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Advances in Green Engineering for Natural Products Processing: Nanoseparation Membrane Technology

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Abstract

Products manufactured from natural materials such as plants, microorganisms and marine organisms are used in a very diverse range of industries, including pharmaceuticals, cosmetics, flavours, fragrances and agrochemicals production. Although synthetic analogs of many compounds are available, they are still not widely used and consumed due to the public perception that compounds derived from natural sources are healthier and safer than their synthetic equivalents. This has led to a resurgence in research and commercial interest in greener production techniques for high value natural products.

Most of the high value natural products are present at relatively low concentrations in their natural source material. The concentration in the source material is usually too low to be used directly, so the natural products are extracted using an appropriate solvent followed by to separation, concentration and purification. The purification step is generally the most challenging aspect of natural compounds production, and thus the development of innovative new technologies and processes for more selective, sustainable and energy efficient separation and purification of high value natural products is the scientific and engineering research focus in this industry.

One of the most actively researched areas of these products is their application in the area of healthcare. A broad range of natural extracts are available that provide medical and health benefits, including the treatment or prevention of diseases, and many of these are sold as registered pharmaceutical products or as over-the-counter nutraceutical formulations. This review is focused on two major extracts that have significant impact in such applications: (i) antioxidants, and (ii) natural lipids extracts. The works reviewed and summarised in this study provide a fundamental understanding of process description, address crucial research gap and hi-light the development and utilisation of membrane technology as an alternative environmental friendly process of high value natural compounds production.

Keywords: Separation Engineering, Membrane Technology, Natural Products

1. Introduction and Scope

This review aims to provide an overview on the use of membrane technology for the processing of natural products. The review is organised in three main sections:

(i) A section on carotenoids and natural lipids, the two natural products selected for this review as representatives of natural products used in medical or health industries. This section provides information on the properties, source and impact of using these two natural products.

(ii) A section providing information on different membrane operations that has been suggested for processing of these two natural materials. The criteria used to select the several works described was initially to use the keywords "membrane", "separation" and either "carotenoids" or "lipids". Then, instead of "membrane", "separation", the terms "polymeric membrane", "ceramic membrane", "microfiltration", "ultrafiltration", "nanofiltration", "filtration" or "membrane extraction", were used in combination with "carotenoids" or "lipids".

(iii) A section on Solvent-Resistant Nanofiltration (SRNF) was introduced considering the importance of SRNF for natural products processing and aiming to provide information to end-users. This section highlights the theoretical and industrial aspects of industrial applications of membranes for natural products processing, reviewing the work performed in the area.

2. Natural Products: Carotenoids and Natural Lipids

In recent decades there has been an increase in consumers' concerns over the quality and safety of many products including food, medicines and cosmetics. Consumer's preference has strongly moved to products produced from natural sources as opposed to synthetic sources. As a result of this market demand, the production of natural products has rapidly expanded and become a global industry. A broad range of natural extracts that provide medical or health benefits including treatment or prevention of diseases have been researched. This work will focus on two major groups of extracts; (i) antioxidants, and (ii) natural lipid extracts.

2.1 Antioxidants: Carotenoids

Natural antioxidants are phenolic or polyphenolic compounds commonly found in plants that have a primary

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function to reduce the rate of oxidation reactions. These compounds interfere with oxidation reactions by reacting with the intermediate or oxidising agent to prevent the formation of hydroperoxides. Hydroperoxides are unstable and highly reactive, and damage cells by oxidising DNA or proteins through chemical chain reactions. The damage to DNA can potentially lead to cancer or genetic mutations while damage to proteins can cause enzyme denaturation or inhibition. Antioxidants can be obtained from both natural and synthetic sources. Most synthetic antioxidants are cheap and widely available. However, global trends have shown that natural antioxidants are preferable as they can not only prevent many human diseases caused by oxidative damage, but also provide better safety, tolerance and lower toxicity than their synthetic equivalents [1]. The most widely consumed natural antioxidants are tocopherols (vitamin E), ascorbic acid (vitamin C), carotenoids, flavournoids, lecithin, citric acid, and polyphenols. Carotenoids have a broad range of application in foods, pharmaceuticals, cosmetics, etc., and have been chosen as the primary antioxidant for this study.

2.1.1 Nature of carotenoids

Carotenoids are a large group of hydrocarbon compounds and their oxygenated derivatives that have various structural features and biological actions in common. About 600 carotenoids have been identified, and the majority of them consist of eight C_5 isoprenoid units joined together to form linear skeleton C_{40}tetraterpenoids. The compounds are naturally found with both acyclic and cyclic structures at one end or both ends (Fig. 1). Carotenoids containing only carbon and hydrogen atoms (i.e. hydrocarbon carotenoids) are classified as carotenes while those containing oxygen atoms are termed xanthophylls. Generally speaking, carotenoids are unstable pigments that are sensitive to light, oxygen, and peroxide. As a result, major degradation and losses of these compounds can easily occur in large-scale food processing. In nature, carotenoids can be found in a large range of plant and animal species with orange, yellow, red, purple, and even green colours. More specifically, in orange and green coloured plants and animals, the major carotenoids found are carotenes, whereas yellow and red organisms contain xanthophylls and capsanthins, respectively. Major sources of natural carotenoids in plants are listed in Table 1-3. Carotenoids are also found in some animal species and their products, for instance, shrimp and several crustaceans, shellfish, salmon, poultry, egg yolks and milk.

Table 1. Plants with high content of carotenoids [2-3,32].

Name	Origin	Major Carotenoids (μg/g fresh weight)	
Broccoli	Maryland	*β*-Carotene (23) Violaxanthin (14)	Neoxanthin (6) Luteins (35)
Chinese cabbage	Australia	*β*-Carotene (22) Violaxanthin (3) Neoxanthin (2)	Zeaxanthin (2) Luteins (27)
Chinese spinach	Australia	*β*-Carotene (20) Violaxanthin (19) Neoxanthin (13)	Zeaxanthin (6) Luteins (29)
Apricot	Maryland	*β*-Carotene (64)	
Grapefruit	Florida	*β*-Carotene (4-9) Phytoene (3-51)	Lycopene (2-33) Phytofluene (2-17)
Guava	Brazil	*β*-Carotene (4-9) Lycopene (53)	Zeinoxanthin (1) Trihydroxy-5,8-epoxy-*β*-carotene (4)
Loquat	Brazil	*β*-Carotene (8) *β*-Cryptoxanthin (5)	Neurosporene (1) Violaxanthin (1.6)
Mango	Brazil	*β*-Carotene (15) Violaxanthins (32)	Luteoxanthins (4) Neoxanthin (2)
Papaya	Brazil	*β*-Carotene (1) *β*-Cryptoxanthin-5,6,epoxide (2)	*β*-Cryptoxanthin (8)
Pepper	UK	*α*-Carotene (6) *cis*-*β*-Carotene (2) Lutein (25)	*β*-Carotene (9) *β*-Cryptoxanthin (8) Zeaxanthin (85)
Pumpkin and squash	Brazil	*α*-Carotene (8-42) *α*-Cryptoxanthin (2) *α*-Zeacarotene (13)	*β*-Carotene (14-79) *cis*-*ζ*-Carotene (1-20) Luteins (9.5)
Tomato	UK	*β*-Carotene (4-22) Lycopene (4-50)	Lutein (1-2)
Cheery	Brazil	*β* -Carotene (4-26)	*β*-Cryptoxanthin (2-4)
Orange, mandarin, and tangerine		See Table 2-3	
Carrot	Canada	α-Carotene (20-50)	*β*-Carotene (46-125)
Banana	n/d	*α*-Carotene (1-2)	*β*-Carotene (1)
Berries, and grapes	n/d	*β*-Carotene (1-2)	Lutein (1-2)
Starfruit	n/d	Cryptoxanthin (11)	
Sweet potato	n/d	*β*-Carotene (5-11)	Lycopene (1)
Apple	Indonesia	*β*-Carotene (1-2) Cryptoxanthin (1-2)	Lycopene (1-3)
Jackfruit	Indonesia	*β*-Carotene (4)	
Pineapple	Indonesia	*β*-Carotene (1-3) Cryptoxanthin (1)	Lycopene (2-6)
Watermelon	Indonesia	*β*-Carotene (3-8) Cryptoxanthin (3)	Lycopene (87-135)

Table 2. Carotenoids distribution in various types and origins of orange and mandarin juice.

Type	Valencia	Earlygold	Hamlin	Budd Blood	Red Navel	Shamouti	Valen-cia	Washington Navel	Michal Mandarin	Various Oranges	Mandarin
Origin	*Brazil*	*California*	*California*	*Califor-nia*	*Califor nia*	*Israel*	*Israel*	*Israel*	*Israel*	*Spain*	*Spain*
Total carotenoids (mg/l)	12.0±6.7	8.3-8.8	3.9	5.4	7.7±1.2	6.0-10.0	10.0-15.0	4.0-7.0	13.7	>1.86±0.19	>8.1±0.04
Carotenoid content (% in total carotenoids)											
Neoxanthins		1.2	2.9	2.5	1.0	4.0	2.5	2.2			
Neochrome		0.5			0.2				0.2		
Trollixanthin						9.6	6.5	9.1	2.6		
Trolichrome		0.5				1.5	2.8	3.5	0.3		
Auroxanthin		0.0				0.6	1.2	4.3			
Antheraxanthin		10.9	8.9	8.4	5.2	6.8	9.3	6.2	12.4		
Violaxanthins	11.7	26.2	20.3	17.5	13.3	3.0	1.9	1.7	3.6		
Luteoxanthins		10.7	12.0	9.7	6.3	10.9	11.5	10.9	4.8		
Mutatoxanthin		2.6	3.3	3.1	3.5	15.1	14.0	13.0	5.7		
Luteins	23.2	17.2	23.0	25.9	11.8	9.2	11.0	15.9	6.5		
Zeaxanthin	19.8	6.5	9.8	9.3	3.7	6.2	10.2	4.8	9.1		
α-Cryptoxanthin		1.8	2.5	3.8	0.9	12.9	9.7	11.0	0.9		
β-Cryptoxanthin	20.7	9.1	10.5	12.6	6.9				41.0	(1.39±0.18	(7.5±0.02

										mg/l)	mg/l)
ζ-Carotene	10.0	0.1			trace	1.4	3.0	1.8	3.3		
α-Carotene	7.2	0.9	1.2	1.4	0.7	0.4	1.0	0.7	0.5	(0.19±0.05 mg/l)	
β-Carotene	7.5	1.3	1.3	1.3	6.6	1.2	2.0	0.8	1.9	(0.28±0.04 mg/l)	(0.6±0.04 mg/l)
Lycopenes					31.0				0.6		
Others	0.1	10.5	4.3	4.5	8.9	17.2	13.5	14.2	6.6		
Reference	[24]	[25]	[26]	[26]	[27]	[28]	[28]	[28]	[29]	[30]	[30]

Table 3. Carotenoids distribution in various types and origins of orange and mandarin pulp and peel.

