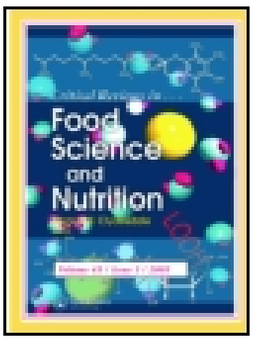

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REVIEW

Membrane separation processes for the extraction and purification of steviol glycosides: an overview

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ABSTRACT

Steviol glycosides (SGs), as natural sweeteners from *Stevia rebaudiana*, are currently employed for replacing sugar and its derivatives in several food products and formulations. Such compounds play an essential role in human health. Their usage provides a positive effect on preventing diseases related to sugar consumption, including diabetes mellitus, cancer, and lipid metabolism disorders. The traditional extraction of SGs is performed by means of solvent extraction, which limits their application since the removal of residual solvents is a challenging task requiring further downstream purification steps. In addition, the presence of residual solvents negatively affects the quality of such compounds. Today, food technicians are looking for innovative and improved techniques for the extraction, recovery and purification of SGs. Membrane-based technologies, including microfiltration, ultrafiltration, and nanofiltration, have long been proven to be a valid alternative for efficient extraction and purification of several high added-value molecules from natural sources. Such processes and their possible coupling in integrated membrane systems have been successfully involved in recovery protocols of several compounds, such as metabolites, polyphenols, anthocyanins, natural pigments, proteins, from different sources (e.g., agro-food wastes, plant extracts, fruits, fermentation broths, among others). Herein, we aim to review the current progresses and developments about the extraction of SGs with membrane operations. Our attention has been paid to the latest insights in the field. Furthermore, key process parameters influencing the extraction and purification of SGs are also discussed in detail.

KEYWORDS

Extraction; integrated membrane process; *Stevia rebaudiana*; steviol glycosides; sweeteners

Introduction

The synthesis of artificial sweeteners including saccharin, cyclamate and aspartame began in 1870 with the aim of enhancing and replacing natural sweeteners (i.e., honey and sucrose), implying the reduction of caloric intake. The food industry has evolved hand-in-hand with the market expansion of products enrich in sucrose, which concurrently contributes to the consumption of sugary products, and therefore increases in obesity around the world. To face such collateral damage, special products for diabetics containing synthetic sugars are massively produced (Weihrauch and Diehl 2004). Unfortunately, the worldwide market of artificial sweeteners has decreased considerably over the last decade due to their possible side effects on human health, such as cancer (Weihrauch and Diehl 2004), obesity (Yang 2010), and diabetes (Brown, de Banate, and Rother 2010). For this reason, natural sweeteners, like steviol glycosides (SGs), have gained increasing importance as food additives (Soufi et al. 2016).

SGs are typical compounds extracted from the *Stevia rebaudiana* plant, also known as "sweet herb" (Mondal and De 2014), which have recently raised their popularity because they can easily exceed the sweetening power of sucrose. Moreover, SGs do not contain carbohydrates or calories, and thus do not affect the consumer's glycemic index (Mondal and De 2014; Yadav and Guleria 2012). To the date, more than 20 different types of SGs have been identified and documented (Table 1), which together represent about 14% of the total dry weight of the leaves *S. rebaudiana*. Typically, SGs compounds are diterpene glycosides based on the kaurene skeletons (Zhang, Kumar, and Kutowy 2000), as illustrated in Figure 1. Stevioside is the most predominant molecule. It is well known that the sweetness depends fundamentally on the plant source, being the rebaudioside B with the highest sweetening power (around 300) (Lindley 2012).

Figure 2 shows a graphical representation of the conventional process for the extraction and purification of SGs, which implies a number of sequential steps based on the use of organic solvents or chelating agents. Such process can be detailed as follows: (1) solvent extraction, (2) concentration, (3) purification with resins, (4) crystallization, and (5) drying (Zhang, Kumar, and Kutowy 2000). Among different extraction processes, the main difference deals with the type

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Table 1. Steviol glycosides contained from *Stevia rebaudiana*.

	According to Figure 1				
Type of SGs	R_1	R_2	General formula	Molecular mass (g mol^{-1})	Relative sweetening power
Steviol	H	H	$C_{20}H_{30}O_3$	318.45	—
Steviolmonoside	H	β-Glc	$C_{26}H_{40}O_8$	480.27	—
Steviol-19-O-β-D-glucoside	β-Glc	H	$C_{26}H_{40}O_8$	480.27	—
Stevioside	β-Glc	β-Glc-β-Glc(2-1)	$C_{38}H_{60}O_{18}$	804.88	143
Steviolbioside	H	β-Glc-β-Glc(2-1)	$C_{32}H_{50}O_{13}$	642.73	125
Rubusoside	—	—	—	642.73	114
Rebaudioside A	β-Glc	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)	$C_{44}H_{70}O_{23}$	967.88	242
Rebaudioside B	H	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)	$C_{38}H_{60}O_{18}$	804.88	300
Rebaudioside C	β-Glc	β-Glc-[β-Glc(3-1)]-α-Rha(2-1)	$C_{44}H_{70}O_{22}$	951.01	50
Rebaudioside D	β-Glc-β-Glc(2-1)	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)	$C_{50}H_{80}O_{28}$	1129.15	221
Rebaudioside E	β-Glc-β-Glc(2-1)	β-Glc-β-Glc(2-1)	$C_{44}H_{70}O_{23}$	967.01	174
Rebaudioside F	β-Glc	β-Glc-[β-Glc(3-1)]-β-Xyl(2-1)	$C_{43}H_{68}O_{22}$	936.99	200
Rebaudioside G	β-Glc	β-Glc-β-Glc(3-1)	$C_{38}H_{60}O_{18}$	804.38	—
Rebaudioside H	β-Glc	β-Glc-[β-Glc(3-1)]-β-Rha(2-1)-β-Glc(3-1)	$C_{50}H_{80}O_{27}$	1112.49	—
Rebaudioside I	β-Glc-β-Glc(3-1)	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)	$C_{50}H_{80}O_{28}$	1128.48	—
Rebaudioside J	β-Glc-α-Rha(2-1)	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)	$C_{50}H_{80}O_{27}$	1112.49	—
Rebaudioside K	β-Glc-β-Glc(2-1)	β-Glc-[β-Glc(3-1)]-α-Rha(2-1)	$C_{50}H_{80}O_{27}$	1112.49	—
Rebaudioside L	β-Glc	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)-β-Glc(6-1)	$C_{50}H_{80}O_{28}$	1128.48	—
Rebaudioside M	β-Glc-[β-Glc-(3-1)]-β-Glc(2-1)	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)	$C_{56}H_{90}O_{33}$	1291.3	250
Rebaudioside N	β-Glc-[β-Glc-(3-1)]-α-Rha(2-1)	β-Glc-[β-Glc(3-1)]-β-Glc (2-1)	$C_{56}H_{90}O_{32}$	1274.54	—
Rebaudioside O	β-Glc-[β-Glc(3-1)]-β-Rha(2-1)-β-Glc(3-1)	β-Glc-[β-Glc(3-1)]-β-Glc(2-1)	$C_{62}H_{100}O_{37}$	1436.59	—
Rebaudioside R	—	—	—	—	—
Rebaudioside S	—	—	—	—	—
Dulcoside A	β-Glc	β-Glc-α-Rha(2-1)	$C_{38}H_{60}O_{17}$	788.87	50
Dulcoside B	H	β-Glc-[β-Glc(3-1)]-α-Rha(2-1)	$C3_8H6_0O_{17}$	788.38	40–60

Notes: Glc, glucose; Rha, rhamnose; Xyl, xylose.
Modified from Ceunen and Geuns (2013); Kumari and Kumar (2017); Pól et al. (2007).

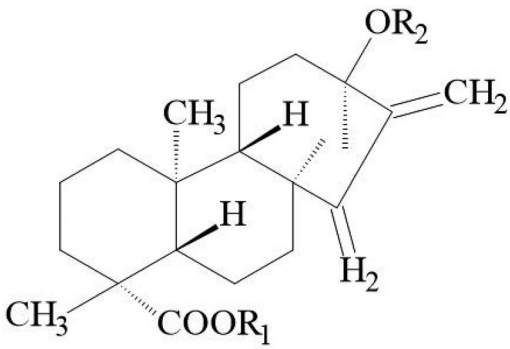

Figure 1. Basic structure of a diterpene glucoside.

of solvent used, in which ethanol, methanol, acetone, chloroform, petroleum ether can be employed. Some other important parameters are operating temperature (in the range 60 °C–100 °C), exposure time (from 30 min up to 24 h), devices and materials (e.g., resins) (Baotang and Qing 2015). Chelating agents, including calcium hydroxide, bentonite, aluminum hydroxide, zeolite, celite, and iron hydroxide can be used to remove organic and inorganic materials as primary clarification. Ion-exchange resins are generally used as purification step. Purity of stevioside between 70% and 90% have been attained by using combinations of anion- and cation-exchange resins (Kumar et al. 2006; Payzant, Laidler, and Ippolito 1999).

Very recently, to improve extraction yields and the purity of the molecules, new extraction techniques have been proposed implying high temperature (e.g., accelerated solvent extraction and rapid solid-liquid dynamic extraction) and high pressure (e.g., pressurized fluid extraction), electrical voltage (e.g., high voltage electrical discharge, pulsed electric field, high-speed counter-current chromatography), radiation (e.g., microwave-assisted extraction), ultrasound (e.g., ultrasound-assisted extraction and ultrasonication-assisted extraction), and chromatographic techniques (e.g., centrifugal partition chromatography and column-chromatographic technique) (Carbonell-Capella et al. 2017; Mondal and De 2014).

