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Natural product extraction via hydrodynamic cavitation

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ABSTRACT

Hydrodynamic cavitation applied to natural product extraction from biological resources is the enabling technology of the bioeconomy. The study identifies the main economic and technical advantages of this relatively new natural product extraction route. Economic benefits chiefly originate from the low cost of manufacturing, low capital expense and superior product quality. The main technical benefits originate from the lack of noxious emissions, ease of scale-up, and highly controllable conditions affording lot-to-lot product consistency. We conclude suggesting arguments for which cavitation technology will be used both by incumbent companies, as well as by new entrants in the natural product market.

1. Introduction

The natural product industry is a highly profitable and global industry whose revenues in 2021 exceeded $150 billion only in the dietary supplement sector (Grand View Research, 2022). The industry, however, is not limited to dietary supplement ingredients but includes the extraction of dyes, tannins, monomers, nucleic acids, lipids and numerous other biomolecules sourced from biological resources for many other uses. Regardless of significant advances in green extraction technology (Chemat and Strube, 2015), the industry still chiefly relies on conventional solid-liquid extraction technology using *n*-hexane and ethanol (but also ether, chloroform and acetonitrile), as main extraction solvents (Joana Gil-Chávez et al., 2013).

Amid the "green" extraction technologies, cavitation (the word means formation, growth and subsequent collapse of vapor and gas cavities in a liquid medium) is clearly promising in light of practical applications (Panda and Manickam, 2019). Extraction is due to collapse and implosion of the cavitation bubbles generating hot spots and shockwaves able to break cell membranes and to increase mass transfer, enhancing water access to the disrupted cells and extraction of water-soluble compounds into the aqueous phase. Hydrodynamic cavitation (HC), generated using a reactor with (Wu et al., 2019) or without (Meneguzzo et al., 2019) moving parts has been far less investigated in comparison to bioproduct extraction using acoustic (or ultrasound) cavitation (AC) (Chemat et al., 2017). The basic mechanism for extraction process intensification using HC is the same also for cavitation generated using ultrasounds (Shirsath et al., 2012).

Several techno economic feasibility studies have been devoted to the use of HC as process intensification technology in environmental remediation (Mukherjee et al., 2020) (aid in pollutant oxidation), biodiesel manufacturing (Gholami et al., 2021), and biomass pretreatment for biogas production by anaerobic digestion (Munagala et al., 2022). The economic and technical advantages of HC in food processing in terms of energy efficiency, low cost and lack of noxious emissions in comparison to conventional (and AC) extraction techniques have been clearly identified, too (Khaire et al., 2021; Albanese et al., 2019a).

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Aptly called "the enabling technology of the bioeconomy" (Pagliaro, 2020), controlled HC is an exceptionally versatile natural product extraction technology whose application potential remains largely untapped. According to Cravotto and co-workers, the high energy efficiency of the HC-based extraction process, the short extraction times and ease of scale-up, "should pave the road to further industrial applications". (Wu et al., 2019).

Yet, it is enough to conduct a Boolean search with the queries "hydrodynamic cavitation" and "natural products extraction" on a research database to identify only 31 research articles (Google Scholar, 2023). Similarly, the 2019 review (Panda and Manickam, 2019) of Manickam and Panda on cavitation technology for greener extraction cites only 3 studies dealing with HC, each reporting significantly higher yields for the product extracted (algae oil (Lee and Han, 2015; Setyawan et al., 2018), and soy (Preece et al., 2017) proteins) when compared to alternative extraction methods.

More recently, extending to mandarin related previous findings concerning the new "IntegroPectin" pectin sourced via HC from lemon (Nuzzo et al., 2020) and grapefruit processing biowaste (Presentato et al., 2020a), scholars in Indonesia have recently reported pronounced bioactivity and lack of toxicity of mandarin IntegroPectin (Putri et al., 2022).

According to Ranade and co-workers, "one of the key reasons of holding back the realization" (Ranade et al., 2023) of the promise of HC as a technology platform would be the "inadequate understanding of inception as well as resulting physico-chemical effects of cavitation" (Ranade et al., 2023). In our viewpoint, the main reasons explaining such delay are twofold, namely *i*) the limited availability of commercial HC-based extractors in comparison to AC-based extractors developed with the emergence of sonochemistry since the early 1990s, and *ii*) the lack of studies clearly identifying the main economic and technical advantages of HC applied to natural product extraction.