	Pulp		Peel			
Type	**Valencia**	**Mandarin**	**Valencia**	**Michal Mandarin**	**Dancy Tangerine**	**Clementine**
Origin	***California***	***Indonesia***	***California***	***Israel***	***Israel***	***Israel***
Total carotenoids (mg/kg)	17	>3.89	28.0	174.1	295	74.6
Carotenoid content (% in total carotenoids)						
Neoxanthins				4.2	3.0	5.3
Neochrome						
Trollixanthin	2.9		0.5			
Trolichrome	3		0.8			
Auroxanthin	12		2.3			
Antheraxanthin	5.8		6.3	4.3	8.5	2.1
Violaxanthins	7.4		44.0	29.6	51.8	14.8
Luteoxanthins	17		16.0	9.1	2.3	10.6
Mutatoxanthin	6.2		1.7	0.2		1.1
Luteins	2.9		1.2	2.6	2.7	2.0
Zeaxanthin	4.5		0.8	1.0	1.5	1.2
α-Cryptoxanthin		(0.74-1.41 mg/kg)				6.2
β-Cryptoxanthin	5.3		1.2	6.4	13.6	
ζ-Carotene	5.4		3.5	0.4	0.3	0.8
α-Carotene	0.5		0.1	0.2	0.2	0.1
β-Carotene	1.1	(1.71-4.76 mg/kg)	0.3	0.3	0.4	0.4
Lycopenes						
Phytoene	4		3.1			
Phytofluene	13		6.1	3.1	2.7	3.8
β-Citraurinene				9.9		15.7
β-Citraurin				26.1	8.2	32.5
Others	9		12.1	2.6	4.8	3.4
Reference	[31]	[32]	[31]	[29]	[29]	[29]

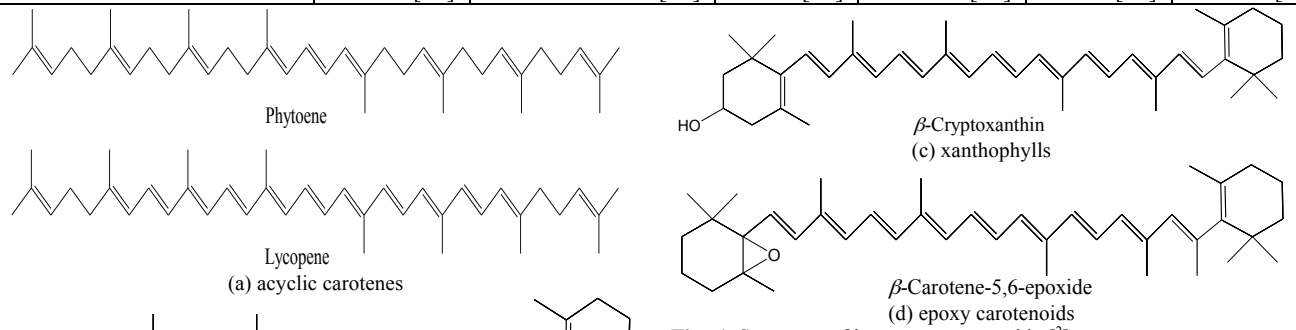


Fig. 1. Structures of important carotenoids. [2].

2.1.2 Antioxidant activity

In humans, carotenoids play two significant roles; they are a precursor of vitamin A, and they provide antioxidant activity. The following paragraph highlights the reaction mechanism of each role.

Carotenoids as provitamin A

It has been shown by various researchers that the main provitamin A carotenoids are β-carotene and α-carotene. The conversion to vitamin A occurs primarily by the cleavage of

carotene; the central carbon-carbon double bond of the compound is deoxygenased with the aid of an enzyme. This chemical conversion is shown in Fig. 2. The most well-known function of vitamin A is its role in vision. More specifically, ingestion of the right amount of vitamin A avoids and reduces the risk of night blindness.

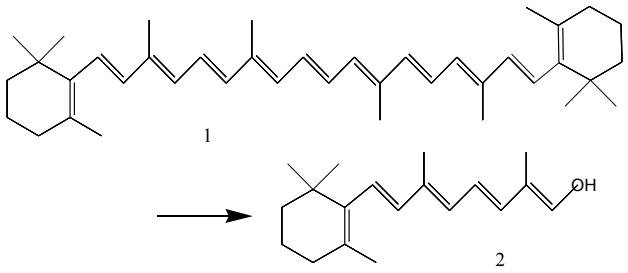


Fig 2. Conversion of *β*-carotene (1) to vitamin A (retinol) (2).

Carotenoids as antioxidants

In general, carotenoids are able to deactivate free radicals and excited oxygen (e.g. peroxides and superoxides) that are generated in cells as a result of various metabolic processes. Several studies have indicated that these oxygen species have the ability to cleave DNA, alter enzyme activity and promote cell death [4]. Various researchers have hypothesised reaction mechanisms for carotenoids with these reactive oxygen species. In this review, the mechanism of reaction of carotenoids with peroxyl radicals is briefly described for illustrative purposes [5]. It has been suggested that the exposure of *β*-carotene to a peroxyl radical could result in two oxidative reactions. For reaction (1), *β*-carotene directly reacts with a peroxyl radical to form a resonance-stabilised radical, while in reaction (2), a carotenoid radical specie is formed.

$$\beta\text{-Carotene} + ROO\cdot \rightarrow ROO\text{-}\beta\text{-Carotene}\cdot \quad (1)$$

$$\beta\text{-Carotene} + ROO\cdot \rightarrow \beta\text{-Carotene}\cdot + ROOH \quad (2)$$

From reaction (2), depending on the concentration of available oxygen, the carotenoid radical can further react with oxygen to form the carotenoid-peroxyl radical (reaction (3)).

$$\beta\text{-Carotene}\cdot + O_2 \leftrightarrow \beta\text{-Carotene-}OO\cdot \quad (3)$$

Subsequently, the radical complex could react with another peroxyl radical leading to the termination reaction as shown in reaction (4).

$$\beta\text{-Carotene-}OO\cdot + ROO\cdot \rightarrow \text{decomposition (inactive) products} \quad (4)$$

2.1.3 Extraction of carotenoids

The extraction of carotenoids from raw and freeze-dried fruits, vegetables and animals has been studied since the 1800s. The main technique used is liquid extraction, particularly by organic solvents. Recently, the extraction of various carotenoids by supercritical fluids (SCF) such as carbon dioxide has been demonstrated. However, SCF is not widely used in industry due to the high operational pressure and subsequently high investment and operating costs. SC CO_2 extraction of carotenoids from crude palm oil, sweet potatoes and carrot have been reported [6-9]. Although the purity of extract was high (i.e. 94% *β*-carotene in an extract of sweet potatoes)[7], the high extraction pressure of more than 400 bar made the process less economically feasible. For the extraction of carotenoids from raw carrot, the yield was found to be low (0.2 mg/g) when extracted at 205 bar and 57^{o}C [8]. It is reported that the yield can be increased to 10 mg/g if the carrot is partially dried [9]. In the past decade, researchers have shown that extraction using organic solvents is more effective in terms of production yield and energy used. Several polar and non-polar organic solvents and their mixtures have been found to provide high extractability of carotenoids from natural sources. Table 4 lists the solvents reported in several studies of carotenoids extraction from natural products. Usually, for extraction from tissues containing water, the use of water miscible polar organic solvents such as acetone, methanol or ethanol is recommended since non-polar solvents have a limited penetration through the mass which surrounds the carotenoids in these tissues [11]. Specifically, carotenes have the highest solubility in non-polar solvents while xanthophylls favour more polar solvents. In a few cases, some carotenoids are also soluble in water [1].

Table 4. List of polar and non-polar organic solvents used in extraction of natural carotenoids [12].

Polar solvent	Non-polar solvent	Mixture
Acetone	Petroleum ether	Acetone. hexane
Methanol	Hexane	IPA: hexane
Ethyl methyl ketone		
Isopropanol (IPA)		
Ethyl acetate		
Ethanol		

Conventionally, acetone is the most common solvent used in extraction processes due to its extraction power, availability and safety [12-14]. Acetone is suitable for carotenoid extraction, as in most cases, carotenoids are extracted from carotene-rich water-containing plants and fruits. In addition to acetone, which has been reported to provide relatively high production yield, mixtures of polar and non-polar solvent have also been shown to provide good extraction power. The study of carotenoids recovery from marine wastes indicates that the mixture 60% hexane, 40% isopropanol (IPA) gave highest carotenoids yield followed by pure IPA, pure acetone, and an acetone and hexane mixture [12] It is also interesting to note that hexane, a non-polar solvent, alone gave relatively low yield compared to the other organic solvents tested.

One of the most important issues to consider when extracting carotenoids from natural sources with organic solvents is the co-extraction of solvent-soluble compounds. In addition to carotenoids, plants contain a wide variety of other constituents which are soluble in solvents, for instance, proteins and lipids can be soluble in hydrocarbon solvent, and hence further purification is often required. The presence of other pigments was reported to promote oxidation reactions and pigments such as chlorophylls have been implicated in the poisoning of nickel catalysts used in hydrogenation reactions [15]. The separation of these compounds is therefore important to achieve acceptable levels of carotenoids purity. Various techniques have been proposed to reduce and eliminate oil or fat fractions in carotenoids extracts. From the several techniques assessed,

saponification has been reported to be an effective means of removing unwanted lipids and chlorophylls [2]. However, when processing fruits, the saponification reaction hydrolyses the carotenoid esters and results in a difficult-to-separate mixture of esters with a variety of fatty acids. Moreover, the reaction can also degrade the carotenoids. In general, the higher the alkali (e.g. methanolic potassium hydroxide) concentration and the higher the saponification temperature, the more carotenoids are degraded [16]. It is reported that provitamin A carotenoids such as α-carotene, β-carotene, γ-carotene, and β-cryptoxanthin can resist saponificantion, while other carotenoids such as lutein, violaxanthin and dihydroxy-, trihydroxy-, and epoxycarotenoids are significantly reduced (degraded) during the reaction and the subsequent washing step [16-19]. Therefore, the saponification technique should be employed with care. For high-lipid extracts, lipase enzymes can be used to hydrolyse the lipid content. For example, *Candida cylindracea* lipase was used to hydrolyse red palm oil at 35^{o}C for reducing the oil content of carotenoids for analytical purpose [20].

