate antioxidants and adequate packaging technologies. Moreover further research should focus on the various esterification processes, the metabolism and medicinal importance and economic feasibility of large-scale production of SLs.

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