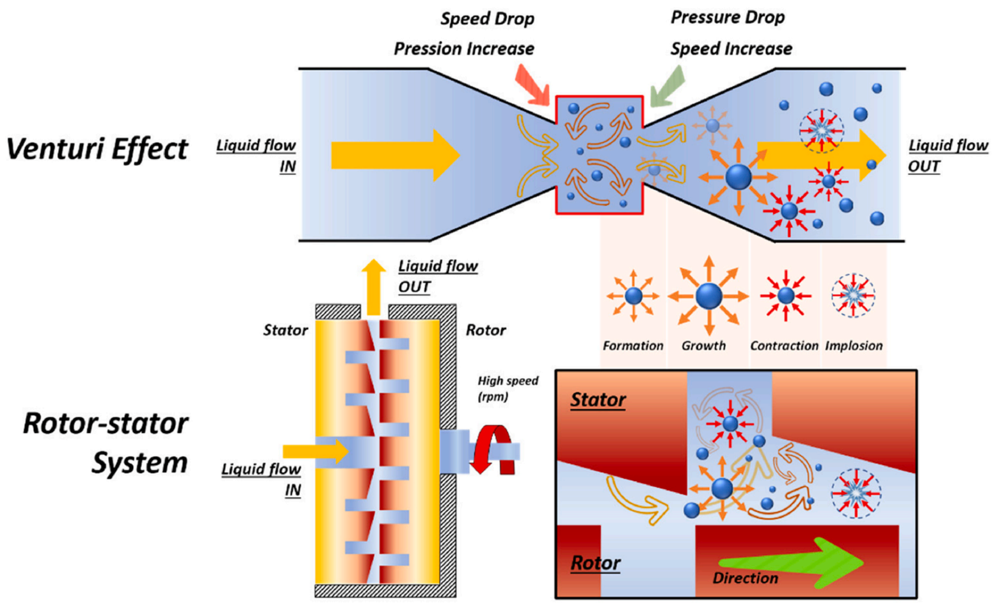
This study addresses the latter gap. Bioeconomy managers needing expanded education (Ciriminna et al., 2022a), and young researchers in this burgeoning field of research at the interface of chemical, life and engineering sciences, will benefit from a study clearly identifying such economic and technical advantages. In the bioeconomy, indeed, collaboration across different disciplines, and integration of academic and industry partners in research, is of paramount importance (Borge and Bröring, 2017).

2. HC reactors for natural product extraction

Ranade and co-workers have classified hydrodynamic cavitation reactors (HCRs) depending on the presence or absence of moving parts, including amid those without moving parts HCRs based on linear flows such as the orifice and the Venturi tube and amid those with moving parts those based on rotor-stator reactors (Ranade et al., 2023). Orifice and Venturi loops, still, also have pumps in the system which obviously include moving parts.

In 2019 Cravotto and co-workers summarized the main HCR geometries and setups identifying their main benefits and limitations in plant and biomass extraction of natural products (Wu et al., 2019). Scheme 1 describes two of the four main experimental setups for both Venturi-type and rotor-stator HCRs (Verdini et al., 2021). The other main HCRs are based on orifice plate (very similar to the Venturi-type reactor) and on vortex diode.

Besides geometric designs, the operating parameters affect the level of intensification. Said parameters (extraction time, cavitation number, flow velocity etc.) can be adapted in a wide range of values enabling to identify the optimal conditions for high quality natural product extraction from widely different biological matrices that span from hard (for example wood) (Verdini et al., 2021) to



Scheme 1. Main experimental setups for Venturi-type (*top*] and rotor-stator (*bottom*) hydrodynamic cavitation reactors. [Reproduced from Wu et al., 2019, Creative Commons license: CC BY 4.0].

soft (for example, basil) (Wu et al., 2019) substrates. Boczkaj in Poland and co-workers based in China have lately discussed at length how to modify said parameters both in HC and AC in the pretreatment and processing of food biowaste (Askarniya et al., 2023). For, example, operating parameters are set so as to minimize radicals formation which can react with many compounds forming secondary pollutants/byproducts as it happens during advanced oxidation processes assisted by AC of wastewater containing nitrite and nitrate ions (Rayaroth et al., 2022).