Since each class of carotenoids has different functions and biological features, the separation of individual classes is also of interest. Although it is usual that one carotenoid class is predominant in one particular plant or animal, many other classes are also found in small quantities. The most popular separation method for isolating carotenoid classes is chromatography. Various chromatographic techniques have been studied and used, for instance, open-column chromatography, high-performance liquid chromatography (HPLC), and centrifugal chromatography [2,21]. Chromatography provides not only the separation of individual carotenoids but also the separation of other co-extracts such as chlorophylls.

As mentioned previously, the polarity of solvent affects the extractability of carotenoids. Thus, different carotenoids-rich extracts can be obtained by using polar solvent followed by non-polar solvent extraction or vice-versa. However, this technique can only enhance the purity of the extracts to a certain degree and further purification may still be required.

In recent decades, great effort has been put into the chemical and biological synthesis of carotenoids [22]. Despite the fact that over 600 different natural carotenoids are known, less than 5% of them can be chemically synthesised. This results from the complex structure of the carotenoids, which is not easily elucidated. Although advances in high resolution spectroscopic methods have allowed improved understanding of the structure of some carotenoids, full characterisation of most carotenoids compounds is still not possible [23]. It is also common in carotenoid synthesis that synthesis of different carotenoids require the development of specific chemical routes rather than the use of one or two generic synthesis protocols. Moreover, chemical synthesis produces mixtures of stereoisomers which may not be as active as the natural isomer and can have undesired side effects [24]. There has also been considerable effort to synthesise carotenoids using biological hosts; as for chemical synthesis, only marginal success has been reported. Due to the large number of carotenoids found in nature, extracts, isolates, and fractions from natural sources are the focus of research interest.

2.1.4 Extraction of carotenoids from orange

Orange is one of the most common and globally consumed fruits. Research has shown that both the edible (i.e. pulp and juice) and inedible (i.e. peel) parts of orange contain high quantities of several carotenoids [25-33]. In most cases, the major carotenoids present in orange are lutein, β-crytoxanthin and violaxanthins. In juice, the concentration of carotenoids was found to be in the range from 4 to 15 mg/L depending on the type of orange and place of origin. The content of carotenoids found in orange pulp is similar to those found in the juice. In contrast to the pulp, high carotenoids pigments are found in the orange peel, with up to 295 mg/kg reported for Israeli tangerine peel [30].

In the orange juice production industry, the peel and tissues are considered as a major by-product of the production process and represent about four-ninths of the total fruit mass [34]. Currently, they are discarded as a waste, which becomes a substantial burden to the environment. There is a challenge to industry to turn these wastes into useful products by extraction of their valuable components. Although the extraction of carotenoids from oranges has been studied and reported by various researchers, these studies are limited to analytical and quantification purposes, rather than production processes [25-33]. For the former purpose, acetone extraction followed by extraction with petroleum ether is broadly recommended (as a media for carotenoids transfer) as orange peel contains a considerable amount of water (Table5) [2]. Despite limited carotenoid production from orange wastes, the extraction of other valuable compounds from their peel has been studied and investigated. Li *et al.* (2006) reported the extraction of phenolics (e.g. flavournoids) from various types of citrus peel using ethanol and methanol as the solvent [35]. The extraction yields of the New Zealand navel orange and mandarin peels were reported to be as high as 74 and 121 mg/100 g peel when extracting with 72% v:v ethanol:methanol. It is interesting to note that enzymed-assisted extraction was also studied, providing lower phenolics recovery than solvent extraction [36]. Liu *et al.* (2006) investigated the extraction of a complex carbohydrate, pectin, from Australian navel oranges using combined water-based hand-pressure and microwave assisted methods [34].

Table 5. Approximate composition of typical orange peel [37].

Composition	%wt
Water	19.30
Crude protein	4.66
Crude fat	1.92
Nitrogen-free extracts	62.67
Crude fibre	8.12
Ash	3.33

For carotenoids production from orange peels, Table 6 lists the solvents used for extraction processes as reported by several researchers. Aravantinos-Zafiris *et al.* (1992) investigated the use of several organic solvents for the extraction of carotenoids from Greek orange peel [38]. They found that acetone was the most efficient solvent with 89% of total carotenoids removed. Other solvents were tested and their ability to extract, in decreasing order, was found to be ethanol, tetrahydrofurane, petroleum ether and hexane.

The production of carotenoids from orange peel using SC CO_2 has also been evaluated in the literature. At an extraction pressure and temperature of 100 to 500 bar and 35 to 60^{o}C, a total yield of 6% w/w, with the last two fractions containing 0.01% carotenoids with a recovery of 1.6 to 3.0 mg/kg peel were reported [39]. The extraction of essential

oil from orange peel was also shown to occur at relatively high operational pressures [40].

Table 6. List of solvents used for carotenoids production form orange peel.

Solvent	Reference
Acetone	[41]
Hexane	[42-43]
Petroleum ether	[38]
Carbon disulphide	[38]
Benzene	[38]
Methylene chloride	[38]
D-Limonene	[44]

2.1.5 Extraction of carotenoids from tomato

Tomato contains significant amounts of different types of carotenoids. Lycopene is the most abundant carotenoid in tomatoes, and represents about 83% of the total carotenoids present [45]. Apart from lycopene, important carotenoids such as *β*-carotene were also found in a considerable amount in many kind of tomatoes [46-50]. Considering each edible part, it was reported that 72 to 92% of the lycopene was found in the skin, pulp and tissue (i.e. 423 mg/kg) while 40 mg/kg of lycopene was found in the water-soluble portion [51]. Other carotenoids found in tomatoes, include phytoene and phytofluene [52].

Various solvents have been used to extract carotenoids, particularly lycopene from tomatoes and its products. Table 7 provides list of reported solvents and solvent mixtures used for carotenoids extraction from tomatoes. Taungbodhitham *et al.* (1998) evaluated six different extraction methods for canned tomato juice and recommended the use of ethanol and hexane, since they provide relatively high yield and possess a low biological hazard [53]. Lin and Chen (2003) studied the extractability of several solvent mixtures and found that, of all tested mixtures, a mixture of ethanol and hexane (4:3 v:v) gave the highest yield of lycopene [46]. Also, some toxic organic solvent such as benzene, chloroform and methylene chloride have also been identified as suitable solvents for lycopene [54]. Choudari and Anantharayan (2006) used cellulase and pectinase enzymes to enhance lycopene extraction from Indian tomato and peel. At the optimised content of enzymes, the yield of lycopene using both enzymes was about twice that compared to extraction with solvent (mixture of acetone and petroleum ether) alone [55].

Recently, SC CO_2 extraction has been developed for carotenoids production from tomatoes. Cadoni*et al.* (2000) extracted ripe Italian tomatoes using SC CO_2 and a mixture of acetone:hexane and found that the yields of lycopene and *b*-carotene from solvent extraction (i.e. 77 and 38 mg/kg) were slightly higher than those obtained from SC CO_2 extraction at a pressure of 275 bar at 80oC (i.e. 64 and 35 mg/kg) [54]. By adding 10% (w/w) vegetable oil as a co-solvent, Vasapollo*et al.* (2004) reported that 60% extraction of lycopene was obtained by SC CO_2 extraction at 450 bar and 65 to 70^{o}C [56]. Apart from these studies, several SC CO_2 extractions of tomatoes and their by-products have also been reported using a similar approach but with slightly different operating conditions [57-58]. Furthermore, Xi (2006) investigated high pressure extraction using ethanol as a solvent [59]. It is reported that 1 min extraction at 5000 bar gave a similar yield to 30 min extraction at ambient pressure using ethanol:water (3:1 v:v) for both cases.

2.1.6 Extraction of carotenoids from Microalgae (H. Pluvialis)

Astaxanthin is a major group of carotenoids found in marine organisms, mainly microalgae (e.g. *Haematococcuspluvialis*), coloured fish (e.g. salmon and trout) and crustaceans (e.g. shrimp, etc.). Table 8 shows the major sources of astaxanthin found in nature. Commercial production of astaxanthin both from natural extraction and chemical synthesis is a growing business worldwide, primarily due to its high antioxidant activity. However, synthetic astaxanthin is not in the same form as that found in nature and provides lower stability and activity compared to natural products. Researchers have therefore been studying the extraction of astaxanthin from natural sources by various methods.

Due to the high content of astaxanthin, extraction of this compound from *H. Pluvialis* has been most widely studied and reported. Similar to other carotenoids, organic solvents such as acetone and hexane are able to effectively extract the compound from its natural sources. Sarada*et al.* (2006) reported the extractability of several solvents; dimethyl sulfoxide (DMSO) in the presence of a few drops of glacial acetic acid at 70^{o}C resulted in 66.6% extractability, which is much higher than extraction with acetone and methanol (i.e. 14.1% and 18.6%) [61]. This study also revealed that with the treatment of 2 M hydrochloric acid (HCl) before acetone extraction, the extractability was as high as 86.4%. Li and Chen (2001) extracted astaxanthin from the microalgae *Chlorococcum* sp. for analytical purposes [62]. In their extraction procedure, a mixture of hexane and ethanol (1:1 v:v) was used and gave good extraction performance. Although organic solvent extraction provides high extractability, the technique particularly with *H. Pluvialis* has some drawbacks. Apart from astaxanthin, the lipids content in this organism is also dissolved well by the organic solvent. This limits the concentration of astaxanthin that can be obtained in extracts. The development of a technique to purify the extract by separating astaxanthin from lipids and other co-extracted products is therefore of interest in the research study worldwide.

Table 7. List of solvents used for carotenoids extraction from tomatoes.

Solvent (volume ratio)	Reference
Acetone	[48]
Petroleum ether	[48]
Ethyl acetate	[46]
Ethanol: hexane (4:3)	[46]
Acetone: hexane (3:5, 4:6)	[46, 53]
Ethanol: acetone: hexane (2:1:3)	[46]
Ethyl acetate: hexane (1:1)	[46]
Acetone: petroleum ether (1:1)	[55]
Chloroform: methanol (2:1)	[53]
Dichlomethane: methanol (2:1)	[53]
Hexane: isopropanol (3:2)	[53]

Table 8. Natural sources of astaxanthin [60].

