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Future views on nanonutrition for critically ill patients: The role of extra virgin olive oil nanoemulsion in sepsis enteral nutrition

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Abstract

Enteral nutrition (EN) can maintain the structure and function of the gastrointestinal mucosa better than parenteral nutrition. Early intervention by enteral nutrition in critically ill patient may help the patient from fatality of multiple organ failure. Oral nutrition is an attempt to provide a physiological nutrition that is expected to trigger the immune system, prevent blood stream infection from the intravenous route, and reduce cost of therapy. One of the problems that inhibits supply of enteral nutrition in critically ill patients is absorption disorders that cause the body's nutritional needs to be hampered. Administration of extra virgin olive oil (EVOO) in the form of nanoemulsion is expected to improve pharmacokinetics and pharmacodynamics in those patients. EVOO is one functional food that has a lot of health benefits. Nanoemulsion-based delivery systems are proven to increase utilization of lipophilic bioactive components in food, personal care, cosmetic, and pharmaceutical applications. So far, there is no report describes the use of enteral nanonutrition in critically ill patients. This review discusses the perspective view of using EVOO nanoemulsion to care the critically ill patients.

Key words: Nanonutrition, critically ill patient, extra virgin olive oil nanoemulsion, oral formulation, emulsion.

Introduction

Enteral nutrition (EN) support can be determined from the supply of calories, protein, electrolytes, vitamins, minerals, trace elements, and fluids through the intestinal route. The early initiation of EN including fibber may prevent atrophy of intestinal mucosa and attenuation of gastrointestinal peristalsis, because the energy substrates for intestinal mucosa are partially supplied via intraluminal. In addition, it is believed that bacterial translocation (BT) can be prevented by early initiation of EN. (1) Prevention of bacterial translocation is one of efforts to prevent sepsis that has high mortality rate.

Sepsis is a serious clinical condition that can result in death, as a result of systemic inflammatory response syndrome including fever leukopenia, hypotension, and failure of many organs. (2) An unbalanced pro- and anti-inflammatory response, inflammatory resolution disorder, and persistent inflammation have an important roles in the acute and/or chronic phases of sepsis. (3)

Oils are very important substances in human nutrition. However, they are sensitive to oxygen, heat, moisture, and light. In recent years, there has been a growing interest in the modification technology of oils. Methods that modify oil characteristics and make oils suitable applications have been increasingly studied. Nanotechnology has become one of the technologies that can revolutionize conventional food science and the food industry. (4,5)

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Nanotechnology, especially nanoemulsions (NEs), has gained increasing interest for researchers. NEs are important in many industries because they have small droplets with a high surface area. The formation of nano-sized emulsions can be divided into two types: high and low-energy methods. High-energy methods are high pressure homogenization, microfluidization, and ultrasonic emulsification. Spontaneous emulsification, phase inversion temperature (PIT), phase inversion composition (PIC), and the less-known phase-D emulsification (DPE) method are emphasized in the low-energy method. The NEs application is explained in three main areas namely food, cosmetics, and drug delivery. (6,7)

NEs are sub-micron sized colloidal particle systems, which act as carriers of drug molecules. As a drug delivery system they enhance the therapeutic efficacy of the drug and minimize adverse effect as well as the toxic reactions. Major application includes treatment of infection of the reticuloendothelial system (RES), enzyme replacement therapy in the liver, treatment of cancer, and vaccination. (8,9)

Early nutrition therapy is recommended for individuals in critical conditions. (10) The parenteral and enteral routes are currently prescribed for critically ill patients. (11) There is increasing evidence that significant benefits are achieved if nutrients are delivered within the gut compared with the parenteral route. However, there is increasing assistance for combined enteral-parenteral therapy in the case of sustained hypocaloric enteral nutrition. (11) Despite limited investigation, a strategic temporary minimal enteral nutrition with hypocaloric content has been recommended, with the aim of avoiding the consequences of overfeeding syndrome and protecting the gut from the threat of hypoperfusion. (12,13) Enteral nutrition may be used with caution during a period of hypotension. Evidences of poor gastrointestinal function such as increased nasogastric tube output, unexplained abdominal pain, and abdominal distention, or the development of dilated loops of bowel or intramural gas (pneumatosis intestinalis) on radiographic studies should be interpreted as potential indicators of gut ischemia. (14)

There is consistent evidence that nutrients delivered by the gut promote significant benefits when compared with the intravenous route. Enteral feeding is associated not only with lower costs but also with shortening of hospital stay and infectious complications. (15) This review article interest giving extra virgin olive oil (EVOO) nanoemulsion in sepsis condition.