Cravotto and coworkers have reported plentiful examples (Wu et al., 2019; Grillo et al., 2019; Boffa et al., 2018) of natural product extraction using a rotor-stator HC reactor (developed in Italy) that allows to effectively extract natural products from solid biological matrices suspended in water (or alcohol-water mixtures) by maximising the cavitation volume inside the cavitation chamber (Rotocav (E-PIC), 2023). The teams of Meneguzzo and Pagliaro, in their turn, have extensively applied HC using a Venturi-shaped reactor to extract all valued bioproducts from the main *Citrus* fruit industrial processing biowastes (Meneguzzo et al., 2019; Nuzzo et al., 2020; Presentato et al., 2020a; Scurria et al., 2021).

The applicability of the technology is general, as shown for example by applying HC to extract the active ingredients from hops in novel beer brewing process (Albanese et al., 2017), or from silver fir needles (Albanese et al., 2019b).

Both aforementioned HC extractors (Scheme 1) are well suited for natural product extraction from solid matrices because they prevent clogging often found in orifice plate HCRs. The rotor-stator device is particularly efficient, but requires maintenance due to the moving parts; whereas the Venturi-type HCR affords diffuse formation of relatively large bubbles requiring multiple passages of the aqueous solid-liquid mixture through the Venturi tube. Orifice plate HCRs, on the other hand, producing an high number of bubbles of relatively small diameter, are better suited for applications requiring relatively high cavitation intensities (Gogate and Pandit, 2005).

Table 1 summarizes selected research papers reporting using HC-assisted natural product extraction, the HCR used and the main results achieved.

3. Technical advantages

Table 2 displays the main technical advantages of HC-based natural product extraction from biological resources.

Table 1
Selected research papers reporting using HC-assisted natural product extraction, HCR used, year of publication, and main results achieved.

Article title (year)	HCR	Reference/Main results
Simultaneous treatment (cell disruption and lipid extraction) of wet microalgae using hydrodynamic cavitation for enhancing the lipid yield (2015)	Orifice plate	Lee and Han, 2015/High yield (26–99%) HC-based extraction of lipids from *Nannochloropsis salina* microalgae in water:hexane biphasic solvent
Optimum extraction of algae-oil from microalgae using hydrodynamic cavitation (2018)	Venturi	Setyawan et al., 2018/HC-based extraction of lipids in high yield from *Nannochloropsis* spp. microalgae in methanol/hexane at 42 °C only with low energy consumption
Intensification of protein extraction from soybean processing materials using hydrodynamic cavitation (2017)	High pressure homogeniser	Preece et al., 2017/Highly productive extraction of protein from soy slurry via high pressure homogenization with yields up to 82% with a single pass of soy slurry at 100 MPa
Plant and biomass extraction and valorisation under hydrodynamic cavitation (2019)	Rotor stator	Wu et al., 2019/HC-based extraction of basil leftovers in a pilot-scale reactor in water only at room temperature, 16 times faster than the exhaustive extraction with aqueous ethanol
Real-scale integral valorisation of waste orange peel via hydrodynamic cavitation (2019)	Venturi	Meneguzzo et al., 2019/HC-based extraction of new *Citrus* pectin from waste orange peel in water only. New pectin of unique polymeric structure and rich in adsorbed flavonoids and terpenes
Cocoa bean shell waste valorisation; extraction from lab to pilot-scale cavitational reactors (2019)	Rotor stator	Grillo et al., 2019/Successful extraction of cocoa butter and hydrophilic fraction rich in flavanols, caffeine and theobromine from cocoa bean shell via a pilot flow HCR
Beer-brewing powered by controlled hydrodynamic cavitation: theory and real-scale experiments (2017)	Venturi	Albanese et al., 2017/ce:cross-ref>/New brewing process relying on HC-based malts extraction with dramatic reduction of saccharification temperature, increased and accelerated starch extraction, with malt dry milling and wort boiling no longer necessary
Acute toxicity evaluation and immunomodulatory potential of hydrodynamic cavitation extract of citrus peels (2022)	Venturi	Putri et al., 2022/Citrus pectin extracted via HC from mandarin peel, is devoid of toxicity and shows immunomodulatory activity, especially anti-inflammation

Table 2
Main technical advantages of HC-based natural product extraction from biological resources.