Natural sources	Astaxanthin[#] (mg/kg)
Salmonids	5
Plankton	60
Krill	120
Arctic shrimp	1200
Phaffia yeast	8000
H. Pluvialis	40 000

[#]Approximate value

Research on SC CO_2 extraction has widely been studied since lipids and carotenoids (e.g. astaxanthin) respond differently to SC CO_2 extraction and can be selectively separated. This resulted in successful extraction of astaxanthin using SC CO_2, however, the required operating pressure is high (e.g. 100 to 550 bar) leading to high investment and operating costs if this was to be used in industry [63-65].

2.2 Natural Lipids

2.2.1 Nature of lipids and oils

Natural lipids are compounds of biological origin that dissolve in non-polar solvents and are relatively hydrophobic due to their long hydrocarbon chains. The primary function of lipids in living organisms is as an energy reserve which can be readily metabolised to provide energy to organisms. Natural lipids consist of the glycerol esters of long-chain carboxylic acids and yield esters in the molecular weight range of 500 to 1200 Da. As glycerol contains three hydroxyl groups, the long-chain carboxylic acids (commonly referred to as fatty acids) can form between one and three ester linkages with one molecule of glycerol. These esters are referred to as glycerides, with a prefix of mono, di or tri depending on the number of ester bonds formed with the fatty acids. In addition to glycerides (mixture of monoglycerides (MG), diglycerides (DG), and triglycerides (TG)), lipids contain free fatty acids (FFA) and minor constituents such as gums, waxy materials, colour and volatile compound that provide taste and odour. TG is the main glyceride found in lipids, which are generally referred as oils and fats (if they are liquid or solid at room temperature, respectively). Products of fat or oil hydrolysis are glycerol and a group of even-carbon unbranched carboxylic acids called fatty acids (Fig. 3). Fatty acids can be categorised as saturated or unsaturated, depending on the type of carbon bonds in the hydrocarbon backbone of the molecules. More specifically, saturated fatty acids are compounds with only single carbon-carbon bonds while unsaturated fatty acids are compounds with at least one double carbon-carbon bond. Table 9 lists some of the most common fatty acids. In nature, fatty acids normally contain two or three carbon-carbon double-bonds and are called polyunsaturated fatty acids (PUFA). It has been reported that various PUFA such as omega-3 and omega-6 are not only essential in the diets of humans but also provide beneficial medicinal and therapeutic effects [1]. This results in an enormous increase in research studies to purify these compounds and to use them in pharmaceutical and food products.

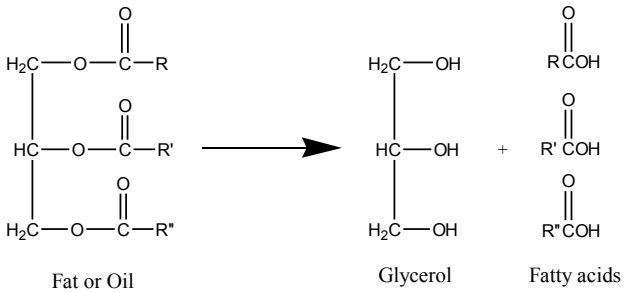


Fig 3. Schematic diagram of hydrolysis of a fat or oil [66].

Omega-3 and omega-6 PUFA are classified as essential to human metabolism as there is no biochemical pathway by which a human cell can synthesise them. Omega-3 PUFA are fatty acids in which the third to last carbon in the chain is part of a carbon-carbon double bond. Long-chain omega-3 PUFA such as docosohexanoic acid (DHA, 22:6 ω-3) and eicosapentanoic acid (EPA, 20:5 ω-3) when incorporated in the diet are believed to provide beneficial health effects to humans. Apart from its ability to lower serum lipids and blood cholesterol, omega-3 PUFA is also suggested to have the ability to reduce the risk of heart attacks, treat certain autoimmune and inflammatory diseases, including rheumatoid arthritis, psoriasis, atherosclerosis, asthma and cancer in several reports [1,66]. Oils from marine organisms such as oily fish (e.g. salmon and tuna), mussels, seaweed fungi and algae are major sources of these PUFA, particularly DHA and EPA. Omega-6 PUFA are fatty acids in which the first carbon-carbon double bond occurs at the sixth carbon in the molecular backbone. In nature, essential omega-6 PUFA such as linoleic acid and arachidonic acid can be found in vegetable oils, meat, poultry and dairy products.

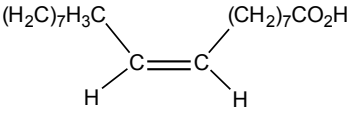
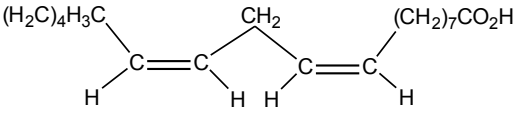
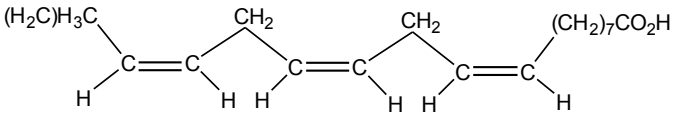
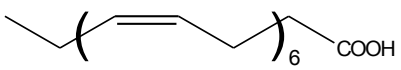
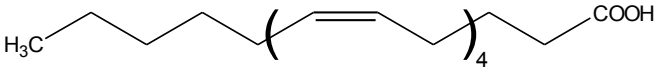
It has been suggested that the correct ratio of omega-3 and omega-6 fatty acids maintains good health and metabolism. In contrast, a shift of the oil balance to the omega-6 side, as is found in today's western diets, has been suggested to promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases; whereas a low omega-6 to omega-3 ratio exerts suppressive effects [67]. In cases where such hypothesis is valid, the separation and fractionation of these PUFA is therefore important, as it could be used as a supplement to prevent or cure adverse medical condition caused by an imbalance of these acids.

2.2.2 Extraction and fractionation of lipids and oils

Extraction of natural lipids has long been studied and has become a well-established industry over the past century. Various techniques have successfully been reported and employed in both industry and research. Table 9 summarises the currently available extraction techniques.

Table 9. List of common fatty acids [66].

Fatty acid	Formula	mp (^oC)
Saturated Carboxylic Acids		
Myristic acid (tetradecanoic acid)	$CH_3(CH_2)_{12}CO_2H$	54
Palmitic acid (hexadecanoic acid)	$CH_3(CH_2)_{14}CO_2H$	63
Stearic acid (octadecanoic acid)	$CH_3(CH_2)_{16}CO_2H$	70

Unsaturated Carboxylic Acids		
Oleic acid (*cis*-9-octadecenoic acid)		4
Linoleic acid (*cis*,*cis*-9,12-octadecadienoic acid)		-5
Linolenic acid (*cis*, *cis*, *cis*-9,12,15-octadecatrienoic acid)		-11
DHA, an omega-3 fatty acid [(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-4,7,10,13,16,19-docosahexaenoic acid]		-44
Arachidonic acid, an omega-6 fatty acid [(5*Z*,8*Z*,11*Z*,14*Z*)-5,8,11,14-eicosatetraenoic acid]		-49

In spite of the high purity provided by distillation (e.g. steam and vacuum distillation) and chromatography techniques, they are practically less favourable due to the difficulty of scale-up (for chromatography), and their high inventory and operating costs. Steam distillation has also been widely used for the extraction of essential oils, however, it is not suitable for many natural compounds as they are sensitive to water and heat.

In recent years, sub- and super-critical fluids such as carbon dioxide and liquefied hydrocarbons have become more popular, as they are low toxicity and are easily separated from the extracts. However, the high operating pressure makes this technique less feasible to employ on an industrial scale. In contrast to these techniques, organic solvents provide features of fast, efficient and gentle extraction, which is reported to maintain high nutritional value of extracts [71]. Hence, it is widely used in the natural product industries for large-scale production.

Plant and animal oils can be extracted using both non-polar and polar solvents [68]. In practical applications, it is common to use a combination of polar and non-polar solvents for the extraction process.

One of the most cited works in the natural product extraction field, is the solvent extraction of lipids reported by Folch *et al*. (1956) [73]. A mixture of chloroform:methanol (2:1 v:v) was used to extract lipids from a mammal's brain. It was reported that all lipids could be removed from the tested brain, with the exception of those present in tissue proteins. This extraction technique was improved and simplified by Bligh and Dyer (1959), in which chorloform:methanol:water (1:2:0.8 v:v) was used [74]. Despite the high yield, the method is rarely used for edible grade extracts due to the high toxicity and flammability of the solvents. Hara and Radin (1978) reported a less toxic system by employing a mixture of hexane:propanol (3:2 v:v), followed by a wash of the extract with aqueous sodium sulphate to remove non-lipid contaminants [72]. In general, the yield from this mixture was similar to that obtained from the chorloform:methanol:water system, however, lower lipids yield were reported when used with microalgae.

Table 10. List of techniques for lipid (and other natural products) extractions [68-72].

Technique	Advantages	Disadvantages
Organic solvent extraction	• High yield/short extraction time • Mild operating conditions (e.g. atmospheric temperature and pressure) • Solvents are generally available • Low operation costs • Readily scalable for large production	• Moderate to low selectivity of solvent-solute in some systems • Requires further purification • Solvent toxicity
Molecular and vacuum distillation	• Very high purity of extracts	• Operates under very high vacuum conditions • Nutritional compounds degradation due to high temperature operation • High inventory and operating costs
Thin-layer chromatography	• High and reliable purity of extracts	• Difficult to scale-up as many TLC plates required for high purity separation
Gas and high performance liquid chromatography	• High and reliable purity of extracts	• Relatively longer separation time compared to solvent extraction

		• More suitable for analytical than preparative proposes
Open column chromatography	• High and reliable purity of extracts • Applicable for large-scale	• Consumes large amount of solvent
Near-critical fluid extraction	• Less toxicity • Moderate to high purity of extracts • Ease of solvent and solute separation	• High operating pressure and/or temperature • High inventory and operating costs

Hexane is the most commonly used solvent for edible oil extraction. However, after it was classified as a hazardous air pollutant, this prompted the search for an alternative solvent and more environmentally friendly solvents such as ethanol, isopropanol, acetone and iso-hexane have been proposed as replacements [75].