Table 2 summarizes some of the available patents related to the extraction and purification of rubososide, rebaudioside A and stevioside, as well as the configuration of the patented protocols according to the scheme provided in Figure 2 (Zhang, Kumar, and Kutowy 2000).

Novel techniques implemented for the extraction of different types of SGs from *S. rebaudiana* are summarized in Table 3. The extraction yields are relatively low varying between 2% and 35%, depending on the solvent and technique used. These low percentage yields and the large amounts of required solvents make difficult a large scale

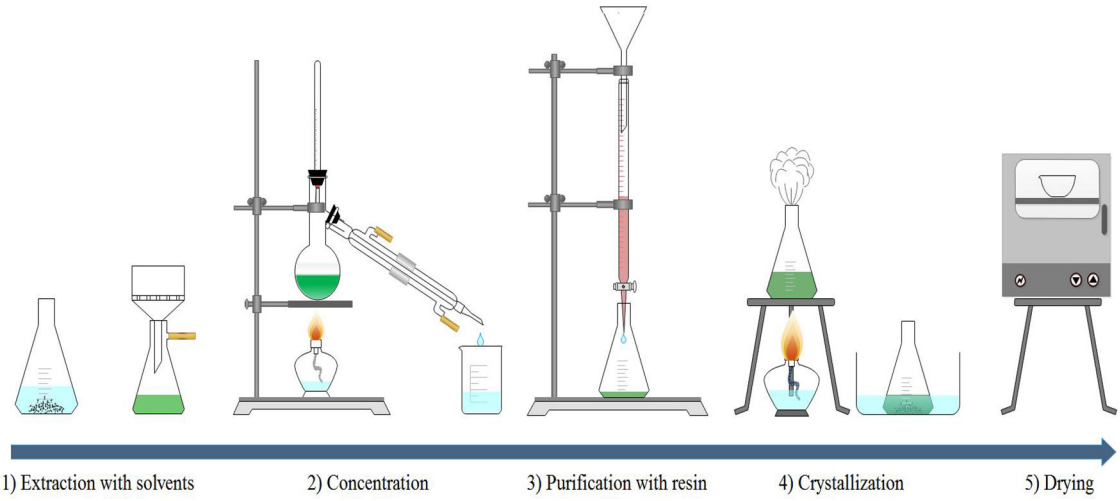

Figure 2. Schematic representation of the traditional extraction of steviol glycosides from *Stevia rebaudiana*.

Table 2. Patented methodologies for the extraction and purification of steviol glycosides from *Stevia rebaudiana*.

Extracted SGs	Methodology (according to Figure 2)	Country patent	Patent No.	Inventors
Rubusoside	1, 2, 3, 4, and 5	China	CN102838644A	Baotang and Qing 2015
	1, 2, 3, and 5		CN104193788B	Yang et al. 2016
	1, 2, and 5		CN106243165A	Jianjun et al. 2016
Stevioside	1, 4, and 5		CN1024348C	Fanbin and Haokui 1994
Rebaudioside A	1 and 5	Canada	CA2185496A1	Payzant, Laidler, and Ippolito 1998
	1, 4, and 5		CA2278083A1	Laidler, Payzant, and Ippolito 2001
	1, 4, and 5	United States	US7923541B2	Yang, Hua, and Qin 2011
Rebaudioside A and Stevioside	1 and 5		US7838044B2	Abelyan et al. 2010
	1, 2, and 5		US5962678A	Payzant, Laidler, and Ippolito 1999

application of the above methodologies (Díaz-Montes and Castro-Muñoz 2019). Moreover, these drawbacks impose economic disadvantages and unprofitable processes (Galanakis et al. 2016).

Membrane-based technologies represent currently a latent tool which has been explored for different approaches, including the treatment of agricultural by-products (Van der Bruggen, Lejon, and Vandecasteele 2003; Cassano, Rastogi, and Basile 2015; Castro-Muñoz and Yañez-Fernandez 2015), recovery of metabolites from fermentation broths (Díaz-Montes and Castro-Muñoz 2019; Faneer, Rohani, and Mohammad 2017) and recovery of high-added value molecules from various natural sources and their by-products (Castro-Muñoz, Barragán-Huerta, et al. 2016; Díaz-Montes, Barragán-Huerta, et al. 2020; Galanakis et al. 2016), to mention just a few. Today, membrane-assisted isolation of natural products, such as polyphenols (e.g. oleuropein) (Avram et al. 2017; Didaskalou et al. 2017; Voros et al. 2019), quercetin (Iben Nasser et al. 2016), theophylline (Algieri et al. 2018), monoterpenes (Janoschek, Grozdev, and Berensmeier 2018), antioxidants (Tundis et al. 2019), dextrans (Díaz-Montes, Yáñez-Fernández, and Castro-Muñoz 2020), is also a current trend in the field. Membrane-based purification processes have been also extended to the recovery of SGs. To date, there is no report compiling and analyzing such development works. Thereby, the present review paper aims to provide the current state-of-the-art of studies that have successfully extracted and purified SGs using membranes. Moreover, the key parameters for successful recovery are addressed, paying particular attention to the most relevant insights in the field. A brief overview of the fundamentals underlying membrane-based technologies is also given.

Brief fundamentals and aspects of membrane-based technologies

An overview of pressure-driven membrane processes

A typical pressure-driven membrane process uses a semipermeable membrane that acts as a selective barrier for the transport of compounds contained in a bulk liquid/fluid solution. Such permselective barrier splits the bulk feed into two different streams, the retentate and the permeate (Hernández et al. 1990; Marcano and Tsotsis 2002). In principle, the retentate contains partially rejected solvent together with all those compounds having higher molecular weight compared to the nominal molecular weight cutoff (MWCO) of the membrane, while the permeate contains most of the solvent and the molecules with a lower molecular weight than the membrane's MWCO (Castro-Muñoz, Conidi, and Cassano 2019). Generally, pressure-driven membrane processes are operated in batch concentration mode for the separation and concentration of target molecules, as illustrated in Figure 3a.

On the other hand, if the bulk feed solution is quite complex to be processed through the installed membranes, a diafiltration (DF) mode is commonly applied for feasible operation.

In the DF configuration mode (Figure 3b) a pure solvent (mainly water) or buffer is typically added to the feed

Table 3. Novel techniques employed for the extraction and purification of steviol glycosides from *Stevia rebaudiana*.

Technique	Extracted SGs	Extraction yield (%)	Reference
Accelerated solvent extraction	Stevioside	7.5–9.9	Bursać Kovačević et al. 2018
	Rebaudioside A	2.1–3.2	
Assisted by ultrasonication extraction	Rebaudioside A	35.0	Gasmalla et al. 2017
Centrifugal partition chromatography	Stevioside	4.2–24.0	Hubert et al. 2015
	Rebaudioside A	17.2–22.0	
	Dulcoside A	6.8–10.0	
Column-chromatographic technique	Steviolmonoside	4.7	Kaur, Pandhair, and Cheema 2014
	Stevioside	10.7	
	Rebaudioside B	7.3	
High voltage electrical discharges	Stevioside	4.5	Carbonell-Capella et al. 2017
	Rebaudioside A	2.0	
High-speed counter-current chromatography	Stevioside	27.0	Huang, Fu, and Di 2010
	Rebaudioside A	18.0	
	Rebaudioside C	6.5	
Microwave-assisted extraction	Stevioside	8.6	Jaitak, Singh, and Kaul 2009
	Rebaudioside A	2.3	
	Stevioside	2.0	Ameer et al. 2017
	Rebaudioside A	1.5	
	Stevioside	4.5	Carbonell-Capella et al. 2017
	Rebaudioside A	2.3	
Pulsed electric fields	Stevioside	3.7	Carbonell-Capella et al. 2017
	Rebaudioside A	2.1	
Pressurized fluid extraction	Stevioside	4.7	Pól et al. 2007
Rapid solid-liquid dynamic extraction	Stevioside	0.5	Gallo et al. 2017
	Rebaudioside A	1.4	
Supercritical fluid extraction	Stevioside	3.7	Erkucuk, Akgun, and Yesil-Celiktas 2009
	Rebaudioside A	1.8	
Ultra sound-assisted extraction	Stevioside	4.2	Jaitak, Singh, and Kaul 2009
	Rebaudioside A	2.0	
	Stevioside	5.1–9.7	Žlabur et al. 2015
	Rebaudioside A	0.4–3.7	
	Stevioside	5.0	Carbonell-Capella et al. 2017
	Rebaudioside A	2.2	