Advantage	Reason
Safe and not harmful to human health	Process carried out in water (no harmful chemicals) generating modest noise
Highly reproducible	Digitally controlled process
Zero emissions	Uses only electricity and water
Low power and energy demand	High energy efficiency
Ease of scale-up	High throughput

3.1. Enhanced health and safety at work

Independently of the shape and configuration of the cavitation reactor, the extraction process takes place in water circulated in the cavitation reactor. Relatively little noise is generated by the pump circulating the extraction mixture containing the solid matrix dispersed in water only. No harmful chemicals are used throughout the process. There are therefore no volatile (and often flammable) organic compounds to breathe and therefore no need for air exhaust systems.

All this greatly reduces health and safety risks for workers, even in comparison to AC-based extraction of natural products where significant (and harmful) noise is generated by the high-frequency wave acoustic generators (horns or bath systems) already used on industrial scale in several countries for the extraction of food and natural extracts (Chemat et al., 2017).

3.2. Enhanced reproducibility

The HC process can be finely controlled by adjusting the process parameters. For example, using the Venturi-shaped tube cavitation reactor, it is enough to control the flow velocity through the nozzle of the cavitation reactor, which depends on the pump's inlet pressure, to control the cavitation number, and thus the extraction process.

We briefly remind that in the Venturi-shaped HCR the liquid velocity and static pressure obey Bernoulli's equation regulating the conservation of the mechanical energy for a moving liquid (Eq. (1)): (Meneguzzo et al., 2019; Gogate and Pandit, 2005)

$$P_1 + \rho v_1^2/2 = P_2 + \rho v_2^2/2 \tag{1}$$

where P_1 and P_2 are the upstream pressure and the pressure at the nozzle, respectively, ρ is the liquid density, and v_1 and v_2 are the upstream and through the constriction fluid velocity, respectively. The pressure drop ($P_2 < P_1$) occurs at the reactor's nozzle due to the Venturi effect for which the fluid accelerates entering the nozzle ($v_2 > v_1$). Micron-sized bubbles are generated locally in the liquid bulk phase when P_2 drops below the vapor pressure.

Shared with ultrasonic cavitation-based extraction, such precise control of the extraction conditions (readily achieved thanks to an electronic control panel) establishes uniquely reproducible and reliable process conditions which, amid the green extraction technologies at room pressure, can be achieved only by microwave-assisted extraction (MAE). (Ciriminna et al., 2016a).

3.3. Zero emissions

Using no chemicals to extract the bioproducts, the HC-based process produces no toxic or polluting effluents. The process uses electricity retrieved from the grid, whose production at thermoelectric power plants results in the emission of toxic effluents in the air and heat in river of seawater. On the other hand, the amount of power required is relatively low and most (if not all) power and energy needed to power the hydrocavitator can be self-produced using a photovoltaic array on the plant rooftop, preferably connected to a digitally controlled energy storage system to maximize energy self-consumption (Ciriminna et al., 2018).

Besides resulting in product degradation, the use of harmful chemicals such as mineral acid or organic solvent to extract natural products requires expensive treatment of the effluents prior to discharge in the environment. Such treatments are often responsible for the high cost (and often shortage) of certain natural products available on the marketplace. One noticeable example is pectin, requiring expensive treatment of the diluted mineral acid aqueous solutions resulting from pectin extraction from citrus peel or apple pomace (Ciriminna et al., 2016a). When, three decades ago new environmental regulations on acidic effluents was enforced in the USA, major producers based in that country relocated their pectin extraction plants abroad where environmental emission limits were lower (Ciriminna et al., 2016b).

3.4. Low power and energy demand

The HC process applied to natural product extraction is much more efficient than AC. For example, comparison of AC (at 20 kHz and 100 W for 15 min using water at 45 °C) and HC (using 1 kg of sample and 15 L water with an absorbed energy of 3.2 kW and a final temperature of 45 °C) in the extraction of biophenols from basil leaves and stems, showed that both cavitation-based extraction routes returned good yields (Wu et al., 2019). However, the specific energy applied for the HC extraction (0.8 kWh/kg of solid) was > 3 times lower than that applied for the AC extraction (2.5 kWh/kg of solid). (Wu et al., 2019).

In general, the HC-based extraction requires a relatively low amount of power (a few kW) to operate the pumps required to circulate the solid-liquid extraction mixture and, after extraction, to transfer the aqueous extract prior to product isolation and purification. Due to extremely rapid cavitation phenomenon of bubble formation and implosion occurring in milliseconds and releasing large amounts of energy, the process is also very quick (Panda and Manickam, 2019; Wu et al., 2019; Meneguzzo et al., 2019). This, combined with the low power demand, ensures low energy (power × time) consumption contrary to what happens in related green extraction technologies such as extraction with microwaves (Ciriminna et al., 2016a) or with supercritical CO_2 (Horvat et al., 2017).