Ethanol and butanol are widely used for lipids extraction as they are relatively cheap, sufficiently volatile to make separation easy and have low toxicity. However, the extracts generated with these solvents need to be further purified. Nagle and Lemke (1990) compared the efficiency of this system to the hexane:propanol (3:2 v:v) and reported that, after further purification by phase separation, 90% yield was obtained by butanol extraction which was better than hexane:propanol (3:2 v:v) (78% yield) and ethanol (73% yield) [76].

Grima *et al.* (1994) extracted lipids from *Isochrysisgalbana* microalgae with various solvents and solvent mixtures at room temperature for 1 h [77]. The yield of fatty acids and omega-3 PUFA are shown in Table11. Cartens *et al.* (1996) used ethanol (96%) and hexane-ethanol (1:2.5) to extract *Phaeodactylumtricornutum* [78]. In consistent with Grima *et al.* (1994), the yield from the former (96% yield) is higher than the latter due to the higher polarity of ethanol.

Table 11. Yields of extracts obtained by lipid extraction from *I. galbana* microalgae [77].

Solvent system (volume ratio)	Yield (%)	
	Fatty acids	Omega-3 PUFA
Chloroform:methanol:water (1:2:0.8)	92.9	100.0
Hexane:ethanol(96%) (1:2.5)	52.2	49.5
Hexane:ethanol (96%) (1:0.9)	49.5	49.2
Butanol	70.4	66.2
Ethanol (96%)	84.4	84.0
Ethanol (96%):water (1:1)	63.3	60.5
Hexane:isopropanol (1:1.5)	66.0	66.0

Alternative and less toxic solvents such as acetone are also used to extract nutritional and pharmaceutical grade PUFA. Moffat*et al*. (1993) developed a technique for omega-3 extraction from fish oil using acetone [79]. It is reported that EPA and DHA concentrations of 57.4% (34.4% in original oil) were achieved by employing acetone at -60^{o}C.

Various research works have shown that organic solvent extraction is capable of extracting a broad range of natural lipids while maintaining their nutritional and medicinal potential values [71,80]. At present, it has been employed in numerous natural lipids processing operations including the deacidification of edible oils (i.e. FFA removal), and fractionation of PUFA and glycerides. To demonstrate the advantages of this technique in term of retention of nutritional value, Kale *et al.* (1999) studied the deacidification of crude rice bran oil by extraction with methanol [80]. Due to the milder operating conditions (i.e. atmospheric pressure and temperature), the deacidified oil is potentially preserved with nutritional compounds [71]. Moreover, Goncalves*et al.* (2007) also reported the use of ethanol extraction for deacidification of palm oil. As high as 99 wt% of carotenoids and 80 wt% of tocopherols were maintained in the ethanol-deacidified palm oil [71].

The importance of PUFA such as omega-3 and omega-6, as described earlier, together with the industrial need for FFA removal in edible oil production, has improved separation and fractionation of these products tremendously in recent years. Although organic solvent extraction provides many advantages over other extraction techniques, the purity of the extracts with respect to the key components is relatively low. Thus, to apply this technique to a practical process, it is of research interest to develop technology which can take advantage of the benefits of extraction with organic solvents, and provide the necessary purity of extracts for their intended use.

3. Green Technology in Natural Extraction: Membrane Process

Membranes are semi-permeable barriers capable of selectively allowing the passage of certain components of a mixture while retaining the other components. In principle, a membrane will separate a mixture into two separate streams; (i) the retentate, which contains the components retained by the membrane, and (ii) the permeate, which is enriched in one or more components not retained by the membrane. A schematic representation of a membrane is shown in Fig. 4. The details of membrane processes are reviewed in this section. At present, membrane technology is a rapidly emerging technology which is increasingly employed in a wide range of applications including petrochemical, fine chemical, food, pharmaceutical and nutraceutical industries. Membrane processes can be classified based on particle size and the driving force for the separation process. Table 12 shows characteristics of various membrane processes. In this section, a range of pressure driven membrane applications (i.e. reverse osmosis, nano-, ultra-, and microfiltration) in natural extraction processes are reviewed.

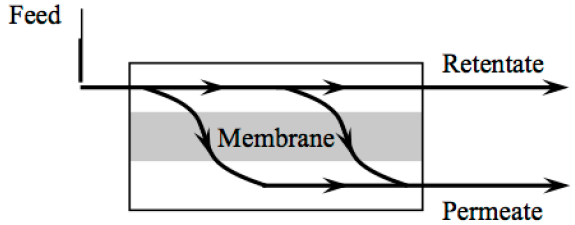


Fig 4. Schematic representation of a membrane process.

3.1 Potential of Membrane as A Green Technology for Natural Extraction

As described in section 3, organic solvent extraction is a robust extraction technique which is relevant to many different raw materials and products. In most cases, particularly in edible oil extracts processing, the crude extracts from solvent extraction cannot be immediately used, and extensive processing such as purification or refining is required [83]. This involves concentrating the desired products and removing unwanted materials together with separating products from an organic solvent. Conventional purification approaches include distillation or evaporation to remove solvents, or the use of additives such as caustic for oil refining processes. The former requires a significant amount of energy, for example, approximately 530 kJ of energy is required to produce one kg of edible oil [81]. Furthermore, the explosive vapours in the process create considerable safety concerns. The addition of chemicals such as caustic to crude extracts can also lead to undesirable results, including molecular cross-linking and rearrangements resulting in a decrease in nutritive value and the formation of toxic compounds [84]. In edible oil refining, it is also reported that FFA removal by addition of caustic results in large yield losses, as soap formed by saponification of the oil traps some of the glycerides [81]. Moreover, from an environmental point of view, conventional processes consume large amounts of water and chemicals, and create heavily contaminated effluents.

Table 12. Characteristics of membrane processes [81-82].

Process	Driving force	Pressure range (bar)	Permeability range ($L/m^2.h.bar$)	Retentate	Permeate
Osmosis	Chemical potential	n/a	n/a	Solutes	Solvent
Dialysis	Concentration difference	n/a	n/a	Large molecules	Small molecules
Microfiltration	Pressure	0.1-2.0	>50	Suspended particles	Dissolved solutes
Ultrafiltration	Pressure	1.0-5.0	10-50	Large molecules	Small molecules
Nanofiltration	Pressure	5.0-60	1.4-12	Small molecules, divalent salts, dissociated acids	Monovalent ions, undissociated acids
Reverse osmosis	Pressure	10-100	0.05-1.4	Solutes	Solvent
Electrodialysis	Voltage/current	n/a	n/a	Nonionic solutes	Ionised solutes
Pervaporation	Pressure	n/a	n/a	Nonvolatile molecules	Volatile small molecules

In recent years, membrane technology has attracted a great deal of attention as an environmentally benign technology for natural extracts purification. The main advantage of this technology over conventional processing operations is that much lower temperatures are required. In addition to the large saving in energy costs, natural extracts are susceptible to thermal damage and thus the milder operating conditions of membrane process can potentially minimise the nutritive value loss due to thermal degradation. Various research works have also shown that by selecting suitable molecular weight cut-off (MWCO)[85]. membranes, this technology can be used to separate molecules in a customised manner [86-89]. The importance of this feature is that, due to the low selectivity of organic solvent extraction, crude natural extracts usually contain a considerable amount of undesired products of a similar molecular weight to the desired product. These undesired compounds, in many cases, reduce the nutritive or medicinal potential value of the extracts or may even be toxic for human consumption. Other reported benefits of using membrane technology are their use in solvent recovery, lower emission rates, increased product yields, simplicity of the process and ease of up-scaling, and ease of combination with other separation processes [82].

Although membrane processes provide numerous benefits for natural extraction processes, the following issues should be considered when employing this technology: concentration polarisation and membrane fouling, membrane lifetime, and relatively low selectivity and flux in some systems [82]. Ongoing research and development work has therefore been conducted to understand, reduce and eliminate these phenomena.

3.1.1 Microfiltration and Ultrafiltration

Microfiltration (MF) and ultrafiltration (UF) are membrane processes in which the pore size of the membranes ranges from 10 to 0.05 μm and 0.05 μm to 2 nm, respectively. The former is commonly used to retain suspensions and emulsions, while the latter is suitable for retaining macromolecules and colloids from a solution, with the lower limit of molecular weight of retained solutes of a few thousand Daltons [82]. MF and UF have long been employed in various natural products purification processes. Table 13 lists examples of current industrial and research applications of MF and UF processes in natural products purification and fractionation. It can be seen that MF and UF are capable of separating a broad range of compounds, particularly macromolecular products in aqueous systems. For the separation of compounds of smaller size, nanofiltration (NF) or reverse osmosis (RO) are typically employed.

3.1.2 Reverse Osmosis and Nanofiltration

RO and NF are processes for the separation of molecules in the range of nanometres in size and 200 to 1000 Da in MWCO. Both systems are used when low molecular weight compounds such as small organic molecules have to be separated from solvent extracts mixtures. Due to their capability to retain nanoscale compounds, both RO and NF have become the subject of great research interest in recent years. Various research works have been reported on the use of NF for purification and fractioning of natural products (Table13). However, the majority of the processes investigated are still limited to preliminary or lab-scale studies.

Table 13. Applications of membrane technology to natural product purification and fractionation.