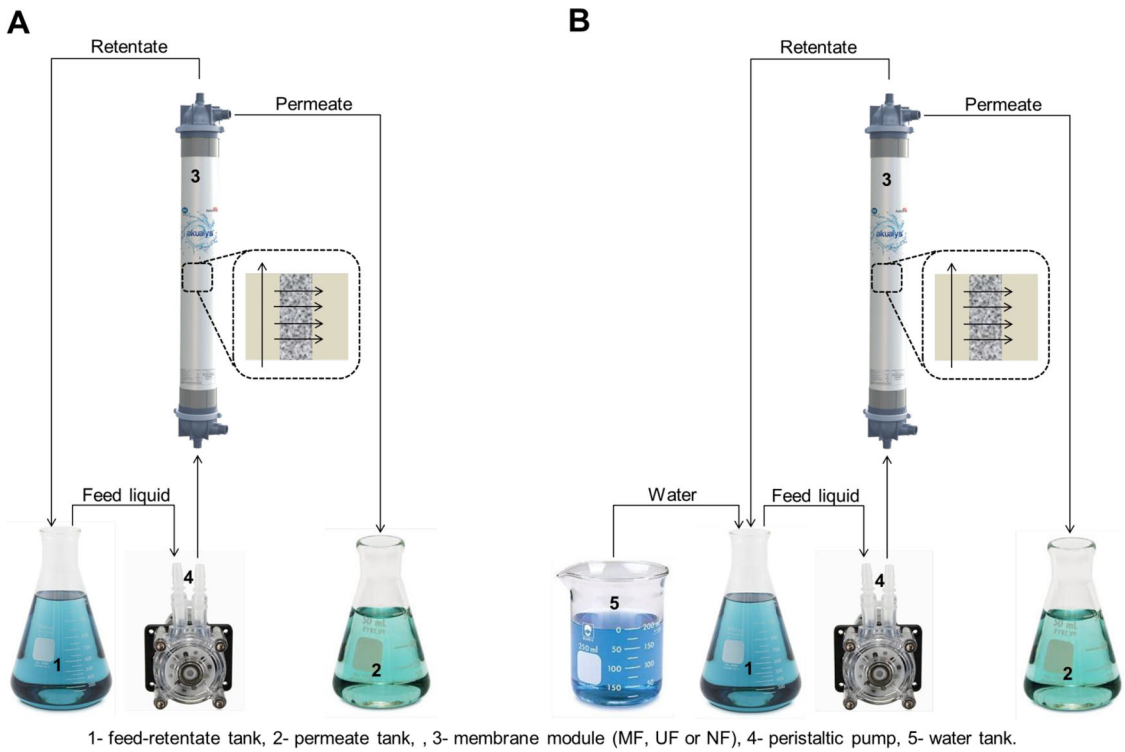

Figure 3. Graphical depiction of a pressure-driven membrane process. (a) Batch concentration mode (Reis et al. 2009); (b) batch diafiltration mode (Roy et al. 2015).

stream in order to dilute the feed and thereby to improve the degree of separation of the retained compounds from the permeate stream (Kolah, Lira, and Miller 2013; Kovács and Czermak 2013; Sen et al. 2011). Depending on the physicochemical composition of the feed stream, microfiltration (MF), ultrafiltration (UF), or nanofiltration (NF) membranes can be suitably used in DF mode (Kovács and Czermak 2013).

Table 4. Classification of pressure-driven membrane technologies.

Membrane process	Pore size (μm)/MWCO (Da)	TMP (bar)	Separation mechanism	Retained compounds
MF	0.05–100 μm	0.1–2	Sieving	Macromolecules Biomass Proteins Carbohydrates
UF	100,000–350,000 Da	0.1–7	Sieving	Micromolecules Sugars Organic acids
NF	120–1000 Da	3–35	Sieving and charge effect	Multivalent ions

Notes: Modified from Castro-Muñoz et al. (2017); Castro-Muñoz, Barragán-Huerta, et al. (2016).

The most common and widely used DF mode is the one operated in batch mode at constant volume (Kovács and Czermak 2013), where the concentration of the micro-components (i.e., lower molecular weight compared to MWCO of the membrane) contained in the feed stream (feed/retentate stream) decreases and the concentration of the macro-components (higher molecular weight compared to MWCO of the membrane) remains unchanged (Kolah, Lira, and Miller 2013; Kovács and Czermak 2013). Besides enhances purification of compounds, this configuration mitigates the membrane fouling (Kolah, Lira, and Miller 2013).

Membrane pore size and MWCO play a fundamental role in the separation of any molecule. These parameters can partially determine the rejection of the solutes (see Table 4), and they are considered as the main barrier to solute separation. However, in addition to this molecular sieving mechanism, other phenomena may occur, including concentration polarization, charge effect, coulombic and hydrophobic interactions, contributing to specific retention coefficients toward target molecules (Crespo and Brazinha 2010; Galanakis 2012).

The performance of the pressure-driven membrane processes is also depending on some other key important parameters, such as the physicochemical composition of the feed stream, operating parameters including transmembrane pressure (TMP), cross-flow velocity, and temperature (Castro-Muñoz, Conidi, and Cassano 2019; Breite et al. 2018; Castro-Muñoz, Barragán-Huerta, et al. 2016; Ulbricht 2006). In addition, the intrinsic membrane properties, such as material type, surface topography, hydrophilicity/hydrophobicity, charge and pore size (in terms of asymmetric structure) may cause chemical interactions between the membrane and the molecules which in turn are responsible of membrane fouling phenomena (Castro-Muñoz and Fíla 2018; Choi et al. 2005). Membrane fouling causes decrease of the permeate flux in time as a consequence of the effective membrane area being reduced due to the deposit of organic or inorganic matter on membrane surface or within the membrane pores. Blocking filtration laws describe typically four mechanisms of membrane fouling: (1) complete pore blocking, (2) standard pore blocking, (3) internal pore blocking, and (4) cake formation (Castro-Muñoz and Fíla 2018) which can be generated by physicochemical interactions (e.g., hydrophobic, polar, or charge transfer) between the membrane and compounds (Breite et al. 2018; Mulder 1995). The complete pore blocking assumes that the size of the solute particles is greater than that of the membrane pores. Therefore, it occurs on the membrane surface rather than inside membrane pores. When particles are smaller than the pores, they enter the membrane pores, thereby reducing the pore volume. This mechanism of fouling is named as standard pore blocking. The intermediate pore blocking assumes that some particles can obstruct the pore entrance but not completely block it. In the cake filtration particles do not enter the pores forming a cake layer on the membrane surface.

Membranes are commonly manufactured using polymeric and inorganic materials, but nowadays, mixed matrix membranes, as the merging of the strengths of inorganic and polymeric membranes (Castro-Munoz et al. 2018), are also developed and hence used in pressure-driven operations (Siddique et al. 2014). To date, polymeric materials are likely the most used in the preparation of MF, UF, and NF membranes (Castro-Muñoz et al. 2020; Russo et al. 2019).

Advantages and drawbacks of membrane technologies compared to conventional separation methodologies

The advantages of membrane processes over conventional separation processes have been clearly demonstrated for different applications. They include low energy consumption (Baker et al. 1991), less extraction time (Cassano, Rastogi, and Basile 2015), high separation efficiency, flexibility, high productivity and easy scaling-up, high quality of products and co-products (Díaz-Montes and Castro-Muñoz 2019; Mondal and De 2014). On the other hand, membranes technologies also present drawbacks during the operation. As mentioned previously, fouling phenomenon is found as the major drawback of these methodologies. Such an issue is directly dependent on the physicochemical composition of the feed bulk, type of membrane material, type of membrane module, and operating conditions. In general, it is known that the permeation rates can be negatively influenced by the fouling. However, the fouling in membranes can be mitigated by handling the membrane' hydrophilicity and membrane charge (Buonomenna 2016; Pichardo-Romero et al. 2020).

Since most of the commercial membrane modules are made on polymeric materials, the membrane processes cannot operate at high temperatures. Basically, polymers do not maintain their physical integrity at temperatures ranged between 90 °C and 100 °C. Herein, according to the low operating temperature, membranes are preferred over other technologies (such as solvent extraction, pulsed electric field, ohmic heating, microwave-assisted extraction, supercritical fluid extraction) due to the fact that display higher

extraction yields of thermolabile compounds. Also, the membranes tend to present low chemical stability by strong acid and alkaline cleaning solutions leading to a significant reduction in membrane life.

Within the implementation of membrane processes, the membrane cost and energy consumption are fundamental. For instance, the major investment regards to the membrane module cost, while the energy consumption of these technologies is recognized as low (Castro-Muñoz et al. 2017; Van Der Bruggen, Vandecasteele, et al. 2003). Herein, it is needed to point out the "cost-benefit" relationship, e.g., membrane processes are environmentally friendly process, which do not need the use of additional phases (e.g., chemical solvents) for efficient separation, while the SGs also require less contact with external agents due to their high purity for food applications. Finally, when comparing with the drawbacks of emerging and traditional extraction techniques (see Table 5), it is quite possible that membrane processes are the most suitable for extracting SGs considering their great water solubility and easy processing. The next section of this paper provides an outlook of the extraction, separation, and recovery of SGs by using membrane technologies.