3.5. Ease of scale-up

Scaled-up HC-based natural product extraction processes, have been widely demonstrated by Meneguzzo, Pagliaro and co-workers in Italy sourcing new pectin and new micronized cellulose from the juice processing biowaste of all three main *Citrus* fruits (orange (Meneguzzo et al., 2019), lemon (Nuzzo et al., 2020), and grapefruit (Presentato et al., 2020a)) directly on semi-industrial scale (120 L water and >30 kg waste citrus peel). During the HC-based natural product extraction an aqueous suspension is re-circulated within the cavitation reactor while kept in a working vessel (Panda and Manickam, 2019; Wu et al., 2019; Meneguzzo et al., 2019).

The process can be easily scaled-up by scaling the size of the working vessel and the power of the pump circulating the mixture through the cavitation reactor.

Meneguzzo and Albanese jointly developed a HC-based extraction plant with a 1700 L nominal capacity for extracting hops at a beer brewing facility in Italy (Meneguzzo and Albanese, 2018; Albanese et al., 2019c), which can be used as such for the extraction of natural products. For example, the same plant can be used without changes obtaining to extract the new “IntegroPectin” *Citrus* pectin in 15 min, taking 2 h only when including all necessary steps such as grinding the peels before the inlet to the processing unit, separating the solid residues, and discharging and packaging the aqueous extract (Meneguzzo et al., 2020a). By making production continuous, an processing up to 500 kg of waste orange peel per session a product output of at least 18.000 L of IntegroPectin aqueous solution per day would be obtained.

4. Economic advantages

Table 3 summarizes the main economic advantages of HC-based natural product extraction from biological sources.

Along with superior product quality, high productivity and lack of harmful emissions (to be treated at economic cost), the main economic advantages are the low capital and operational expense.

4.1. Enhanced product quality

In general, HC-based extraction takes place under tightly controlled conditions which ensure that the microbubble implosion release sufficient energy to extract all valued bioproducts from a biological matrix, without damaging the inner metal surface of the HC reactor (low cavitation intensities) (Gogate and Pandit, 2005). The absence of chemicals such as mineral acids, base or organic solvent potentially degrading or contaminating the extracted bioproducts ensures lesser product degradation and superior product quality for bioproducts extracted via cavitation technology (Panda and Manickam, 2019; Wu et al., 2019; Meneguzzo et al., 2019; Askarniya et al., 2023). Furthermore, the different extraction mechanism based on the localized release of immense amounts of energy ensures formation of different bioproducts, when compared to products sourced via conventional extraction technologies.

For instance, the IntegroPectin (Meneguzzo et al., 2019; Nuzzo et al., 2020; Presentato et al., 2020a) *Citrus* pectins extracted from citrus processing waste are low-methoxyl (LM) pectins retaining most of the lateral chains comprised of neutral sugars (rhamnogalacturonan-I region). This significantly affects and enhances the bioactivity of said pectins (Nuzzo et al., 2020; Presentato et al., 2020b; Piacenza et al., 2022). On the other hand, citrus pectin commercially extracted with acid is a high-methoxyl (HM) pectin whose ramified galacturonan chains chiefly comprised of neutral sugars are nearly entirely removed during the industrial extraction from lemon peel or apple pomace with mineral acid (Ciriminna et al., 2022b).

In other words, the HC technology applied to the extraction of natural products allows to obtain *new* and *better* bioproducts from the *same* biological resources. The same is true, for example, for cellulose obtainable from citrus processing waste. Whereas conventional extraction with mineral acids (followed by digestion with diluted NaOH at 80 °C) affords 62.5% of α-cellulose and 25.3% of microcrystalline cellulose (Ejikeme, 2008), the HC-based extraction affords a new form of micronized cellulose (Al Jitan et al., 2022), that can be used to produce exceptionally strong and flexible pectin-cellulose films (Scurria et al., 2022).

The tightly controlled conditions of the HC-based extraction process, in their turn, ensure better product lot-to-lot consistency, which is a particularly important requirement when using bioproducts in advanced applications such as in cosmetic, nutraceutical, and pharmaceutical formulations (Barbero et al., 2022).