The active absorption of materials, particularly sugars and amino acids, causes a major increase in oxygen consumption and is dependent on an adequate supply of oxygen and blood flow. Passive absorption appears to be primarily a function only of blood flow. It is conceivable that a portion of local vascular control during active absorption could be related to a decrease in tissue PO2 during absorption. Although Svanvik, et al have shown that arterial PO2 must be reduced by approximately one-half to increase intestinal blood flow to about 200% of control, this does not necessarily negate a possible role for oxygen in absorptive hyperemia as Svanvik, et al have proposed. Duling has recently demonstrated that a decrease in general tissue PO2 causes substantial vasodilation, even though a comparable change in PO2 at the arteriolar wall when tissue PO2 is normal has a minor dilatory effect. The basic question is whether or not intestinal tissue PO2 is sufficiently decreased by active absorption to cause a dilatory response. (16)

Extra virgin olive oil

The major components of olive oil are fatty acids that represent more than 98% of its composition. Fatty acids contained in olive oil consist of monounsaturated fatty acids (MUFAs), such as oleic acid (55-85% of the total fatty acids). Beside that, it also contains polyunsaturated fatty acids (PUFAs), such as linoleic acid and saturated fatty acids (SFAs) like stearic or palmitic acids. (17)

EVOO contains around 36 phenolic compounds including tyrosol, hydroxytyrosols, oleocanthal, and oleuropein and carotenes. These phenolic compounds enter brain and produce neuroprotective effects through their antioxidant, anti-apoptotic, and anti-inflammatory activities. (18) In addition to polyphenols, virgin olive oil contains vitamins such as α- and γ-tocopherols (around 200 ppm) and β-carotene, phytosterols, pigments, terpenic acids, flavonoids, and squalene. (19)

The consumption of olive oil is associated with a low incidence of cardiovascular diseases, neurological disorders, and breast cancer. (20) It is well known that polyphenols concentration of extra virgin olive oils may differ, depending on both cultivars, degree of ripeness of the olives as well as the extraction procedure but only tyrosol, oleuropein, gallic acid, caffeic acid, and vanillic acid are the most important agents responsible for the antioxidant activity in olive oils. (21) It is clear that the antioxidant effects in vivo of EVOO and olives are strictly linked to the bioavailability of these molecules from the diet. Nutritional trials in human and

animal models reported that olive phenols are rapidly absorbed in a dose-dependently manner from the gastrointestinal tract and distributed through all organs as conjugated forms. (22) Olive oil, tyrosol and hydroxytyrosol, are dose-dependently absorbed in humans after ingestion and that they are excreted in the urine as glucuronide conjugates. (23)

The impact of an in vitro procedure that mimics the physiochemical changes occurring in gastric and small intestinal digestion on the bioaccessibility and antioxidant activity of phenols from 10 extra virgin olive oil samples was assessed. EVOO phenols were totally extracted in the aqueous phase, which reproduces gastric fluids during the digestion procedure. EVOO with different phenolic compositions would show a different capacity to act as a potential antioxidant after ingestion. (24) Polyphenols are considered to be the main contributors to the antioxidant activity of olive oils. (25)

Depending on the manufacturing process, we can find different types of oil: (17)

- Virgin olive oil: obtained directly from the ripe fruit by mechanical procedures. It is the only consumed raw without the use of any solvents, so it keeps all its properties intact. Olive oil has excellent antioxidants such as polyphenols and vitamin E, which are lost if the oil is subjected to refining processes. "Extra virgin" olive oils are those that have no taste defects and have a very low acidity rate (0.8%). They are the most expensive ones. Those labeled as "Virgin" olive oils have modest taste defects and a slightly higher acidity level (2%).
- Pure olive oil: which is a blend of refined olive oil and virgin olive oil. In the market, there are varieties of intense flavor and mild taste depending on whether more or less virgin olive oil is added, respectively.
- Olive pomace oil: which is obtained from the pulp and seeds of olives after extraction of virgin olive oil using chemical solvents. It must pass a refining process and virgin olive oil is added after to make it suitable for consumption.