Extraction/purification of SGs via pressure-driven membrane processes

Table 6 summarizes the main research works devoted to the separation of SGs using single membrane steps. Initially, some authors have studied MF processes to evaluate the performance of membranes with different pore size and to assess the influence of the TMP, as a driving force, on the retention capacity of SGs from *S. rebaudiana*. Reis et al. (2009) investigated the use of MF membranes for stevia extract clarification and purification in order to get a product with high commercial acceptability. The process was carried out by using ceramic membranes with different pore sizes (0.05, 0.1, and 0.2 μm) and at different TMP values (2, 4, and 6 bar). Experimental results indicated that the permeate flux increased by increasing the operating pressure, although it decreases along the time due to fouling phenomena. The type of membrane as well as the nature of the extract did not allow to reach the limiting TMP, in which the permeate flux is governed by fouling and concentration polarization phenomena (Cassano et al. 2007). Importantly, the absence of critical flux should be advantageous since membrane fouling implies higher energy consumption for operation, as well as an increase in using reagents for membrane cleaning. Thus, operating under hydrodynamic conditions that belong to the pressure-controlled region (i.e., sustainable flux) represents an economic and operational sustainability of membrane filtration operations (Wei et al. 2011). The best condition for the flux was obtained with the membrane of 0.2 µm at 6 bar: in these conditions, the initial permeate flux of about 160 L/m^2 h decreased up to 80 L/m^2 h after 90 min of continuous operation under a batch concentration configuration. On the other hand, the best clarification results were obtained with the membrane of 0.1 µm at 4 bar. For all tested membranes and conditions, the recovery of sweeteners resulted higher than 90%. In a previous work, the stevia crude extract was pretreated by adsorption on modified zeolites and then microfiltered with the same ceramic membranes (Silva et al. 2007). Recuperation of stevioside with the 0.2 μm membrane at 6 bar resulted of 91.75%. These studies were primarily aimed at the clarification of the extracts and most of the SGs were recovered in permeate streams. The slight rejection of the MF membranes can be associated to fouling phenomenon, which may be also influenced by the driving force (Castro-Muñoz and Yañez-Fernandez 2015). The rejection of low molecular weight compounds (e.g. phenolic compounds and some derivatives) commonly increases with increasing the TMP (Díaz-Reinoso et al. 2009). On the other hand, the increase in operational TMP results in a greater effect on membrane fouling (Cassano et al. 2018). The fouling phenomenon is well denoted by the so-called film layer theory, which assumes the formation of a thin layer of a specific thickness at the adjacent area to the membrane surface, where the concentration decreases from the surface to the bulk. In addition to this, concentration polarization and fouling are highly promoted at higher TMP values, in agreement with the formation of an additional selective layer on the membrane surface and increasing of the retention coefficient (Todisco, Tallarico, and Gupta 2002).

Stirring of feed solutions are able to mitigate the adverse effects of concentration polarization and fouling due to deposition of the contaminants on the membrane surface (Mohammadtabar et al. 2019). Chhaya, Majumdar, and De (2013) evaluated the effect of stirring speed (from 500 to 2500 rpm) and TMP (from 1.38 bar to 2.76 bar) on the performance of a 0.2 μm MF membrane used for primary clarification of crude stevia extract. Stirring speed increased the flux significantly: after 25 minutes, at 1.38 bar, 2.4 times flux enhancement occurred when the stirring speed increased from 500 to 2500 rpm. The recovery of stevioside resulted higher at lower TMP, reaching the highest recovery of ~89% at 1.38 bar. The permeate flux value at 2.74 bar and 2500 rpm stirring speed was of 30 L/m^{2}h. Authors observed that the combination of centrifugation and MF technologies may also be useful to improve the clarification of the extract through a better elimination of suspended solids, organic matter and some other macromolecular compounds.

UF processes based on the use of membranes with smaller pore size than MF have been largely investigated for the extraction of several types of SGs, e.g. stevioside, rebaudioside A and rebaudioside C. Polysulfone (PSF) and polyvinylidenedifluoride (PVDF) membranes in tubular configuration (PCI BX-6 and FP-100, from Paterson Candy International Ltd.), with MWCO of 25 and 100 kDa, respectively, were used to remove impurities and recover SGs from a crude extract of leaves (Fuh and Chiang 1990). The UF process removed more than 96% of the pigments, with SGs recoveries of about 28% and 50% for the 25 kDa and 100 kDa membranes, respectively. The 25 kDa membrane was operated at higher pressure (12 bar) providing a lower permeate flux (of ~20 L/m^2 h) when compared to the

Table 5. Disadvantages of emerging and traditional techniques employed for the separation of valuable compounds (Díaz-Montes and Castro-Muñoz 2019).

Technique	Characteristics	Extracted metabolites	Disadvantages	Reference
Solvent extraction	Use organic solvents (e.g., ethanol, methanol, hexane, and acetone) and reflux to metabolites extraction.	Flavonoids and carotenoids	Low extraction yield Long processing time High energy consumption Destructive effect	Prommuak, De-Eknamkul, and Shotipruk 2008; Yan et al. 2018
Pulsed electric fields	Non-thermal method that uses short pulses of electricity to increase the permeabilization.	Sugars and oils	High cost of initial investment High energy dissipation	Mohamed and Eissa 2012; Sarkis et al. 2015
High voltage electrical discharges	Method that applies a high voltage electric field causing the propagation of shock waves of pressure in the surrounding media, while the cavitation of gas bubbles achieves an increase in the electrical conductivity and the permeability of the intracellular material.	Flavonols and polyphenols	High cost of initial investment High energy consumption	Brianceau et al. 2016; Roselló-Soto et al. 2015
Pulsed ohmic heating	A thermal technology that heat foods by means of electric current flowing through them.	Lipids and polyphenols	Toxicity because of electrodes	El Darra et al. 2013; Kim, Park, and Kang 2018; Samprovalaki, Bakalis, and Fryer 2007
Microwave assisted extraction	Irradiates samples (solids or semisolids) that are immerged in a solvent. The energy of the waves leads to the molecule's vibration.	Anthocyanins and aromatic hydrocarbons	Use of solvents	Liazid et al. 2011; Yuan et al. 2019
Subcritical fluid extraction	A technique based on a distillation that uses low pressures, suitable for the separation of substances of high boiling point, high viscosity, and sensitive to heat.	Anthocyanins and oils	The equipment is not commercially available	Bleve et al. 2008; Hrnčič, Cör, and Knez 2018
Supercritical fluid extraction	Technique that uses fluids (e.g., CO_2) with characteristics of solvents (high diffusion capacity and low viscosity), this accelerates the speed of transport and improves the separation of lipids at low temperatures.	Oils and flavonoids	High equipment cost Low processing capacity High production costs	Alvarez et al. 2019; Sun et al. 2018
High pressure processing	A non-thermal treatment that destroys microbial agents and gives stability to the product without affecting its sensory properties.	Anthocyanins and flavonoids	Loss of nutrients Loss of functional compounds	Corrales et al. 2009; Escobedo-Avellaneda et al. 2011
Accelerated solvent extraction	Technique based on the heating process of the solvent accompanied by a high pressure.	Polyphenols and carotenoids	Formation of toxic compounds (e.g., furfural)	Rajha et al. 2014; Xie et al. 2019
Extraction assisted by hydrotropic solvents	Green extraction because used solvents are chemically inert, easily separable, reusable, and selective.	Polyphenols	Long processing time High concentration of solvent	Nagarajan et al. 2016; Prakash et al. 2014
Ultrasound-assisted extraction	Technique based on the propagation of ultrasound waves that cause the cavitation phenomenon, solvent infiltrates in the samples causing the extraction of compounds.	Polyphenols	Use of solvents	Malićanin et al. 2014; Paz et al. 2015
Column-Chromatographic technique	Separation method based on a system of two phases.	Aromatic compounds and terpenoids	Small volume processing	Bilal et al. 2018; Chatterjee, Kim, and Cho 2018

100 kDa membrane which showed a flux of ~65 L/m^{2}h at 8.5 bar. Therefore the 100 kDa membrane was selected to extract stevioside and rebaudioside A in a two-stage integrated system. The overall process consisted in a UF step in concentration operation mode followed by a UF process in DF mode with the aim of recovering the remaining

Table 6. Conventional membrane processes using single steps for the recovery of steviol glycosides from *Stevia rebaudiana*.

		Membrane type			Operating parameters					
Process	MWCO	Material type	Configuration	Manufacturer	TMP (bar)	Flow rate (L m^{-2} h^{-1})	Recovered SGs	Solvent used	Extraction yield (%)	Reference
MF	0.05 μm	Ceramic	—	—	2.0	~25.0	Stevioside	Water	90	Silva et al. 2007
							Rebaudioside		95	
					4.0	~30.0	Stevioside		62	
							Rebaudioside		69	
	0.1 μm	Ceramic			6.0	~35.0	Stevioside		56	
							Rebaudioside		49	
					2.0	~50.0	Stevioside		65	
							Rebaudioside		72	
	0.2 μm	Ceramic			4.0	~60.0	Stevioside		61	
							Rebaudioside		74	
					6.0	~70.0	Stevioside		83	
							Rebaudioside		79	
					2.0	~60.0	Stevioside		44	
							Rebaudioside		52	
					4.0	~70.0	Stevioside		79	
							Rebaudioside		84	
					6.0	~80.0	Stevioside		92	
							Rebaudioside		70	
MF	0.05 μm	Ceramic	n.r.	n.r.	2.0	~25.0	Stevioside	Water	97	Reis et al. 2009
							Rebaudioside		95	
					4.0	~30.0	Stevioside		83	
							Rebaudioside		93	
	0.1 μm	Ceramic			6.0	~35.0	Stevioside		50	
							Rebaudioside		51	
					2.0	~50.0	Stevioside		94	
							Rebaudioside		91	
	0.2 μm	Ceramic			4.0	~60.0	Stevioside		98	
							Rebaudioside		95	
					6.0	~70.0	Stevioside		92	
							Rebaudioside		94	
					2.0	~60.0	Stevioside		95	
							Rebaudioside		94	
					4.0	~70.0	Stevioside		92	
							Rebaudioside		97	
					6.0	~80.0	Stevioside		86	
							Rebaudioside		97	
MF	0.2 μm	PES	Batch stirred membrane cell	Sartorius Mechatronics	1.4	~5.0	Stevioside	Water	87	Chhaya, Majumdar, and De 2013
						~10.0			89	
					2.1	~15.0			88	
						~13.0			87	
					2.8	~20.0			85	
						~25.0			88	
						~20.0			85	
						~25.0			84	
						~38.0			81	
MF	0.2 μm	Ceramic	Tubular	—	0.9	—	Stevioside	Water	86	Martínez-Alvarado, Torrestiana-Sánchez, and