4.2. High productivity

Being highly effective due to the extreme values of temperature and pressure and shockwaves generated by the bubble implosion, extraction time is generally short and extraction yields are high. Seminal work of Gogate and Pandit demonstrated in the early 2000s that the “cavitational yield” (Gogate and Pandit, 2005), namely the quantity of product formed per unit of supplied energy, is one order of magnitude higher for HC (working directly with a 10 L orifice place reactor) when compared to AC (using a 55 mL acoustic reactor). Along with the unique possibility to make the extraction process continuous, this maximizes productivity.

For example, comparison with exhaustive extraction with organic solvent of AC and HC extraction of biophenols from basil leaves and stems, indicates that both cavitation-based extraction routes returned good yields (though lower than with exhaustive solid-liquid extraction with 75% ethanol at 85 °C for 4 h affording a 30.87% yield for the leaves and 25.87% for the stems) (Wu et al., 2019). In detail, the AC extraction gave a 28.60% yield for leaves and 23.95% for stems, whereas the HC-based extraction in a pilot-scale reactor gave 18.75% for leaves and 16.25% for stems (Wu et al., 2019). Yet, the HC extraction was conducted in water only at room temperature, and was 16 times faster than the exhaustive extraction with aqueous ethanol. A unique extraction cycle of 15 min achieved 187 g of extract per kg of material. Hence, in 30 min it can recover more than the exhaustive method (giving 308 g in 240 min). (Wu et al., 2019).

Table 3
Main economic advantages of HC-based natural product extraction from biological resources.

Feature	Reason
Enhanced product quality	Lesser product degradation and better product lot-to-lot consistency
High productivity	Short extraction times
Low cost of manufacturing	Low capital and operational expenses

4.3. Low cost of manufacturing

A key advantage of the technology is the low capital cost of the modular HC-based extractor consisting of HC reactor connected to a working vessel and a set of pipes. All components consist of readily accessible and long-lasting stainless steel parts connected with each other. There are no expensive parts such as microwave generator used in MAE (Ciriminna et al., 2016a).

Furthermore, the use of a cavitation-based extractor results in significant reduction of production space and equipment, when compared to all extraction technologies with the exception of capital-intensive MAE (which can also be made continuous). (Ciriminna et al., 2016a).

Another key economic advantage of the HC-based extraction technology is the low operational cost due to high energy efficiency, and to low maintenance costs. In general, the cost of manufacturing any natural product (COM) is the sum (Eq. (2)) of the direct manufacturing cost (DMC), the fixed (indirect) manufacturing cost (FMC), and general expenses (GE) (Pereira et al., 2013):

$$\mathrm{COM} = \mathrm{DMC} + \mathrm{FMC} + \mathrm{GE} \tag{2}$$

The direct manufacturing cost is composed of the costs of raw material (CRM), operational labor (COL), utilities (CUT, including electricity and cooling water) and waste treatment (CWT). In the case of natural products obtained from biowaste, the CRM is zero or negligible because agri-food companies supplying their production by-products save substantial biowaste treatment costs. The HC-based extraction process carried out in water does not generate waste (CWT = 0). The only expenses contributing to the DMC are the cost of labor (COL) and those of electricity (CUT) needed to power the pumps and the dryer (typically, today, a spray dryer), as well as of water used as only extraction medium.

The general expenses (GE) are independent of the extraction technology being those required to maintain the business, including administrative (salaries and other administration costs), sales (marketing, product delivery, and other costs related to sales), and research and development costs.

The "fixed" costs (FMC in Eq. (2)) do not depend on production rate, being paid even if the process is halted, and consist of the equipment, equipment depreciation rate (usually 10%/year), maintenance, taxation, and insurance (the latter paid to protect the company, generally 1–3% of fixed capital investment) expenses. The cost of the equipment generally comprises the extractor, including the extraction tank, the pumps, a filtration (with a water recovery) unit, and a drying system.

In the HC-based extraction of natural products, the cost of the equipment as well as of maintenance are low. Only in the case of the agitated bed solid-liquid extraction, these costs are lower than in HC-based extraction. During the latter process, however, there is no need of an expensive reservoir solvent tank nor of a solvent recovery unity. The aqueous phase is dried to separate the bioproduct from water, whereas in certain cases customers are supplied directly with a concentrated aqueous solution.

Furthermore, in comparison to conventional technologies for natural product extraction in which the amount of labor (COL) required is relatively high because the simple extraction technology has a low degree of automation (Pereira et al., 2013), extraction using an integrated HC-based extractor has a high degree of automation, reducing the COL voice in Eq. (2).