Advantages and disadvantages of EVOO are shown in **Table 1**. Although EVOO is prone to oxidation during production and storage, phenolic compounds have been demonstrated to remain stable under appropriate storage conditions. (26) EVOO quality can be safeguarded by using proper packaging, ideal storage conditions (cool and dark), and having an accurate best before date. (27)

Various studies (in vivo and in vitro) have demonstrated that olive oil phenolic compounds beneficially alter microbial activity, oxidative processes, and inflammation. (26)

The antimicrobial activities of olive oil phenolics were tested against three foodborne pathogenic bacteria: Escherichia coli O157:H7, Listeria monocytogenes, and Salmonella enteritidis in vitro. A synergistic interaction was noted amongst various olive oil phenolic compounds and this synergism appeared to increase antimicrobial capacity compared to that of individual compounds. The study's authors concluded that the use of EVOO in foods may help to prevent foodborne disease. (28)

Emulsions and nanoemulsions

Nanoemulsions are biphasic dispersion of two immiscible liquids: either water in oil (W/O) or oil in water (O/W) droplets stabilized by an amphiphilic surfactant. (29) Nanoemulsions are considered excellent delivery systems for sensitive bioactive compounds improving the solubility and bioavailability of the bioactive compounds. (30) Nanoemulsion has droplets covering the size range of 100-600 nm. In the present work, nanoemulsions were prepared using the spontaneous emulsification mechanism, which occurs when an organic phase and an aqueous phase are mixed. (31,32)

An interesting in vitro and in vivo studies about the influence of the droplet size on the anti-allergic and anti-inflammatory activities of a curcumin NE was conducted by Onodera, et al (2015). The tested curcumin NE was prepared by a thin-film hydration method. Soybean oil and hydrogenated egg yolk phosphatidylcholine (HEPC) were dissolved in the organic solvent chloroform, as curcumin and Tween-80 separately. All three solutions were mixed and dried afterwards by rotary evaporation and vacuum desiccation. The so obtained dry thin film was hydrated with distilled water and sonicated at 25-55 °C till the desired oil droplet size of 50 nm, 100 nm, and 200 nm were obtained. Remarkable, both in vivo tests in orally fed mice and in vitro cell culture tests revealed the advantageous properties of 100 nm curcumin NE despite curcumin NE with 50 nm or 200 nm. (33)

In context to this, nanoemulsions have gained great attention and have been used as a delivery system for not only enhancing the stability, solubility as well as bioavailability of bioactive compounds in body, but also protecting them from adverse environmental conditions (pH, light, moisture, temperature, etc.). Nanoemulsions are used to reduce the separation of particles via sedimentation or creaming and improve the appearance (clear suspension) as well as other physico-chemical proper-

ties of food systems in which bioactive compounds are incorporated. (34)

The result from Rao and McClements (2011) indicated that relatively stable nanoemulsions could be formed at pH 6 and 7, and stable microemulsions at pH 5 and 6, but extensive particle growth/aggregation occurred at lower and higher pH values. Microemulsions were relatively stable to salt addition (0-200 mM NaCl), but nanoemulsions exhibited droplet aggregation/growth at ≥50 mM NaCl after 1 month storage at pH 7. Microemulsions formed gels at low temperatures (5 °C), were stable at ambient temperatures (23 °C), and exhibited particle growth at elevated temperatures (40 °C). Nanoemulsions were stable at refrigerator (5 °C) and ambient (23 °C) temperatures, but exhibited coalescence at elevated temperatures (40 °C). (35)

Tan and Nakajima (2005) had successfully prepared b-carotene in nanoemulsions using high-pressure homogenization. They studied the influence of phase ratio and homogenization conditions on droplet size and b-carotene content. (36) Silvia, et al (2011) prepared b-carotene in nanoemulsions using high-energy emulsification with evaporation technique. Their work presented a proof-of-concept of the use of a high-energy emulsification-evaporation technique to produce oil in-water nanoemulsions of b-carotene, without the need of using high-pressure homogenization. The results showed that time and shear rate of homogenization were the most significant processing parameters influencing nanoemulsion size distribution. (37)

Preparation of nanoemulsions

Formulation aspects and method of preparation of nanoemulsion

NEs can be prepared in three ways: (1) oil-in-water (O/W) NEs where oil is disseminated in a continuous aqueous phase; (2) water-in-oil (W/O) NEs where water is dispersed in a continuous oil phase; and (3) the bicontinuous phase. NEs have a variety of shapes as they can be seen as spherical swollen micelles or bicontinuous structures. (38)