										Aguilar-Uscanga 2017
							Rebaudioside A		85	
UF	25 kDa	PSF	Tubular	—	12.0	~20.0	Stevioside	Water	~35	Fuh and Chiang 1990
							Rebaudioside A		~38	
	100 kDa	PVDF	Tubular		8.5	~65.0	Stevioside		~52	
							Rebaudioside A		~56	
UF	30 kDa	PES	Hollow fiber	Permionics Membranes	5.0	7.5	Stevioside	Water	72	Rao, Prasad, et al. 2012; Rao, Reddy, et al. 2012
UF	5 kDa	TFC	n.r.	Permionics Membranes	4.1	~42.0	Stevioside	Water	~37	Chhaya, Mondal, et al. 2012
	10 kDa	PES			4.1	~25.0			~20	
	30 kDa	PES			4.1	~60.0			~50	
	100 kDa	PES			4.1	~30.0			~12	
UF	30 kDa	PES	n.r.	Permionics Membranes	2.8	~7.0	Stevioside	Water	48	Chhaya, Mondal, et al. 2012
						~13.0			48	
					4.1	~17.0			47	
						~10.0			48	
					5.5	~17.0			51	
						~27.0			46	
					6.9	~13.0			38	
						~23.0			30	
						~33.0			29	
						~17.0			38	
						~27.0			30	
						~37.0			35	
UF	30 kDa	PES	—	Permionics Membranes	2.8	~6.0	Stevioside	Water	72	Chhaya, Sharma, et al. 2012
						~9.0			58	
						~12.0			49	
					4.1	~15.0			49	
						~5.0			49	
						~13.0			45	
					5.5	~15.0			43	
						~18.0			40	
						~12.0			45	
					6.9	~16.0			41	
						~18.0			40	
						~20.0			37	
						~13.0			37	
						~17.0			30	
						~21.0			31	
						~23.0			28	
UF	5 kDa	PSF	—	Permionics Membranes	2.8	~1.5	Stevioside	Water	~52	Mondal, Rai, and De 2013
					4.1	~2.0			~37	
					5.5	~2.5			~37	
	10 kDa	PES			6.9	~3.0			~28	
					2.8	~1.5			~20	
					4.1	~2.5			~20	
	30 kDa	PES			5.5	~3.0			~19	
					6.9	~3.5			~19	
					2.8	~2.0			~58	

(*continued*)

Table 6. Continued.

		Membrane type			Operating parameters					
Process	MWCO	Material type	Configuration	Manufacturer	TMP (bar)	Flow rate (L m^{-2} h^{-1})	Recovered SGs	Solvent used	Extraction yield (%)	Reference
	100 kDa	PES			4.1	~3.0			~50	
					5.5	~4.0			~51	
					6.9	~5.0			~54	
					2.8	~1.0			~15	
					4.1	~2.0			~12	
					5.5	~3.0			~13	
					6.9	~4.0			~15	
UF	30 kDa	PES	—	Permionics Membranes	2.8	~2.0	Stevioside	Water	48	Mondal, Chhaya, and De 2012
						~3.5			48	
					4.1	~5.0			47	
						~2.5			48	
					5.5	~5.0			51	
						~7.5			46	
					6.9	~3.0			38	
						~6.0			30	
						~8.0			29	
						~5.0			38	
						~7.5			30	
						~10.0			35	
UF	3 kDa	CR	Filtration centrifugal	Merck Millipore	—	–	Stevioside	Water	~50	Lorenzo et al. 2014
									~48	
	5 kDa	CR							~25	
									~60	
UF	90 kDa	CAP-PAN	Membrane cell	Homemade	1.4	—	Stevioside + Rebaudioside	Water	~53	Roy and De 2015
									~53	
									~56	
					2.8				~56	
									~64	
									~65	
					4.1				~67	
									~68	
									~67	
					5.5				~68	
									~71	
									~72	
									~67	
									~69	
									~72	
									~73	
UF	90 kDa	CAP-PAN	Membrane cell	Homemade	2.8	11.0	Stevioside + Rebaudioside	Water	68	Roy and De 2014
UF	30 kDa	CAP-PAN	Hollow fiber	Homemade	0.2	—	Stevioside + Rebaudioside	Water	63	Roy et al. 2015
						—			62	
					0.3	—			64	
						—			60	
					0.7	~4.7			61	
						~3.2			63	

					1.0	—			55	
						—			57	
						—			58	
						—			49	
						—			51	
						∼5.7			52	
UDF	30 kDa	CAP-PAN	Hollow fiber	Homemade	0.3	81.0	Stevioside + Rebaudioside	Water	94	Roy et al. 2015
UF	10 kDa	PES	—	Permionics Membrane	3.1	∼2.7	Rebaudioside A	Water	∼16	Das et al. 2015
					4.1	∼3.3			∼14	
	20 kDa	PES			5.2	∼4.0			∼13	
					3.1	∼2.7			∼18	
	30 kDa	PES			4.1	∼3.2			∼17	
					5.2	∼3.4			∼14	
	50 kDa	PES			3.1	∼3.0			∼24	
					4.1	∼3.6			∼24	
					5.2	∼3.5			∼22	
					3.1	∼0.7			∼14	
					4.1	∼1.5			∼12	
					5.2	∼3.0			∼11	
UF	30 kDa	PES	—	Permionics Membrane	1.4	∼2.7 to ∼9.0	Stevioside	Water	29–37	Das et al. 2015
							Rebaudioside A		27–36	
					2.8	∼10.8 to ∼16.2	Stevioside		34–39	
							Rebaudioside A		31–40	
					4.1	∼18.7 to ∼20.9	Stevioside		34–44	
							Rebaudioside A		31–43	
UF	50 kDa	PSF	Hollow fiber	Koch Membrane System	3.0	—	Stevioside	Water	66	Kootstra, Elissen, and Huurman 2015
							Rebaudioside A		66	
	100–150 kDa	PES			3.0		Rebaudioside C		65	
							Stevioside		83	
	50 kDa	PSF			3.0		Rebaudioside A		82	
							Rebaudioside C		84	
							Stevioside		78	
							Rebaudioside A		76	
							Rebaudioside C		75	
UF	30 kDa	PSF	Hollow fiber	Koch Membrane System	1.5	—	Stevioside	Water	81	Kootstra, Elissen, and Huurman 2016
							Rebaudioside A		81	
	50 kDa	PSF			1.5		Rebaudioside C		84	
							Stevioside		80	
							Rebaudioside A		79	
							Rebaudioside C		81	
UF	3 kDa	Ceramic	Multichannel	—	0.9	—	Stevioside	Water	57–61	Martínez-Alvarado, Torrestiana-Sánchez, and Aguilar-Uscanga 2017
							Rebaudioside A		54–60	
					1.1		Stevioside		55–60	
							Rebaudioside A		51–55	
	15 kDa	Ceramic			1.2		Stevioside		54–59	

(*continued*)

Table 6. Continued.

		Membrane type			Operating parameters					
Process	MWCO	Material type	Configuration	Manufacturer	TMP (bar)	Flow rate (L m^{-2} h^{-1})	Recovered SGs	Solvent used	Extraction yield (%)	Reference
							Rebaudioside A		48–57	
					1.1		Stevioside		61–70	
							Rebaudioside A		56–67	
					1.3		Stevioside		57–64	
							Rebaudioside A		51–62	
					1.5		Stevioside		59–67	
							Rebaudioside A		52–65	
NF	200 Da	A/B-S	Flat sheet	Koch Membrane System	30.5	—	Stevioside	Water	86	Kootstra, Elissen, and Huurman 2016
							Rebaudioside A		87	
	1 kDa	A/B-S			30.5		Rebaudioside C Stevioside		88	
							Rebaudioside A		93	
							Rebaudioside C		93	
									95	
NF	200–400 Da	PA	Thin film	Filmtec	40.0	—	Stevioside	Water	72–99	Kootstra, Elissen, and Huurman 2015
							Rebaudioside A		68–97	
							Rebaudioside C		76–100	

permeable SGs. The authors claimed that an increase of 38% in the recovery of the SGs in relation to the extraction was obtained using only the process in concentration mode. By comparing the membrane-based system with an extraction by precipitation with inorganic salts (i.e., calcium hydroxide), the authors found that the yield in both methods were similar; however, the SGs obtained by precipitation showed 40% less purity, which was attributed to metals linked to calcium salts. Thereby, membrane processes offer comparable recovery efficiencies in comparison with traditional recovery protocols, but high purity degrees can be reached since membrane processes do not use additional agents.