Accurate estimates of the production costs in different parts of the world, with different taxation regimes, labor and electricity costs can be readily obtained via process simulation using a software for process, scale-up and economic simulation (Vieira et al., 2013). What matters here is that, thanks to low DMC and FMC costs, the cost of manufacturing natural products from biowaste via hydrodynamic cavitation is generally low.

4.4. Ease of scale-up

In a recent review systematically examining two different types of HC reactors from the lab scale and pilot scale to the commercial scale (including a review of selected commercial cavitation reactors), scholars based in Canada concluded that "scaling up cavitation-based processes remains a major challenge due to a lack of reliable models for the prediction of cavitation and poorly understood scale-up processes from the bench to commercialization" (Zheng et al., 2022). Remarkably, the review mentions wastewater treatment, the food and beverage industry, and biomedical devices as main fields of application of HC, excluding natural product extraction.

Showing evidence that scale-up of HC-based extraction processes is easy and straightforward, scaled-up HC-based natural product extraction has been widely demonstrated directly on semi-industrial scale (120 L water and >30 kg waste citrus peel) by Meneguzzo, Pagliaro and co-workers in Italy sourcing new pectin and new micronized cellulose from the *Citrus* juice processing biowaste of all three main *Citrus* fruits (Meneguzzo et al., 2019; Nuzzo et al., 2020; Presentato et al., 2020a).

The team furthermore described the main technology components of a complete HC-based natural product extractor applied to waste citrus peel for the production of orange IntegroPectin in early 2020 as potential therapeutic agent against COVID-19 (Meneguzzo et al., 2020b). Cravotto's team in collaboration with industry demonstrated both cavitation-based continuous extraction processes from grape pomace and olive leaves using both AC and HC cavitational pilot scale reactors in 2018 (Cravotto et al., 2018).

5. Outlook and conclusions

In summary, the technical and economic advantages of hydrodynamic cavitation applied to natural product extraction from biological resources, truly make it the enabling technology of the bioeconomy (Pagliaro, 2020).

The main reasons explaining the limited uptake of HC-based extraction in the natural product industry are similar to those behind the poor application of several new technologies such as flow chemistry and heterogeneous catalysis in the fine chemical industry (Ciriminna et al., 2021). Both are highly profitable segments of the chemical industry supplying active ingredients to even more profitable companies such as those in the cosmetic, personal care and pharmaceutical manufacturing sectors. Said industries focus on product innovation, and not on process innovation. Hence, they generally rely on technologies developed several decades (or even more than a century) ago such as synthetic organic reactions and natural product extraction carried out in batch vessels with organic solvent.

Switching to new "green" technology for these chemical industry companies becomes practically relevant only in the case of quick, retrofit innovation not requiring replacement of existing equipment (Ciriminna et al., 2021).

This is a unique feature of the HC technology. Contrary to acoustic cavitation, a cavitation element can be simply and quickly installed inline in a loop with the aforementioned extraction vessel and a pump when multiple passages into the cavitation element are needed to extract the desired phytochemical mixture. This, in its turn, means that the cavitation technology for the extraction of natural products will be used both by incumbent companies, as well as from new players. Indeed, the first companies commercializing hydrocavitators for natural product extraction advertise their products emphasizing how their device "can be installed as a retrofit to existing process line performance" (Andritz, 2023); or the shorter extraction times affording "higher active principle concentration in extract, yield improvement and operative cost saving" (E-PIC, 2023); or underlining their cavitator's energy efficiency (Infinity Supercritical, 2023).

Whether using HC or AC, new entrants in the natural product market using cavitation-based extraction technologies will chiefly use continuous processes, in agreement with the production principles developed by Ohno for the lean production of goods (Melton, 2005) increasingly adopted by the chemical industry (Pagliaro, 2019). This will also allow them to run the extraction (production) cycles on demand, flexibly producing in small plants the bioproduct amount required by the customer and no over production (and creation of inventory).

Finally, by significantly lowering the cost of manufacturing and the capital expense, cavitation technology dramatically lowers to barriers to entry into the natural product market, including the market of "botanicals" for the dietary supplement industry in which process innovation plays an increasingly central role (Delisi et al., 2021). Hydrodynamic cavitation, we forecast in conclusion, will shortly have a profound and long lasting impact on the whole natural product industry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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