Nanoemulsion systems can be formulated by appropriate proportions of water, surfactant, and oil. In order to determine the optimum formula of w/o nanoemulsions, various combinations of oil-surfactant-water were tested. Emulsifiers are surface-active molecules that are capable of adsorbing to droplet surfaces, facilitating droplet disruption, and protecting droplets against aggregation; thus their selection is one of the most crucial factors considering the proper design of a nanoemulsion. (39,40)

Nanoemulsions are prepared using low-energy, high-energy, and combined methods. The high-energy methods include high-shear stirring, ultrasonic emulsification, high-pressure homogenization, in particular, microfluidics and membrane emulsification. The most widely used low-energy methods include the PIT method, the emulsion inversion point (EIP) method, and the spontaneous emulsification in nonequilibrium systems. The combined methods include high-shear stirring to obtain macroemulsions containing special substances (so-called nano-emulsifiers) as the first step. (41)

In the high-energy mechanism, the average droplet size on a nanoscale is difficult to obtain. To overcome this drawback, a multipass regime must be adopted as the maximum degree of dispersion of the system is not reached by the single-pass regime and the efficacy decreases when high viscosity systems are used. (41,42)

Formulation of nanoemulsion includes active drug, additive, and emulsifier. The preparation of nanoemulsion include two methods: (a) high-energy emulsification and (b) low-energy emulsification. (8) The high-energy emulsification method includes high-energy stirring, ultrasonic emulsification, high-pressure homogenization, microfluidization, and membrane emulsification. The low-energy emulsification method includes phase inversion temperature, emulsion inversion point, and spontaneous emulsification. Using a combined method, which includes the high-energy and low-energy emulsification, it is possible to prepare reverse nanoemulsion in a highly viscous system. (8)

High-energy dan low-energy

Three methods are described for nanoemulsion preparation, namely high-energy emulsification (using homogenisers), low-energy emulsification whereby water is added to an oil solution of the surfactant, and the principle of the phase inversion temperature (PIT). (43)

In general, the high-energy process is followed by two steps: first, the deformation and disruption of macrometric droplets into the smaller droplets; second, the surfactant adsorption at their interface (to ensure the steric stabilization). (44) Low-energy process depends on the intrinsic physicochemical properties of the surfactants, co-surfactants, and excipients composing the formulation. (45) Recently, the interest in the low-energy methods for nanoemulsion generation has grown considerably being a mild process for the sensitive molecules and energy-saving process for large-scale production. (41)

Ultrasonic emulsification

Ultrasonic emulsification is very efficient in reducing droplet size. In ultrasonic emulsification, the energy is provided through sonotrodes called as sonicator probe. It contains piezoelectric quartz crystal which can expand and contract in response to alternating electric voltage. As the tip of sonicator contacts the liquid, it produces mechanical vibration and cavitation occurs. Cavitation is the formation and collapse of vapour cavities in liquid. Thus, ultrasound can be directly used to produce emulsion; it is mainly used in laboratories where emulsion droplet size as low as 0.2 micrometer can be obtained. (8) Process mechanism, advantages, and disadvantages of nanoemulsion are shown in **Table 2**. (46)

Nanoemulsion verification

Cryogenic-temperature scanning electron microscopy (cryo-SEM) is an excellent technique for imaging liquid and semi-liquid materials of high vapour pressure, which are highly viscous or contain large (>0.5 μm) aggregates. (47)

On the other side, cryogenic transmission electron microscopy (cryo-TEM) methods have recently begun to be applied to engineered nanoparticles (48). The advantages and disadvantages of cryo-TEM are shown in **Table 3**.

Nutrition in critically ill patients

Enteral nutrition is the preferred method to provide nutritional support in critically ill patients. Despite the advantages of enteral feeding, enteral nutrition may not be tolerated by all patients and may cause complications such as diarrhea, constipation, aspiration, and bowel ischemia. (49) All of these complications make the patient condition becomes worst. The idea of giving nanoemulsion as enteral nutrition to patients with sepsis based on sized and encapsulation is expected to benefit the patient.