Chhaya, Mondal, et al. (2012) evaluated the performance of four UF membranes with different MWCO (5, 10, 30, and 100 kDa) in terms of permeate flux and recovery of stevioside in the permeate. The highest yield of about 50% was obtained with the 30 kDa membrane. Pore blocking phenomena resulted severe for membranes with highest pore size (100 kDa) and lower for lower cutoff membranes. Therefore, permeate fluxes for higher cutoff membranes were not necessarily higher than those measured for lower cutoff membranes. The authors examined also the effect of stirring speed (i.e., 600, 1200, and 1800 rpm) on the performance of the 30 kDa membrane. According to the results, the yields varied from 29% to 51% while the purity was ranged from 50% to 67%. Particularly, the highest yield was obtained with a purity of 65% when the system was operated at 1200 rpm and 4.1 bar. In another study, authors observed that cake filtration was the most prevailing mechanism of flux decline for all selected membranes and. According to resistance in series analysis, the cake resistance resulted of several orders of magnitude higher than the membrane resistance. It was independent of TMP drop, indicating the incompressible nature of the cake (Mondal, Rai, and De 2013). A mathematical model during stirred continuous mode of operation based on models available in literature was formulated by Mondal, Chhaya, and De (2012) in order to predict the performance of the 30 kDa membrane during clarification of stevia extract. Estimated values of diffusivity of gel forming material in Stevia extract and gel concentration were $(3.7 \pm 0.8) \times 10^{-11}$ m^2/s and $51.5 \pm 1.5\ kg/m^3$, respectively. The model predictions were in good agreement with the experimental data.

Das et al. (2015) estimated the rebaudioside A extraction efficiency of different polyethersulfone (PES) membranes with MWCO of 10, 20, 30 and 50 kDa in batch and cross flow operation. Steady state permeate flux as well as recovery of rebaudioside A in the permeate stream increased with TMP and flow rate. Among the selected membranes, the 30 kDa membrane was found to be the most effective for rebaudioside A separation. Recovery of 45% and permeate flux values of 5.86×10^{-6} m^3/m^2 s were obtained in optimized conditions of TMP (4.1 bar) and Reynolds number (1667).

Roy and De (2014) evaluated the performance of tailor made UF membranes cast from blend of cellulose-acetate pthalate (CAP) and polyacrylonitrile (PAN) polymers for the extraction of SGs. The produced membranes had a MWCO ranging from 7 to 104 kDa, depending on the blend composition. 90 kDa membranes provided the best results in terms of steady state permeate flux (11 L/m^2 h), recovery (68%) and purity (34%) of glycosides. In another study, authors found that recovery and purity of glycosides with such membranes were strong functions of TMP and Re. Flux declines (80%–90%) were attributed mainly to pore blocking during filtration (Roy and De 2015). The threshold pressure, defined as the maximum value of TMP up to which point the flux–TMP relationship remains linear, increased with the Reynolds number. In addition, as Re number increased, the threshold TMP approached the limiting TMP confirming that increase in turbulence reduced the formation of polarized layer significantly. The use of DF enhanced recovery and purity of SGs up to 94% and 54%, respectively, in the treatment of Stevia extract with CAP-PAN (4:16) blend membrane of MWCO 30 kDa at an operating pressure of 0.3 bar and cross flow rate of 10 L/h (Roy et al. 2015).

Kootstra, Elissen, and Huurman (2016) employed two PSF membranes (30 and 50 kDa) to recover stevioside, rebaudioside A, and rebaudioside C. About 80% of the SGs were recovered regardless of the membrane used. However, the purity of the final extract was low (15% to 20% of SGs in the dry matter).

In general, most of the studies have been focused on optimizing the operational parameters during the recovery process. UF membranes with MWCO of 30 kDa were found to be the most suitable for the recovery of different types of SGs. It is likely that the fouling phenomenon (e.g. pore blocking) as well as hydrodynamic properties of these membranes provide the suitable features for SG compounds. Moreover, it is a fact that MWCO and permeability are two factors which are not always dependent on each other; in other words, higher MWCO membranes do not necessarily provide higher permeability and vice versa.

Integrated membrane processes

The combination of membrane unit operations in integrated membrane systems is an emerging tool in the processing of different liquid foods and vegetable extracts since it offers new prospects for development, reengineering, or retrofitting of industrial processes within the logic of the process intensification and zero-discharge strategies (Cassano et al. 2018). This approach offers significant advantages in terms of increased purity of recovered compounds, control of membrane fouling, improvement of product quality, reduction of energy consumption and environmental impact (Knozowska et al. 2017; Thuy and Boontawan 2017). Integrated membrane systems have been proposed for the recovery of phenolic compounds and anthocyanins from several natural products, such as pomegranate juice (Conidi et al. 2017), artichoke extracts (Conidi et al. 2015), wine lees (Giacobbo, Bernardes, and de Pinho 2017), olive mill (Cassano et al. 2013) and nixtamalization wastewaters (Castro-Muñoz and Yañez-Fernandez 2015; Díaz-Montes, Yáñez-Fernández, and Castro-Muñoz 2020). According to

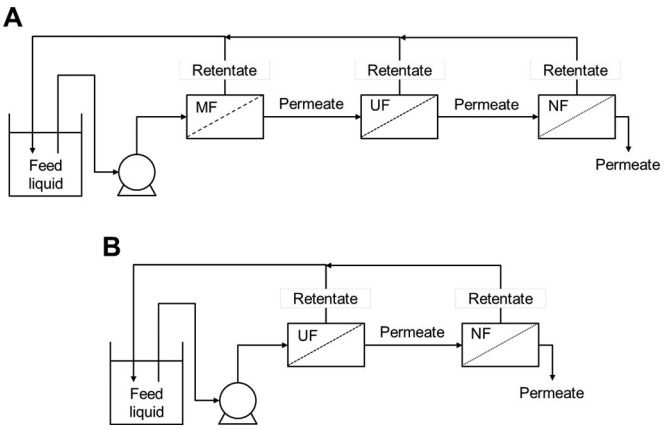

Figure 4. Scheme of the integrated membrane processes employed for the recovery of steviol glycosides from *Stevia rebaudiana*. (a) Microfiltration (MF)-ultrafiltration (UF)-nanofiltration (NF) process; (b) ultrafiltration-nanofiltration process.

the relevant insights provided by such approaches, the concept has been proposed and therefore also developed for the extraction of SGs from *S. rebaudiana*. From a practical and general point of view, MF technology was selected as the pretreatment aimed at eliminating organic matter and the non-soluble compounds, and narrow pore size membranes were implemented in downstream steps. The most used configurations include a combination of MF, UF, and NF membranes (Figure 4).

Chhaya, Sharma, et al. (2012) implemented an integrated membrane process based on a preliminary clarification of centrifuged stevia extract by cross flow UF followed by a concentration of the clarified extract by NF. UF was performed by using a rectangular cross-flow cell equipped with a flat-sheet PES membrane with a MWCO of 30 kDa. NF was performed by using a stirred batch cell equipped with a 400 Da membrane consisting of a polyamide skin over a PSF support. The recovery of stevioside in the UF permeate was in the range of 30%–56% depending on the applied pressure (it was maximum for lower operating pressure of 2.7 bar). The UF permeate was concentrated maximum twice at 12.4 bar and 1500 rpm of stirrer speed within 1 h of operation. Maximum recovery and purity (of about 60%) was obtained for a particular set of operating conditions.

Rao, Prasad, et al. (2012) develop a rapid and effective methodology of production of natural SGs to overcome the disadvantages associated with extraction processes. In this approach the dry treated leaves were grounded, defatted, and extracted through pressurized hot water extractor (PHWE). The aqueous extract was clarified with a 30 kDa UF membrane in batch mode and then concentrated through a NF membrane made on hydrophilized polyamide (HPA) with a MWCO ranging from 200 to 250 kDa. The NF membrane rejected all SGs recovered in the UF permeate (100% rejection) throughout the range of feed pressure studied. The NF retentate was extracted with organic solvent, followed by crystallization of SGs by adding polar solvent (ethanol): the purity of the stevioside was increased to 97.66% and total yield steviosides was 9.05 g per 100 g stevia leaves (Rao, Reddy, et al. 2012). The extraction yields were influenced by the thermal pretreatment indicating possible heat-lability of SGs compounds. In addition to this, organoleptic and biological characterization of the recovered compounds was carried out, demonstrating that the recovered SGs presented a greater power in terms of flavor and antioxidant activity comparing to the commercial ones.

A conceptual process flow diagram for producing glycoside-based sweetener concentrates was proposed by Zhang, Kumar, and Kutowy (2000). Development of this process involved several distinct operations including: (1) aqueous extraction of dried Stevia leaves; (2) clarification of the extract with a ceramic tubular membrane with a mean pore size of 0.35 μm (from US Filter); (3) treatment of the clarified extract with a 2.5 kDa UF membrane (from Liumar Technologies) at a TMP of 4.4 bar in DF mode (a DF volume of 3 was found to be adequate for eluting sweeteners); (4) final treatment of the UF permeate by a NF membrane (Duratherm; Osmonics/Desalination) operating at a TMP of 5.1 bar in a DF mode followed by a concentration mode. The NF process at high temperatures (80 °C) resulted effective in removing the impurities and consequently improving the taste profiles of the sweeteners.

In another approach, the stevia leaves were enzymatically pretreated in an aqueous phosphate buffer followed by PHWE. The filtered solution was treated through a MF step with a cartridge of 5 μm pore size and the clarified solution was fed to a spiral-wound UF membrane (10 kDa MWCO). A series of five DF units was implemented to remove leaf cell debris and other unknown impurities from the clarified extract and further recovery of the stevioside. The obtained permeate was concentrated by NF until 80–90% of water was removed (Rao et al. 2015). The enzymatic pretreatment enhanced the yield of stevioside up to 72%, with 98% purity, which resulted higher in comparison to existing methods.