Entry	Membrane	Process/Applications	Solvent System	Conclusion Remarks	Ref.
1	UF/MF	Fractionation and concentration of diary products	Aqueous	• Good separation of lactose and soluble salts from protein, fat and insoluble salts in milk can be achieved using UF PES, PS, and PVDF membranes. • Increase in yield of cheese 10 to 30% by pre-filtering the milk with UF membrane. • Fat separation, bacterial removal and casemate concentration can be successfully performed by using MF membranes. • *β*-casien protein isolated by ceramic MF membrane has a potential biological activity for pharmaceutical applications.	[81], [100]-[101]
2	UF	Separation of non-sugar impu- rities from beet/cane extracts	Aqueous	• Macromolecular impurities such as proteins and colloids can be separated using UF membranes resulting in less viscous and 60 to 90% colour removal juice.	[92]-[93]
3	UF	Isolation of proteins from plants extracts	Aqueous	• Removal of undesirable oligosaccharides, phytic acid and typsin inhibitors from soy extracts by UF membranes resulting in 70% protein concentrate.	[81]
4	NF/UF/MF	Edible oils refining	Organic solvent	• Degumming (UF): Very high rejection and 97% oil recovery were obtained. • Deacidification (NF): FFA removal can be performed and no alkali needed. • Dewaxing (MF): Wax can be removed by membranes at -10 to 20^{o}C. • Solvent recovery (NF): High purity recovered solvent and less energy consumed.	[81], [94]
5	MF	Dextrose clarification of corn glucose syrup	Aqueous	• MF process provides 99 to 99.5% yield of clarified corn syrup with more than US$1000 saving per gallon production compared to RVPF conventional process.	[95]
6	RO/NF/UF/MF	Fruit juices and extracts processing (apples, apricots, carrot, berries, grape, kiwi, lemon, melon, orange, peach, pear, tomatoes, and pineapple)	Aqueous	• Clarification of juices (UF/MF): Less complicated, higher yield (95 to 99%), shorter process time (2-4 h) compared to conventional process (apple juice). • Concentration (RO): Juice concentrates of 42 to 60^{o}Brix can be produced. • Debittering (UF): combined UF and adsorbent resin process can be used to remove bitter compound such as limonin, hesperidin and polyohenols from citrus juices. • Deacidification (NF): Acidity of citrus juices can potentially be removed by NF.	[81], [96]-[97]
7	UF/NF	Removal of colour pigments	Aqueous/ Organic solvent	• Pigments, phosphorous, and gossypol derivative can be removed from cryde cotton seed, soybean, canola, peanut and meadowfoam oils using UF membranes. • Chlorophyll and *β*–carotene were rejected and 71 to 83% of gossypol was removed while hydratable and non-hydratable phospolipids were completely removed. • By coupling to other techniques, chlorophyll level was reduced by more than 90%.	[98]-[99]

One area with potential for using NF is in edible oil refining. Cheryan (1998) presented a conceptual refining process where conventional operations were replaced with membrane technology [81]. The main role of NF in this system are solvent recovery during deacidification and removal of pigments [81,83]. Careful selection of the NF membrane would potentially also allow the separation of FFA from solvents and to recover very high purity of solvent for further operations. However, it was also noticed that the proposed process could potentially result in high losses in triglycerides which are dissolved in the FFA-enriched solvent phase.

3.1.3 Solvent-Resistant Nanofiltration

Although NF has the potential to provide many advantages over conventional separation methods, the majority of applications to date are still limited to aqueous solution systems due to the lack of NF membranes that are stable in organic solvents. However, recent advances in membrane materials and engineering have allowed Solvent-Resistant Nanofiltration (SRNF) membrane systems to develop. SRNF is a solvent-resistant membrane separation which is able to selectively retain solutes with molecular weight in the range of 200 to 1000 Da and allow smaller molecules to pass through the membrane. Recent research work has shown that SRNF can be applied to a broad range of applications and solvent systems, including chiral separation of drug intermediates, homogeneous catalyst recovery, monomer separation from oligomers, and solvent exchange. Only a few research works reported the use of available solvent-stable membranes for natural product separation process. The main limitations identified in such works are low fluxes and/or poor separation characteristics [83]. As a result, there is a research challenge to develop solvent-stable membranes, tailored for use in natural product purification, capable of performing molecular/nanoscale separations. Overall, the use of SRNF in the natural products area is still unexplored [85,100].

Several researchers have tried to apply SRNF membranes to FFA removal or for solvent-recovery in edible oils refining. However, despite these efforts, there has not been a breakthrough in taking such successful technology for industrial use. Bhosle and Subramanian (2005) listed the limitations of available membrane approaches for this particular process but unfortunately did not provide details of the membranes used. For deacidification with hexane, they noted partial reduction of FFA (40%) concentration while with acetone, better selectivity was observed but with a very low permeate flux. Over the past 10 to 15 years, polyamide (PA) and cellulose acetate (CA) membranes have been widely used in the research literature. These membranes were designed for use in aqueous system and have a limited degree of stability in solvents, which include hexane, ethanol, 2-propanol and acetone. Some researchers also noted that direct exposure to organic solvents such as ethanol significantly degrade the performance of these membranes designed for aqueous systems [83,101]. Koseoglu *et al.* (1990) reported that Osmonics PA membranes (MWCO of 300 to 400 Da) were stable in hexane for solvent recovery process in oil refining, but poor flux and oil rejection were observed [102]. Similarly, Osmonics PA membranes (MWCO of 500 Da) were found to be stable in ethanol , however, a high content of oil (7 %) was present in the recovered solvent and the flux was unacceptably low. Krishna Kumar and Bhowmick (1996) performed a FFA removal process using Osmonics PA and CA membranes in an alcohol mixture. Reasonable flux (67 $L/m^2.h$) and retention (62% and 87% FFA in feed and permeate, respectively) were achieved. However, it is important to note that no long term stability testing of the membranes was performed in these works [103].

For antioxidant applications, there is no research evidence to date of the use of SRNF membranes to fractionate a range of pigments such as carotenoids and chlorophyll. However, an SRNF process, in principle, could be employed. As mentioned earlier, carotenoids have the property of reducing the rate of oxidation reactions and can be extracted with many solvents. However, the co-extracts such as chlorophyll and other pigments are often found to be toxic and enhance oxidation and therefore have to be removed. Koseoglu *et al.* (1990b) screened 15 UF membranes for their ability to remove pigments, phosphorous and gossypol derivatives from various plants oils [98]. Five membranes, whose identity was not published for commercial reasons, were found to be stable in hexane, and chlorophyll and β–carotene were removed successfully. Additionally, up to 82% of gossypol was removed from cottonseed oils. Diosady *et al.* (1992) compared the use of membrane technology with other techniques for chlorophyll removal from canola oil [99]. It was reported that more than 90% of the chlorophyll could be removed by the combination of membrane technology with other techniques.

Recently, there has been an increase in interest in polyimide (PI) as a polymer for manufacturing SRNF membranes. Commercially available PI membranes, trade name STARMEM^{TM} (W.R. Grace & CO., USA), have been widely used in several SRNF applications. The STARMEM^{TM} series of membranes offers a range of MWCO from 200 to 400 Da. The list of solvents compatible with these membranes is shown in Table14. From the solvent compatible data, STARMEM^{TM} SRNF membranes are considered as a potential candidate for natural extracts purification applications.

Table 14. Chemical compatibility of STARMEM^{TM} SRNF membranes [1^{04}].

Chemical group	Solvents
Alcohols	Butanol, IPA, ethanol, methanol
Aromatics	Toluene, xylene, dichlorobenzene
Ethers	Methyl-tert-butyl-ether
Ketones	MEK, MIBK
Others	Acetic acid, acetonitrile

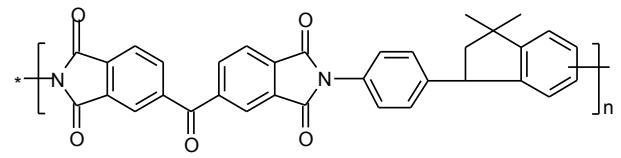
4. Solvent-Resistant Nanofiltration (SRNF) Membranes and Module Preparation

This section reviews formation of solvent-stable nanofiltration membranes and fabrication of the membranes into modules. For non-aqueous systems, polymeric membranes are the most advanced and fastest-growing materials used for industrial applications. Inorganic or ceramic membranes, although they potentially provide high solvent-stability, are not yet suitable for many SRNF applications as they are commonly available only in UF/MF ranges and even if they were available, the membranes may be too expensive for such applications [94]. This work will focus on the synthesis and application of polymeric membranes, which covers the choices of polymers, current synthesis techniques, and design of membrane modules.

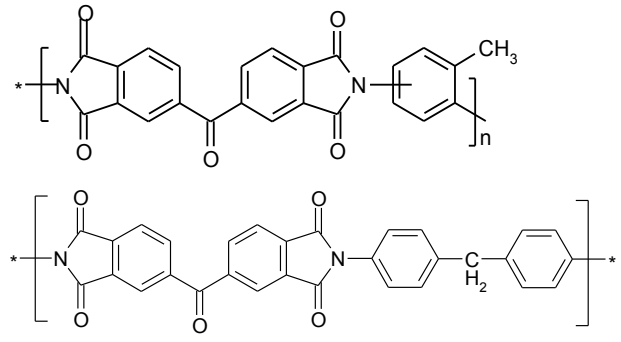
4.1 Membrane Materials

The majority of industrial solvent-stable membranes are made from natural or synthetic polymers. Polymers selected for such applications (e.g. SRNF) are required to exhibit outstanding chemical and thermal stability and compaction resistance. In addition for SRNF, the membrane must be capable of nanoscale separations. These membranes can be prepared from common high molecular weight polymers such as polyimide (PI) and poly(amideimide) [105].

Polyimides can be synthesised in various structures, but in principle, they are made by a general reaction of diamines (DA) and pyromelliticdianhydrie (PMDA) in an aprotic solvent such as dimethylformamide (DMF) or dimethylacetamide (DMAC). Commercial polyimide materials which are used to form SRNF membranes include Matrimid-5218 (Ciba Geigy Corp., USA) (Fig. 5a) and Lenzing P84 (HP Polymers, Austria) (Fig. 5b). The former is a copolymer of 5(6)-amino-1-(4'-aminophenyl)-1,3-trimethylindane and 3,3'-4,4'-benzophenonetetracarboxylic dianhydride while the latter is a copolymer of 3,3'-4,4'-benzophenonetetracarboxylic dianhydride and a mixture of di(4-amino-phenyl)methane and toluenediamine. Both polymer types were reported to provide excellent chemical resistance, economically viable flux and high rejection of hydrocarbon species in polar and non-polar organic solvent systems [106-107]. However, the polymer is unstable in amines and many polar aprotic solvents, in which most of the membranes made from this polymer swell or dissolve [108]. Commercially available cross-linked PI membranes (NITTO Co., Japan) provide better chemical stability, however they are limited to the UF range and are not suitable for operation at elevated temperature [105]. The chemical cross-linking of this polymer for SRNF applications is currently being researched in the Separation Engineering and Technology Research Group at Imperial College London, and significant improvements of the chemical stability and separation performance have been observed [108]. The PI cross-linked membranes developed to date are stable in various commonly used difficult solvents such as DMF, dichloromethane (DCM), tetrahydrofuran (THF) and n-methyl-2-pyrolidone (NMP), and good separation properties have been reported. This membrane type has potential to be employed in natural extraction and purification applications and will be reviewed in this work.



(a) Matrimid 5218



80% 20%

(b) Lenzing P84

Fig. 5. Commercial polyimide for polymeric membrane synthesis.