Splanchnic ischemia of septic origin and the cascade of biochemical and biologic events leading to multiple-organ dysfunction has reached such proportions in most intensive care units (ICUs) that it is fast becoming the most common cause of death in critically ill surgical patients. Over the last three decades, nutritional support of the critically ill patient has progressed from an afterthought to a vital part of the intensivist's therapeutic armamentarium. The initial purpose of parenteral or enteral nutrition administration was the caloric cover of the energy demands of the patient. Later it became apparent that enterally administrated nutritional support prevents mucosal weight loss, increases epithelial proliferation, and improves maintenance of gut mucosal integrity. Several investigators have suggested that these beneficial effects of intraluminally supplied elements on the gut mucosa are derived from the improved supply of absorbed nutrients to the mucosal epithelium or from the release of trophic hormones. (2) In contrast, this trophic benefit could reflect improved mucosal blood flow due to food absorption-induced hyperemia. (3) Based on that explanation, nanoemulsion may be a good idea for patient in ICU.

The previous article by Sadikot, et al (2017) was one of the example reports of nanotechnology application in critically ill patient. They reported about the nanomedicine for acute respiratory distress syndrome (ARDS) caused by sepsis. ARDS represents an unmet medical need with an urgency to develop effective pharmacotherapies. Multiple promising targets have been identified that could lead to the development of potential therapies for ARDS; however, they have been limited because of difficulty with the mode of delivery, especially in critically ill patients. Nanobiotechnology is the basis of innovative techniques to deliver drugs targeted to the site of inflamed organs, such as the lungs. Nanoscale drug delivery systems have the ability to improve the pharmacokinetics and pharmacodynamics of agents, allowing an increase in the biodistribution of therapeutic agents to target organs and resulting in improved efficacy with reduction in drug toxicity. Although attractive, delivering nanomedicine to lungs can be challenging as it requires sophisticated systems. Here we review the potential of novel nanomedicine approaches that may prove to be therapeutically beneficial for the treatment of this devastating condition. (50)

The illustration we mentioned above gives us some view that nutrition still could be given closely to the physiologic condition. Enteral nutrition with nano scale of delivery system make it possible because the particle size is the primary precondition that can make interaction with immune cell. Nowadays, nanotechnology-based modulation of the immune system is presented as a cutting-edge strategy, which may lead to significant improvements in the treatment of severe diseases. The different immune responses can be elicited by tuning nanosystems properties. (51,52)

Enteral nutrition absorption in sepsis

Possible applications of nanoemulsions are strongly limited by the stability of nanoemulsions, except for nanoparticle preparation when the process of physical or chemical solidification takes place

within the period of stability of nanoemulsions. Nanoemulsions are proposed for numerous applications in pharmacy as drug delivery systems because of their capacity of solubilizing non polar active compounds. Due to the stability problems, most of proposed formulations are self-emulsifying systems and the nanoemulsions are produced just before their application. Although there have not been reported too many applications in other fields, there is a great potential for nanoemulsion applications if Oswald ripening destabilization mechanism is limited by using very insoluble oils. (53) Nanoemulsions can be used for the encapsulation and oral delivery of bioactive lipophilic components, such as nutraceuticals and pharmaceuticals. (54,55)

The previous study by Gosche, et al (1990) mentioned that the hyperemia induced by direct application of glucose to the mucosal surface of the small intestine is able to overcome the flow-restrictive effect of live E coli bacteremia. Restoration of blood flow appears to have been the result of a reversal in arteriolar vasoconstriction that occurs at multiple levels in the intestinal microcisrculation during hyperdynamic sepsis. We suggest that this direct hyperemic effect of transmucosal absorption of nutrients on the intestinal microvasculature is one factor that accounts for the maintenance of mucosal integrity associated with enteral alimentation. (56)

The gastrointestinal tract may not absorb with normal efficiency (due to edema, etc.) and insufficient energy is delivered to cope with the metabolic stress. (57) Improved understanding and recent innovations in technology and informatics that are applicable to the bedside promise to advance the precision and appropriateness of our future nutritional care. The idea is to utilize modern advances in technological, molecular science, and informatics to better monitor and deliver nutritional requirements for optimized and nuanced care for the individual through all stages of critical illness. (57) When mucosal immunity is successfully induced, mucosal antibodies (IgA) are produced, and the T-cell-mediated immune response and a systemic antibody response occurs. Oral delivery is considered the gold standard at present, with better patient compliance and a lower social healthcare burden. (58) Here, enteral nanonutrition may have some good impact to the critically ill patient who has poor gastrointestinal tract function based on basic theory in the previous study about mucosal immunity. (59)