Vanneste et al. (2011) evaluated the performance of a three-stage process with commercial as well as tailor-made PES membranes for the purification of SGs from plant extracts. The integrated system based on the use of a PES MF membrane with a pore size of 0.05 μm followed by a NF step with a 600–800 Da sulfonated PES NF membrane operating in DF mode (nanodiafiltration, NDF) allowed to obtain 19% of the SGs with a purity of 32%. The three-stage process MF-UF-NDF with the use of a PES UF membrane with a MWCO of 10 kDa led to a 30% recovery of stevioside and rebaudioside with a purity of 37%.

Kootstra, Elissen, and Huurman (2015) investigated three integrated systems implementing UF and NF operations. PSF membranes with different MWCO of 50, 100–150, and 50 kDa (at 3.0 bar) were used in the first stage of the integrated process. The membranes were individually tested for the recovery of stevioside, rebaudioside A and rebaudioside C and the recovery rates were further improved using a polyamide NF membrane of 200–400 Da operated at 40 bar. The recoveries of SGs through the three systems varied between 53–60%, 80–85%, and 52–57%, respectively, being the system with the 100–150 kDa membrane the most efficient (over 80%). The recovery efficiency of SGs resulted similar to that obtained with an extraction by acidification, finding that both methods displayed similar recovery values.

Table 7. Integrated membrane processes used to recover steviol glycosides from *Stevia rebaudiana*.

Process	MWCO (material)	Material type	TMP (bar)	Recovered SGs	Solvent used	Yield (%)	Purity (%)	Reference
UF-UDF	UF: 100 kDa	PVDF	8.5	Stevioside	Water	90	46	Fuh and Chiang 1990
	UDF: 100 kDa	PVDF	8.5	+ Rebaudioside A				
MF-UDF-NDF-NF	MF: 0.35 μm	Ceramic	1.0	Stevioside	Water	80	89	Zhang, Kumar, and Kutowy 2000
	UDF: 2.5 kDa	n.r.	4.4					
	NDF: n.r.	n.r.	5.1					
	NF: n.r.	n.r.	n.r.					
MF-NDF	MF: 0.05 μm	PES	3.0	Stevioside	Water	19	32	Vanneste et al. 2011
	NDF: 600–800 Da	PES	8.0	+ Rebaudioside				
MF-UF-NDF	MF: 0.05 μm	PES	3.0	Stevioside		30	37	Vanneste et al. 2011
	UF: 10 kDa	PES	3.0	+ Rebaudioside				
	NDF: 600–800 Da	PES	8.0					
UF-NF	UF: 30 kDa	PES	5.5	Stevioside	Water	41–48	59–57	Chhaya, Mondal, et al. 2012
	NF: 400 Da	PES	8.3					
UF-NF	UF: 30 kDa	PES	5.5	Stevioside	Water	46–51	61	Chhaya, Mondal, et al. 2012
	NF: 400 Da	PES	9.7					
UF-NF	UF: 30 kDa	PES	5.5	Stevioside	Water	48–54	58–61	Chhaya, Mondal, et al. 2012
	NF: 400 Da	PES	11.0					
UF-NF	UF: 30 kDa	PES	5.5	Stevioside	Water	51–61	57–60	Chhaya, Mondal, et al. 2012
	NF: 400 Da	PES	12.4					
UF-NF	UF: 30 kDa	PES	5.0	Stevioside	Water	83	98	Rao, Prasad, et al. 2012
	NF: 200–250 Da	HPA	15.0	Rebaudioside A		8	98	
UF-NF	UF: 30 kDa	PES	5.0	Stevioside	Water	97	98	Rao, Reddy, et al. 2012
	NF: 200–250 Da	HPA	15.0					
MF-UDF-NF	MF: 5 μm	n.r.	n.r.	Stevioside	Water	72	98	Rao et al. 2015
	UDF: 10 kDa	PES	6.9					
	NF: 250 Da	HPA	17.7					
UF-NF	UF: 50 kDa	PSF	3.0	Stevioside	Water	59	—	Kootstra, Elissen, and Huurman 2015
	NF: 200–400 Da	PA	40.0	Rebaudioside A		60		
				Rebaudioside C		53		
UF-NF	UF: 100–150 kDa	PSF	3.0	Stevioside	Water	82	—	Kootstra, Elissen, and Huurman 2015
	NF: 200–400 Da	PA	40.0	Rebaudioside A		80		
				Rebaudioside C		85		
UF-NF	UF: 50 kDa	PSF	3.0	Stevioside	Water	56	—	Kootstra, Elissen, and Huurman 2015
	NF: 200–400 Da	PA	40.0	Rebaudioside A		52		
				Rebaudioside C		57		
MF-UF-NF	MF: 0.6 μm	PES	1.5	Stevioside	Water	74	—	Kootstra, Elissen, and Huurman 2016
	UF: 30 kDa	PSF	1.5	Rebaudioside A		73		
	NF: 1 kDa	A/B-S	30.5	Rebaudioside C		76		
MF-UF-NF	MF: 0.6 μm	PES	1.5	Stevioside	Water	70	—	Kootstra, Elissen, and Huurman 2016
	UF: 30 kDa	PSF	1.5	Rebaudioside A		70		
	NF: 200 Da	A/B-S	30.5	Rebaudioside C		74		
UDF-NF	UDF: 4 kDa	n.r.	n.r.	Stevioside	Water	18	—	Panagiotou et al. 2018
	NF: 400–500 Da	n.r.	n.r.	Rebaudioside A		68		
				Rebaudioside C		5		

Recently, Kootstra, Elissen, and Huurman (2016) investigated the use of two UF membranes (30 and 50 kDa) and two NF membranes (200 and 1000 Da) to purify and concentrate stevioside, rebaudioside A and rebaudioside C from an aqueous extract of Stevia. Distinctively, a pretreatment of the extract by using a MF (0.6 μm) membrane was applied. In general, yields of the three SGs were of about 73%.

More recently, Martínez-Alvarado, Torrestiana-Sánchez, and Aguilar-Uscanga (2017) employed a MF step with a 0.2 μm ceramic membrane operated at 0.9 bar to clarify two *S. rebaudiana* extracts, i.e. A and B, from different regions. The extraction yields of stevioside and rebaudioside were around 86% and 58% and 85% and 78% for the extract A and B, respectively. The main difference between both extracts was the initial content of solids, being higher for the extract A ~19.5 g L^{-1} *vs.* ~12.7 g L^{-1} for the extract B. Indeed, membrane fouling phenomenon exhibited a marked effect during the clarification process of the extract A regarding B, which was in agreement by analyzing the resistance due to fouling.

Panagiotou et al. (2018) evaluated the effect of stevia, SGs and stevia extract on glucocorticoid receptor signaling in normal and cancer blood cells. SGs were purified from a water-based Stevia leaf extract by using a combination of UF and NF membranes with MWCO of 4 kDa and 400–500 Da, respectively. The UF system was operated in DF mode to improve the recovery of target molecules. The NF retentate was finally freezed-dried to obtaine the dry crude extract. The achieved yields toward stevioside, rebaudioside A and rebaudioside B were of about 18%, 68% and 5%, respectively. These results were lower when compared with those reported by Kootstra, Elissen, and Huurman (2015) who proposed a similar UF-NF configuration but with different membranes (50 kDa and 200–400 Da) operating according to a batch concentration mode. These results can be attributed mainly to the higher retention of SGs (i.e. stevioside and rebaudioside C) for tight UF membranes (in the range of 1–4 kDa), as those used by Panagiotou et al. (2018). Integrated membrane systems for the recovery of SGs from *S. rebaudiana* are summarized in Table 7.

The whole results indicate that a proper selection of membranes, operating conditions and modes of operation (i.e., DF) is a viable approach for refining glycoside-based sweeteners with enhanced recovery rates of specific SGs

which can be used in several applications. Thereby, the following section provides an overview of the potentialities of the SGs extracted by membrane-based technologies.

Potentialities of SGs extracted by membrane processes

Since 2008, the Food and Agriculture Organization and the World Health Organization expert committee on food additives have stipulated and considered the SGs as safe for human consumption (Savita et al. 2004). These compounds can be incorporated into multiple food and beverages, including tea, coffee, ice creams, cakes, soft drinks, fruit juices, and as color enhancers (Yadav and Guleria 2012). Many countries (e.g., China, Japan, Russia, Korea, Paraguay, Argentina, Indonesia, Malaysia, Australia, New Zealand, and some countries of South America) have begun to replace cane sugar with SGs derived from *S. rebaudiana* leaves (Gasmalla, Yang, and Hua 2014; Mehrotra, Singh, and Tiwari 2014). The organoleptic characteristics, the thermal stability and non-fermentation of these SGs allow them to compete with other low calorie sweeteners such as saccharin and aspartame (Gasmalla, Yang, and Hua 2014).

It is worth noticing that SGs increase palatability of foods. Apparently, this property can impart improved flavor and aroma to products (González et al. 2014). SGs have been used to sweeten different types of foods (including canned foods and candied fruits) and drinks (e.g., tea, sodas, wine and coffee) (Carocho, Morales, and Ferreira 2015; Gasmalla, Yang, and Hua 2014; Mehrotra, Singh, and Tiwari 2014). Table 8 enlists the main food products that have been enriched in SGs. It can be noticed that most of the food categories have been supplied by SGs.