Apart from PI, poly(dimethylsiloxane) (PDMS), polyoctenamer, and poly(ethylene-co-propylene-co-diene) (EPDM), poly(acrylonitrile) (PAN), crosslinked PAN and poly(amideimide) (PAI) are also used in non-aqueous applications. Although PDMS membranes have been reported to provide high permeability, the applications are limited due to high swelling of the polymer in many solvents and their unreliable performance [109-111]. Peinemann *et al.* (2001) studied the use of PAN and PAI with cross-linked PAN as a porous support for composite membranes for rapeseed oil separation in acetone and hexane [112]. It is reported that as high as 99% oil retention was obtained from an acetone system by employing a cellulose-ether coated PAI membrane. Moreover, the membranes developed from this study (i.e. PAN and crosslinked PAN) are stable in various organic solvents including acetone, ethyl methyl ketone (MEK), ethyl acetate (EA), ethanol, THF, DMF, NMP, etc. However, the membranes are limited to UF applications with a molecular weight cut-off around 3 to $25x10^4$ Da. Zwijnenberg *et al.* (1999) reported the use of poly(amide-b-ether) copolymer (PEBAX) and cellulose-type top layer membranes for vegetable oil deacidification [11[3]]. Reasonable fluxes (1.8 to 4.2 $L.m^{-2}.h^{-}1.bar^{-}1$) were observed for processing palm and rapeseed oils. With 5wt% TG and 5wt% FFA as a feed solution, high TG rejection (95 to 99.97%) was obtained from a PEBAX membrane operating at 20 bar at 25^{o}C. Rejection of the FFA was relatively high (55 to 62%) which could result in low oil yield. Moreover, the membrane is not commercially available and thus not fully characterised under different operating conditions, and the reproducibility of these membranes can be poor. It is also worth noting that all the results reported in Zwijnenberg's work were carried out at less than 10wt% solute concentration. This indicates the use of high volume of solvents and thus makes the application less feasible from an economic point of view.

4.2 Polymeric membrane formation

Polymeric membranes can be prepared by various preparation techniques including but not limited to phase inversion, thin-film formation on a porous support, sintering, stretching, leaching out, and track-etching. The first two techniques, phase inversion and thin-film formation are the most commonly used approaches and will be discussed in more detail.

4.2.1 Phase inversion membranes

Phase inversion is a process whereby a polymer is transformed from a liquid to a solid state in a controlled manner. In other words, this solidification process is the transition of one of the liquid phases (the high polymer concentration phase) into solid matrix form. The membrane structure resulting from this technique can be porous or dense depending on the polymers. This preparation approach covers a range of different techniques includes solvent evaporation, vapour phase precipitation, thermal precipitation and the most widely used technique, immersion precipitation.

For the manufacture of flat membranes, a schematic diagram of the immersion precipitation process for phase inversion membrane preparation is shown in Fig. 6. The polymer-solvent mixture (usually referred to as casting solution or dope solution) is cast directly onto a supporting non-woven material by means of a casting knife. The casting thickness can be varied in the range of 50 to 500 μm. The

polymer film is then immersed in a coagulation bath which contains the non-solvent (typically water, or methanol in some cases). The polymer solidifies during this stage as the exchange occurs between the solvent and non-solvent. In this preparation process, the important parameters affecting the properties of membranes (e.g. flux and selectivity) are determined; these include polymer concentration, composition of casting solution, choices of solvent and non-solvent pair, evaporation time, humidity, temperature.

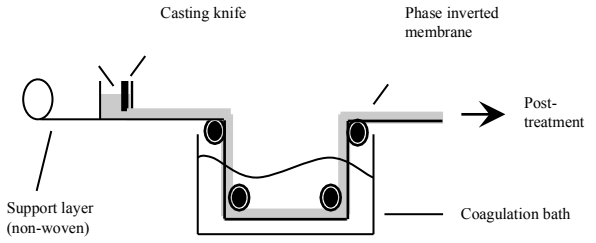


Fig. 6. Schematic representation of flat membrane preparation via phase inversion technique.

Integrally skinned asymmetric membranes may be formed from phase inversion. The resultant membranes can possess a range of separation properties depending on the solvent and non-solvent combinations. For example, PI membranes such as STARMEM^{TM} and PAN membranes are both manufactured using phase inversion but STARMEM^{TM} has NF properties whist the latter possesses UF properties and consequently serve as a support for composite NF membranes to be discussed in the following section.

4.2.2 Thin-film composite membranes

Alternative to integrally skinned asymmetric membranes, thin-film composite membranes can be prepared by the formation of an ultra-thin polymeric layer on a microporous support (typically UF or MF integrally skinned asymmetric membranes made of materials such as polyacrylonitrile (PAN), polyvinylidene fluoride (PVDF), hydrophobic polyetherimide (PEI) and polyphenylenesulphone (PPSu). The membrane layer is usually formed by interfacial polymerisation. Fig. 7 indicates how the thin-film composite membrane is prepared. In general, the porous support material (Fig. 7a), which usually is an asymmetric phase inversion UF or MF membranes, is immersed in an aqueous solution containing a water-miscible reactive monomer (e.g. a diamine) (Fig. 7b). The support with the film of monomer is then immersed in the second bath containing an organic solvent and a water-immiscible reactive monomer (e.g. an acid chloride) (Fig. 7c). Hence, a dense film polymeric layer is formed by the reaction of these two reactive monomers (Fig. 7d). Heat treatment is applied to complete the reaction and cross-link the monomers. The advantage of this membrane is that each layer can be optimised independently and the interfacial polymerisation is a self-inhibitive process in which the formation of the film will obstruct the passage of the monomer resulting in an extremely thin film thickness. However, a very thin film is subject to minute defects or pinholes in the permselective skin which can render the membrane useless for nanoscale separations [114]. Apart from interfacial polymerisation, solution coating is also a very simple and commonly used technique for preparing composite membranes with a very thin but dense top layer.

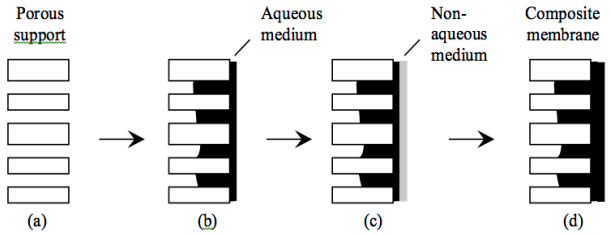


Fig. 7. Schematic representation of thin-film composite membrane preparation via interfacial polymerisation.

Interfacial polymerisation typically produces PA membranes, whereas rubbery top layers are usually applied by solution coating, for example, PDMS. The combination of PDMS on a PAN support is probably the most widely reported membrane for SRNF. [109,112, 115-121].

4.3 Membrane module designs

Polymeric membranes as described in the previous section are available in many different shapes as shown in Fig. 8. Flat sheet membranes can be fabricated into two different module designs, plate and frame module and spiral-wound, for use on larger scales. Table15 compares the characteristics of four module designs. Tubular modules are relatively expensive and are only used for small applications when a high resistance to fouling and or ease of cleaning are essential, whereas hollow-fibre modules, despite providing significantly higher surface area per unit volume, are commonly limited to gas permeation applications due to their poor resistance to fouling.

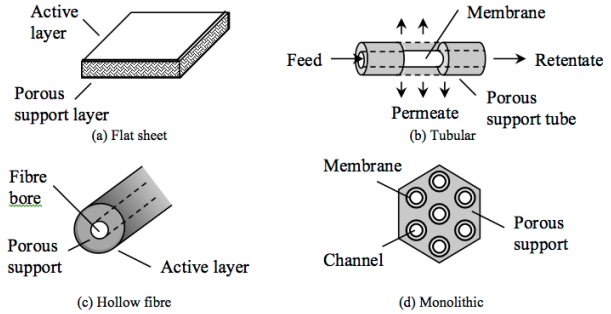


Fig. 8. Common membrane shapes. (Adapted from [11[4]].)

Table 15. Typical characteristics of various membrane designs [114].

	Plate and frame	Spiral-wound	Tubular	Hollow-fibre
Packing density (m^2/m^{-3})	30 to 500	200 to 800	30 to 200	500 to 9000
Resistance to fouling	Good	Moderate	Very good	Poor
Ease of cleaning	Good	Moderate	Excellent	Poor
Relative cost	High	Low	High	Low

Spiral-wound modules are the most popular design for industrial applications because of their inexpensiveness and reasonable resistance to fouling. The main advantages of this module type over plate and frame are the higher packing density and relatively low capital costs of the plant required to use this type of module. An outlines of this module design is shown in Fig. 9. The module consists of two membrane layers separated by spacers to allow the feed and the permeate to flow. The membrane envelope is wound around a central perforated permeate tube to form a membrane module that is inserted into a pressure vessel housing. The feed flows lengthwise along the module in the channels between the membrane and the feed spacer, while the

permeate passes through the membrane and flows radially toward the central tube. The thickness and porosity of the feed spacer varies depending on the application. More specifically, a thicker and more porous feed spacer is used to reduce feed side pressure drop along the modules which is usually used for viscous fluid applications [81]. However, an increase of feed spacer thickness and porosity may reduce the mechanical strength of the module and therefore the selection of spacer should be carefully considered. Another modification of the module is to use multi-leaf winding-i.e. more than one membrane envelope, "leaf", is used to provide the membrane area. This minimises the permeate side pressure drop, as the permeate has to travel less distance for the same membrane area.

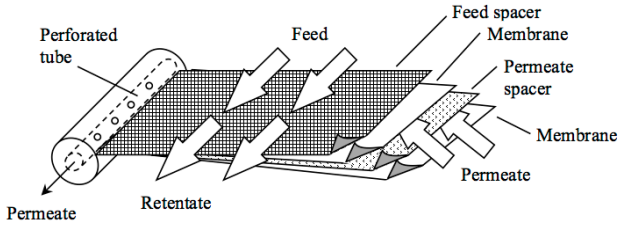


Fig. 9. Schematic drawing of a spiral-wound membrane module. (Adapted from [82].)

Currently, only a few commercially available spiral-wound membranes are robust enough for SRNF applications. Commercial modules such as FilmTec (Dow Chemical, USA), DESAL (GE Osmonics, USA), and Helecon (Millipore, USA) have been designed for aqueous system applications. STARMEM™ (W.R. Grace & CO., USA) (range of membranes are a commercially available spiral-wound module designed for SRNF applications, as mentioned earlier. Long-term stability and chemical compatibility studies of these membranes could be performed to evaluate their applicability to natural extraction and purification.