Fat metabolism in sepsis

Septicaemia is a major cause of morbidity and mortality among critically ill patients. In the United States alone, the incidence of septic shock is 200,000 per annum and 40 percent of these cases Gram-negative organisms are the cause. Lipid metabolism is altered in septic shock; Gram-negative septicaemia can induce profound change (**Table 4**). (60,61) Some abnormalities result from failure of specific organs, while others are part of a host response. Increasingly, artificial nutrition is used to meet the raised metabolic fuel demands in affected individuals, and lipids have become an important source of this fuel. The regulation of lipid metabolism in the patient with sepsis is complex and still unclear. In this review an attempt is made to elucidate the mechanisms influencing this regulation, the consequences for the host and the relevance in terms of nutritional support. (62)

The elevation in serum triglycerides in patients with infection caused by Gram-negative bacilli cannot be explained by an increase in absorption of dietery fat, for there were no increase in chylomicrons. However, these elevations were associated with increases in pre-beta-lipoproteins. Pre-beta lipoproteins, which contain 50 to 80 percent triglycerides, are sinthezised mainly in the liver. Therefore, it is likely that the elevations in triglyceride levels were associated with decreased pheripheral utilization or increase production by the liver that could have been secondary to increased mobilization of fatty acids from pripheral lipid store. (61)

Nanoemulsion with lipid based delivery system is the important thing when we try to modulate cells activity. The factors of nanoparticle that could influenced the cells are particle size, surface charge, surface hydrophilicity/lipophilicity, and antigen-adjuvant binding strength. (63) The scientific report by Bielinska, et al (2014) informed that giving nanoemulsion oil-in-water through nasal administration has a unique mechanism of action. Nanoemulsion activates innate immunity, induces specific gene transcription, and modulates NF-kB activity. (64) This article gives an idea that if we give nanoemulsion as adjunct nutrition through enteral pathway may has the same effect as the reported article by Bielinska, et al (2014). Lipid is needed to manipulate the cell surface and the size of lipid give the opportunity to be absorbed in optimum result. (65,66) The previous study by Serra, et al (2017) reported that extra virgin olive oil nanoemulsion has good effect in modulating immune response induced by dietary and endogenous cholesterol oxidation products in human immune cells and may hold benefit in controlling chronic

immune and/or inflammatory processes. (67)

Particle size and immunology repsonse

The previous research by Bandi, et al (2020) informed that particle size was the most important factor that influence the absorption. (68) This article support that nanonutrition may give the optimal impact to the critically ill patient. Many natural chemicals in food are in the nanometer size range, and the selective uptake of nutrients with nanoscale dimensions by the gastrointestinal tract (GIT) is a normal physiological process. How if the patient is in the abnormal condition, such as sepsis that has GIT failure? We need a mode of delivery that can against the GIT barrier that in the abnormal condition caused by sepsis. The answer may come from nano technology.

The complex pathophysiology of sepsis actually provides many opportunities for treatment at a cellular level, and even at a molecular level. But since these therapies aiming a target at the molecular or cellular level are applied at a systemic level, they generally cannot be translated to safe and effective therapies. Applications of nanotechnology may serve to design better therapies that can apply treatment and can monitor results at the level of the proposed effect, and may instantly modify the amplitude and direction of therapy accordingly at the molecular or cellular level. (69)

Material sizes between 20-40 nm have been found to be an optimal measure of absorption of nanoparticles by dendritic cells. (70,71) The size of the nanoprticles (20-40 nm) penetrates the tissue barrier and circulates through the lymphatic flow faster than the larger nanoparticles (>100 nm). Large nanoparticles are retained by cells and require dendritic cells to facilitate transport to lymph nodes. So that smaller nanoparticles will begin to activate the adaptive immune response more effectively. (72)

Future obsession

Nanoemulsions are of great interest in food industry finding various food applications. Many studies on nanoemulsions have been presented recently, however there are only few references found in food systems, because of the limited number of food grade surfactants able to facilitate the nanoemulsion formulation. Some surfactants are not permitted in foods whereas others may be added only at low concentrations. (73) The distribution of surfactant between the interfacial region and the oil phase depends upon a number of factors, such as: hydrophilic-lipophilic balance (HLB) value of surfactant, nature of oil, interfacial forces, thermal conditions, and interaction between the surfactant and the system composition. According to relevant studies nonionic food grade emulsifiers with HLB values ranging from 6 to 12 are able to form w/o nanoemulsion.