Today, important food processing industries, such as Coca-Cola Company, Cargill, Inc. and Merisant Company, have implemented and therefore commercialized multiple processed products using SGs, mainly rebaudioside A. According to recent reports, SGs have been incorporated without any further chemical treatment (Gasmalla, Yang, and Hua 2014; Yadav and Guleria 2012).

Besides the minimal nutritional value of the different types of SGs, the use of these compounds has been also stimulated by intensive interest in their putative biological properties. Table 9 reports the main applications of the SGs from *S. rebaudiana* facing several diseases, highlighting the most relevant results. In the last two decades, extensive efforts have been focused on studying the biological properties of SGs for the treatment of cancer, diabetes, hypertension, kidney problems, gastroenteritis and cholesterol. Some other diseases generated by pathogenic microorganisms and dental issues have been addressed as well (Chatsudthipong and Muanprasat 2009; Goyal and Goyal 2010; Mondal and De 2014; Yadav and Guleria 2012).

Economic overview of membrane-based processes in SGs separation

In general, it is well-known that the price of the high-added value compounds of interest for the food and pharmaceutical sectors, including food additives (e.g., sweeteners, acidulants, natural colorants, etc.) proteins, betalains, phenolic compounds, anthocyanins, is considerably elevated. Moreover, there is a clear trend in the increasing demand in worldwide market for these products (e.g., food additives, flavors and nutraceutical ingredients). In 2004, such global market was estimated about €13 billion in 2006, however, US market was recently projected around €5.5 billion in 2014 (food 36%, cosmetics and toiletries 27%, beverages 15%) (Brazinha and Crespo 2014; Crespo and Brazinha 2010). Finally, such demand has been expected to increase 3% per year (Castro-Muñoz, Conidi, and Cassano 2019). The required high purity of final products due to the benefit of such products into human health is the primary role in their overall production cost. For example, to obtain a high purity degree in SGs, chromatographic or adsorption techniques are generally used (Liu et al. 2011). Within such techniques, the cost of a standard quality adsorbent phase is about $5000 per kilogram and the adsorbent is generally not reusable. Moreover, there is also a need for other supplies (e.g., high purity solvents), making limited the development of these chromatographic processes at large scale (Rodenburg et al. 2016). In this regard, it is likely that the implementation of membrane technologies may offer an alternative at the large production processes, at least assisting the final purification stages of the SGs. In any production process using a membrane process, the membrane cost is likely the major cost in the production process, but the cost of the recovered product may be higher. However, the continuous increasing of membranes' sales (expected to increase 8%–10% per year) for other applications (e.g., water purification, wastewater treatment) could favor the reduction of membrane costs through their consolidation in the global

Table 8. Applications of steviol glycosides from *Stevia rebaudiana* in foods.

Food category	Examples
Beverages	Dairy drinks, wine, water, tea, coffee, soft drinks, juices, and milk
Desserts	Sweet corn, bread, cakes, cereals, biscuits, and dried fruits
Yogurt	Semisolid and liquid
Cold confectionery	Ice cream
Confitures	Jams, jellies, and marmalades
Sauces	Soybean
Canned food	Pickles, vegetables in vinegar, fruits, vegetables, fruit nectars, and vegetable nectars
Delicacies	Dry sea foods
Candies	Chewing gum, mints, and chocolates

Modified from Carocho, Morales, and Ferreira (2015); Gasmalla, Yang, and Hua (2014); González et al. (2014); Mehrotra, Singh, and Tiwari (2014); Puri, Sharma, and Tiwari (2011); Tijhuis et al. (2011).

Table 9. Potential applications of *Stevia rebaudiana* leafs and their sweet compounds for medicine and health purposes.

Disease	Model organism	Summary of results	Reference
Cancer	Human cells	The acetone extract of *S. rebaudiana* was nontoxic to normal cells. It also had both anticancer and antiproliferative activities against cancerous cells.	Jayaraman, Manoharan, and Illanchezian 2008
	Mice	The consumption of stevioside provided an immunostimulator effect due to the enhanced macrophage function and substantially modulated the T and B cell proliferation.	Sehar et al. 2008
Diabetes mellitus	Humans	The consumption of SGs did not produce either hypoglycemia or hypotension.	Barriocanal et al. 2008
		The consumption of rebaudioside A did not affect glucose homeostasis or resting blood pressure.	Maki et al. 2008
	Rats	The consumption of stevioside exerted antihyperglycemic and insulinotropic and glucagonostatic actions.	Jeppesen et al. 2002
		The consumption of stevioside improved the insulin response and suppressed glucagon levels. It also had antihyperglycemic effects and did not elicit hypoglycemia, accomplishing a pronounced suppression of blood pressure.	Jeppesen et al. 2003
	Mice	The stevioside had a potential role as antihyperglycemic agent.	Jeppesen et al. 2000
		The consumption of stevioside enhanced insulin secretion.	Chen et al. 2006
Hypertension	Humans	The consumption of stevioside decreased significantly the systolic and diastolic blood pressure.	Chan et al. 2001
		The consumption of stevioside decreased significantly the systolic and diastolic blood pressure.	Hsieh et al. 2003
	Rat cells	The consumption of stevioside provided an antihypertensive effect.	Lee et al. 2001
Renal problems	Rabbits	The stevioside reversibly inhibited transepithelial transport of p-aminohippurate resulting in a reversible effect on renal proximal tubular secretory function.	Jutabha, Toskulkao, and Chatsudthipong 2000
Gastroenteritis	Monkey cells	Extracts from *S. rebaudiana* inhibited the replication of all four serotypes of human rotavirus.	Takahashi et al. 2001
Cholesterol	Chicks	The consumption of stevioside caused a significant decrease in the total concentration of short chain fatty acids, blood glucose, triglycerides and triiodothyronine.	Atteh et al. 2008
Microbial disease	Virus and bacteria	Extracts from *S. rebaudiana* showed greater activity against gram-positive organisms compared to gram-negative ones.	Jayaraman, Manoharan, and Illanchezian 2008
Dental disease	Humans	Extracts from *S. rebaudiana* diminished plaque formation.	Maria and De Slavutzky 2010

market (Castro-Muñoz et al. 2017, Castro-Muñoz, Conidi, and Cassano 2019). Finally, it is a tough task to make cost analysis and estimation of the total process since reported studies found in the literature are focused on recovery stages at lab-scale experiments.

Concluding remarks and future trends in the field

Membrane technology has long been proven to be a reliable methodology to recover, fractionate and concentrate SGs from *S. rebaudiana*. According to the most recent reports, the extraction and recovery yields have been in the order of 25–80%, which depends on several parameters, such as operating parameters, intrinsic properties of the membranes and pretreatment steps. The highest recovery efficiencies have been obtained via integrated membrane processes according to the suitable selection of the membranes. Since the yields reached by single processes or integrated processes surpass the extraction yields and purity commonly obtained by conventional methods, membrane technologies seem to be a promising protocol for the extraction and concentration of SGs. The current interest of food technicians on using SGs as healthy sweeteners will encourage the scale-up of membrane-based technologies as alternative to satisfy their increasing demand. Moreover, the reported proofs and evidences of several health benefits related to the bioactive activity of SGs may promote their use. Based on this current review, we can state some future trend in the field:

- To handle the membrane fouling, it is likely that composite membranes will continue being explored in the coming years since the change of the physicochemical properties (mainly hydrophilicity) of the pristine membranes favors the mitigation of membrane fouling (Buonomenna 2016; Ursino et al. 2018). Moreover, the implementation of composite membranes also leads to the enhancement of other membrane' properties, including mechanical, chemical and separation performance (e.g., flux and rejection) (Avramescu et al. 2003; Kanagaraj et al. 2015).
- Since solvents are the core of the food, cosmetic, agrochemical, pharmaceutical, chemical, and biotechnological process technologies, they should be the initial point for the smart design of extraction processes toward valuable compounds. In the case of SGs extraction, it seems to be that the universal solvent (i.e., water) is enough for their extraction. However, either membrane-assisting separation or any extraction techniques using solvents, the use of green solvents (e.g., supercritical fluids, ionic- and deep eutectic solvents) is becoming attractive for

researchers since they display the ability to separate specific biomolecules (Choi and Verpoorte 2019). Furthermore, such solvents have several advantages including biodegradability, recyclability, extremely low vapor pressure, low costs, low toxicity of most used compounds, and their primary bulk chemicals are often from natural origin (Cseri et al. 2018; Cseri and Szekely 2019; Figoli et al. 2014; Russo et al. 2020). Importantly, green solvents have been initiated to be implemented in the extraction of bioactive molecules from natural products, aiming for the replacement of conventional organic solvents (Choi and Verpoorte 2019).

Disclosure statement

The authors declare no conflict of interest.

List of acronyms and nomenclature

A/B-S	acid/base stable
CA	cellulose acetate
CAP	cellulose acetate phthalate
CR	cellulose regenerated
DF	diafiltration
Glc	glucose
HPA	hydrophilized polyamide
MF	microfiltration
MWCO	molecular weight cutoff
NDF	nanodiafiltration
NF	nanofiltration
PA	polyamide
PAN	polyacrylonitrile
PES	polyethersulfone
PHWE	pressurized hot water extractor
PSF	polysulfone
PTFE	polytetrafluoroethylene
PVC	polyvinylchloride
PVDF	polyvinylidenedifluoride
Rha	rhamnose
SG	steviol glycoside
TFC	polyamide composite
TMP	transmembrane pressure
UDF	ultradiafiltration
UF	ultrafiltration

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