Attempts to manufacture lab-scale and pilot-scale spiral-wound modules have also been undertaken [94,122-123]. However, to date, no breakthrough product suitable for SRNF applications has been fabricated. The manufacture of SRNF spiral-wound modules is a challenge because not only the polymers, but also the adhesives, spacers, support materials and all other parts of the module have to be solvent-resistant. The study and development of SRNF spiral wound modules are a necessity if this technology is to be widely employed in the solvent extraction of high value natural products.

4.4 Characterisation and Transport Processes in SRNF Membranes and Modules

A membrane process is characterised by its selectivity and mass transfer properties. For a given solute, membrane separation characteristics are commonly expressed as rejection and retention. Rejection (R_i) is defined as:

$$R_i = 1 - \frac{C_{P,i}}{C_{R,i}} \tag{5}$$

where $C_{P,i}$ and $C_{R,i}$ are the concentrations of species i in the permeate and retentate, respectively. Retention (R_i') is a measure of the percentage of solute that remains in the retentate relative to the amount of solute fed. It is expressed as

$$R_i' = \frac{C_{R,i}V_R}{C_{F,i}V_F} \tag{6}$$

where $C_{F,i}$ is the concentration of species i in the feed, V_F and V_R are the volumes of feed and retentate, respectively.

The permeate flux (N) or permeation rate is defined as the volume passing through the membrane per unit area and time, caused by a driving force. It is expressed as

$$N = \frac{V_P}{At} \tag{7}$$

where A is the membrane effective area, and t is the time to produce permeate volume V_P . In practical applications, the membrane flux changes, or in most cases, declines, over a period of time. Factors such as membrane compaction, fouling and gel layer formation can all contribute to the decrease in flux. This phenomenon is undesirable as a reduced production rate leads to an increase in the overall costs of the membrane process. This results in the necessity to understand and develop the transport model for a particular process and use this model to optimise process parameters and minimise such effects.

In general, transport in SRNF membrane processes is based on a Fick's law expression:

$$N_i = \left(\frac{P_{M,i}}{l_M}\right)(driving\ \ force) \tag{8}$$

where N_i is the molar transmembrane flux of species i, $P_{M,i}$ is the permeability constant and l_M is the thickness of the membrane. The driving force for this process can be concentration or partial pressure depending on the mechanism of transport. For the former, the solution-diffusion model, where the transport is induced by concentration gradient and pressure is constant throughout the membrane, is widely used. For the latter, the pore flow transport model has been developed and proposed. Machado *et al.* (2000) developed a pore flow model for solvent-stable membranes, which involves a series of three resistance parameters; resistance in the membrane active layer, resistance in the porous support and the hydrophilic/hydrophobic resistance [124]. The transport equation proposed was:

$$N_i = \frac{\Delta P}{\varphi\left[\left(\gamma_M - \gamma_{solvent}\right) + f_1\mu\right] + f_2\mu} \tag{9}$$

where, ΔP is pressure gradient, μ is solvent viscosity, γ_M and $\gamma_{solvent}$ are the surface tension of membrane and solvent, respectively. φ , f_1 and f_2 are constants which are a combination of membrane characteristics parameters (porosity, turtuosity and membrane thickness). The advantage of this transport model is that the surface tensions

of both membrane and solvent are considered and hence, the model can potentially provide better flux prediction for non-aqueous systems due to the impact of organic solvent on the hydrophilicity and hydrophobicity of the membrane. However, the model does not give any insights regarding the flux behaviour of solutes in different solvents. This could lead to errors in flux prediction, as the selectivity of the membrane may vary in different solvents [125].

For SRNF membranes, the solution-diffusion transport model has been used to describe the behaviour of the SRNF transport process [126]. Research has also shown that, for SRNF systems, the solution-diffusion model gives better experimental agreement than the pore flow model [127]. This concentration-driven transport model assumes that a homogenous solution of solute and solvent permeates through the membrane by diffusion in an uncoupled manner. The solute concentration profile is shown in Fig. 10, and the flux profile from Fick's law is predicted by equation (10):

$$N_i = \left(\frac{D_i}{l_M}\right)\left(C_{FM,i} - C_{PM,i}\right) \tag{10}$$

where D_i is the diffusitivity of species i. When a chemical potential balance is established at both sides of the membranes, the flux profile can be expressed in terms of pressure and a sorption coefficient:

$$N_i = \frac{P_{M,i}}{l_M}\left[C_{F,i} - C_{P,i}\exp\left(\frac{-v_i \Delta P}{RT}\right)\right] \tag{11}$$

where v_i is molar volume of species i, R is ideal gas constant and T is temperature.

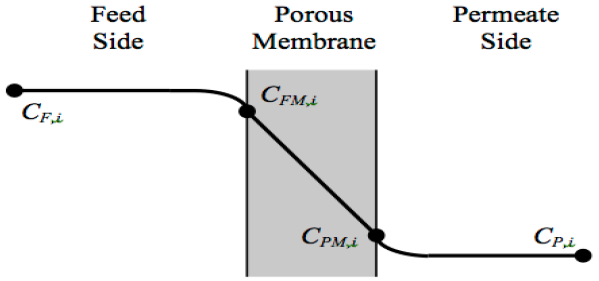


Fig. 10. Typical concentration profile for solute transport through porous membranes.

Apart from these commonly used models, other fundamental equations such as the Stefan-Maxwell transport model have also been considered. The basic assumption of the Stefan-Maxwell model is that the driving force on component i is equal to the friction of components i with other components. However, the problem in implementing this equation is the difficulty of determining the values of parameters such as diffusion frictional coefficients and therefore the need to greatly simplify this equation is a very practical one.

In the majority of membrane transport studies, the concentration of fluids at the surfaces of the membrane have been assumed equal to their respective bulk concentrations [128-130]. In contrast to gas permeation, this is not always true for SRNF. It is very possible that the build-up or depletion of species in the boundary layer due to mass-transfer resistance could form a thin film across the active layer of SRNF membrane surface resulting in a concentration difference between this layer and bulk fluid (Fig. 10). This effect is referred to as concentration polarisation. Concentration polarisation in SRNF is attributed to slow diffusion through the membrane and can greatly reduce the flux of the solvent and increase the flux of the solute.

Peeva *et al.* (2004) studied the effect of concentration polarisation by employing the solution-diffusion transport model with the consideration of film theory for the liquid boundary layer [126]. The total flux from film theory of mass transfer for a component i is given by:

$$\frac{N_i}{k_i} = \ln\left(\frac{D_i}{l_M}\right)\left(\frac{C_{i,FM} - C_{i,P}}{C_{i,F} - C_{i,P}}\right) \tag{12}$$

where k_i is the mass transfer coefficient of species i. The results from Peeva's study shows that SRNF cannot be described simply by neglecting concentration polarisation. For docosane- and tetraoctylammonium bromide (TOABr)-toluene SRNF systems, good agreement between experimental and simulated flux and rejection data were found by coupling equation (11) to (12), emphasising the denotation of mass transfer limitation induced by concentration polarisation.

There are a large variety of expressions available for mass transfer correlations. Typically, the liquid film mass transfer coefficient can be obtained from a general empirical film-model correlation

$$Sh = k_i \frac{d_H}{D_i} = a\,\mathrm{Re}^b\, Sc^{0.33}\left(\frac{d_H}{l_M}\right)^d \tag{13}$$

where Sh is Sherwood number, Re is Reynolds number ($= d_H u\rho/\mu$), and Sc is Schmidt number ($= \mu/\rho D_i$), with d_H being the hydraulic diameter. The values of *a, b* and *d* are correlation constants that vary depending on the flow type and channel geometry. Widely used correlations include the expression used by Schock and Miquel (1987) to calculate the performance of various commercial spiral-wound modules:[131].

$$k_i \frac{d_H}{D_i} = 0.065\,\mathrm{Re}^{0.875}\, Sc^{0.25} \tag{14}$$

For NF systems where concentration polarisation effects should be considered, Yang *et al.* (2003) suggested using pressure-driven bulk flow theory, assuming constant concentration along the flow channel coupled to Eriksson's mass transfer correlation (which is generally in agreement with equation (14)) [132]. They concluded that this mass transfer expression is the best choice when concentration polarisation is significant.

Overall, for spiral-wound membrane modules, all the work published to date has been for aqueous system [131-135]. Silva and Livingston (2008) proposed the modelling of spiral-wound modules by employing a modified solution-diffusion and film theory [136]. Two level of complexities of model have been investigated; a simple and a complex model. The former assumes uniform pressure and concentration throughout the module while the latter takes variation of pressure, cross-flow velocity and concentration into account. Both models describe the experimental flux

and rejection reasonably well. However, the system engaged in this study is a binary system, which is not applicable to natural products applications where many components are incorporated. Hence, there is a research challenge to develop these multi-component system models to extend their scope to natural extracts processing.

5. Concluding Remarks

In recent years, membrane technology has attracted a great deal of attention as an alternative separation technology. The main advantage of employing membrane technology for further purification of natural extracts is that a much lower operating temperature is required compared to conventional processing operations. In addition to the large saving in energy costs, natural extracts are often susceptible to thermal damage and thus the milder operating conditions of a membrane process can minimise the nutritive value loss from thermal degradation. It has been reported that by selecting suitable molecular weight cut-off (MWCO) membranes, this technology can be used to separate molecules in a customised manner. The critical feature is that membranes can potentially be used to fractionate molecules of similar molecular weight (e.g. in the 200-100 Da range) into retentate and permeate streams and thus separate the desired extract species from the co-extracts. However, the vast majority of commercial membranes have been developed for use in aqueous systems and provide only limited stability in a small range of organic solvents; these membranes are not suitable for use with many of the solvents used to extract important natural products.

Recent advances in materials science and engineering has led to the development of Solvent-Resistant Nanofiltration (SRNF). SRNF is a solvent-resistant membrane separation that is able to selectively retain solutes with molecular weights in the 200-1000 Da range and allow lower molecular weight compounds to pass through the membrane. Successful research work has shown that SRNF can be applied to a broad range of applications involving many different organic solvents. These include the chiral separation of drug intermediates, homogeneous catalyst recovery, monomer separation from oligomers, etc. Commercially available SRNF membranes are stable in several organic solvents including toluene, methanol, ethyl acetate, etc., however, their stability (or instability) in many common natural extraction solvents is not well documented. As a result, there is a need to carry out research and development in this field to establish the viability of using existing commercial SRNF membranes for natural product processing applications. For situations where they are not stable or suitable there is a need to develop new materials and synthesis techniques to generate membranes suitable for use in these natural extracts separation and purification applications.

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