Very rarely patients in ICU without using nasogastric tube. Its condition gives the chance for using nanoemulsion in nutrition composition. The obstacles in the form of various pH condition in human GIT could be avoid. The hope is the absorption will works optimal without any influence of the various pH. But in fact the obstacle comes from the stomach which has pH 1-3, small intestine has pH 6-7.5, and colon pH is 5-7. (38) The challenge of nanoemulsion formulation to be well absorbed is still an ongoing research material. The application of nanonutrition in sepsis patient may be supported by transcellular mecahnisme, typically absorption occurs by an endocytosis mechanism. We hope that nano-emulsion could be expected to do immune regulation by communication between cell and nanoparticle that contain of advantageous bioactive.

Summary

Extra virgin olive oil nanoemulsion is a promising food ingredient to be given to septic patients. Nanoemulsion sized is expected to improve absorption of extra virgin olive oil, while encapsulation form will protect the bioactive content in extra virgin olive oil.

Table 1. Advantages and disadvantages of EVOO

Advantages	Disadvantages	References
• More economical and beneficial in the long run • Potential cancer preventative agent • Antidiabetic, cardioprotective, nephroprotective, and neuroprotective effects in the body	• The price of extra virgin olive oil is much more expensive than the other types of oil • Prone to oxidation during production and storage	17,27,74,75

Legend: EVOO=extra virgin olive oil.

Table 2. Nanoemulsion process mechanism, advantages, and disadvantages

Nanoemulsion process		Advantages	Disadvantages	References
High-energy	Ultrasound generators	• Less expensive than the other high-energy equipment • More flexible on surfactant • Internal structure selection than low-energy process	Limited to small batches	41,44,45,53
	High-pressure homogenization	• More flexible on surfactant • Low process time • Internal structure selection than low-energy process	• High cost • Not recommended for thermo- or shear- sensitive compounds	
	Microfluidization	• Controlled size droplets • Allows multiple emulsion preparation	• High cost • Not recommended for large scale production	
Low-energy	Phase inversion composition	• Low cost • Easy to scale up • No need to heat up	• Requires gradual addition of one phase to another • Requires to the presence of LC or mid-range ME phases	41,44,45,76
	Phase inversion temperature	• Low cost • Easy to scale up	• Limited to the nonionic surfactant • Requires to the presence of LC or mid-range ME phases • Heat energy is required	
	Spontaneous emulsification	• Low cost • Easy to scale up	• Limited amount of oil phase • Presence of solvent	

Legend: LC=liquid crystal; ME=microemulsion.

Table 3. Advantages and disadvantages of cryo-TEM

Advantages	Disadvantages	References
• A powerful way to visualize nanostructures in 3D, which can resolve ambiguity present in 2D projection images • Can be applied to nanostructures that have a uniform and homogeneous structure, such as icosahedral viruses, the vault particle, and DNA-origami frames • Provide detailed information about cells and viruses	• Image contrast in 2D cryo-micrographs can be quite low • Frozen specimens are highly beam sensitive and they can only tolerate a low electron dose before significant damage occurs to the sample	48,77

Legend: cryo-TEM=cryogenic transmission electron microscopy; DNA=deoxyribonucleic acid.

Table 4. Effect of sepsis on lipid metabolism as shown by the concentration of glycerol, non-esterified fatty acids and triacylglycerol, and the rate of appearance of glycerol and non-esterified fatty acids

	Plasma glycerol concentration (μmol/1) (7)	Rate of appearance of glycerol (μmol/kg/min) (8)	Plasma NEFA concentration (μmol/1) (5)	Rate of appearance of NEFA (μmol/kg/min) (8)	Plasma TAG concentration (μmol/1) (5)
Normal subjects	70 (4) (n=16)	2.4 (0.2) (n=5)	970 (270) (n=5)	6.5 (0.8) (n=5)	1250 (100) (n=5)
Patients with sepsis	130 (22) (n=7)	6.3 (1.1) (n=12)	6450 (1600) (n=13)	13.1 (3.0) (n=12)	5020 (970) (n=13)

Legend: NEFA=non-esterified fatty acis; TAG=triacylglycerol. Values are mean (standard error of the mean).

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13