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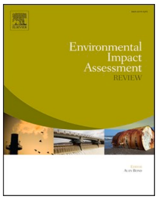

Delving the potential of quercetin-grafted chitosan from a technological and environmental perspective

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ABSTRACT

The transition to a sustainable bioeconomy requires the development of advanced materials with improved functional properties, in particular bio-based products that could have a low environmental impact. Chitosan, derived from crustacean chitin, is a biodegradable biopolymer with multiple applications in the pharmaceutical, cosmetic and food sectors. Similarly, quercetin is a bio-based flavonoid extracted from plants with potent antioxidant and antimicrobial activities. However, its poor solubility, bioavailability and rapid degradation limit its use. This manuscript proposes a synergistic action for the formulation of a bioactive biopolymer based on the enzymatic oxidation of quercetin and its enzymatic grafting onto chitosan. This biopolymer protects the active ingredients from chemical, enzymatic, thermal and light degradation and increases their bioavailability. In addition, other advantages such as vectorization and controlled release are envisaged. This production scheme was modeled using the SuperPro Designer® tool to estimate operational data to be used as a Life Cycle Inventory for environmental assessment and Green Chemistry score determination. The Life Cycle Assessment (LCA) methodology was used to assess the environmental impacts, while the Greenness Grid (G2) tool allows the assessment of safety, efficiency, productivity and renewability aspects related to sustainability. The results showed that electricity is the main hotspot of the environmental profile, with an average value of 74.22 %, while the contribution of chemicals is less significant, between 15 % and 40 % of the total impact. Sensitivity analyses were proposed to improve the profile, where the use of renewable electricity represents the largest reduction of the total impact. Moreover, Monte Carlo analysis has also been developed for assessing uncertainty in the scores obtained. For the G2 tool, the final score is 11.55 out of 15, which means that the production model is in the "sustainable potential" range.

1. Introduction

Antimicrobial resistance (AMR) is a growing concern in present and future societies and is considered a threat to global health, as it could imply the emergence of difficult-to-treat diseases and infections (Cave et al., 2021; Chen et al., 2021). This concern is a consequence of the excessive use of antibiotics, as well as the difficulty of removing them in wastewater treatment plants due to their recalcitrant nature, and most wastewater treatment plants do not have effective treatments to ensure their complete elimination (Alam et al., 2021; Polianciuc et al., 2020). AMR is recognized as a critical concern in the EU Farm to Fork Strategy, which includes a target of reducing antimicrobial use in the farming sector by 50 % by 2030. In light of this, the scientific community is searching for alternative antimicrobial agents that have the potential to control microbial infections, avoiding the indiscriminate use of antibiotics. Cellular oxidative stress is another aspect that has a significant impact on the development of cardiovascular, cancer and neurodegenerative diseases (Rotariu et al., 2022; Hayes et al., 2020). Against this background, the consumption of antioxidant products could help control oxidative stress and prevent these adverse effects.

Another sector of interest in relation to antioxidant and antimicrobial bioproducts is the food sector (Cruz et al., 2023), where consumers prefer natural rather than artificial food preservation products. Furthermore, the reduction of plastic content in food packaging is an increasingly implemented initiative (Cucina, 2023; Arias et al., 2021; Etale and Siegrist, 2021). Both aspects could be partially overcome by the use of functional films, obtained by cross-linking biopolymers with functional additives, such as natural preservatives with antimicrobial

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agents and antioxidants, such as flavonoids (Arias et al., 2022a, 2022b, 2022c). In response to these challenges, there is a need to search for natural products with bioactive properties that can have an effect on slowing down antimicrobial resistance and food spoilage. At the same time, is important to frame new packaging products free of plastics, in order to enhance a sustainable transition, avoiding the impacts of its inadequate management (Zhang et al., 2024a, 2024b; Ingrao et al., 2022). The scope of this research report delves into the development of a biopolymer with enhanced functional properties, namely quercetin-activated chitosan, which stands out for its bioactive characteristics.

Chitosan is the second most abundant natural biopolymer, extracted from crustacean exoskeletons, derived from the deacetylation of chitin (Aslam et al., 2022; Sharkawy et al., 2020). Its multiple properties include its antimicrobial activity, biocompatibility and biodegradability, which broaden its applications in a wide range of fields, such as biomedical, nutraceutical, cosmetic and food (Barik et al., 2024; Sahdev et al., 2022). It could be used as a drug delivery system, as a tissue recovery agent, as a bioplastic, given its biopolymeric nature, among others (de-Oliveira et al., 2023; Priyadarshi and Rhim, 2020). However, its physicochemical properties such as poor solubility, reduced chemical modification, low mechanical strength and high biodegradability could limit its potential application (Yadav et al., 2023; Jiang et al., 2014). Therefore, in order to increase their versatility, grafting or cross-linking with other bioactive compounds could be a possible solution (Cirillo et al., 2019). Combination with quercetin could be an interesting option given its recognized antioxidant and anti-inflammatory functions (Dhanaraj, 2023; David et al., 2016) and is expected to enhance the bioactive properties of both compounds (Lawson, 2023; Nataraj et al., 2018). For example, in the food sector it could be used as a bio-packaging material with preservative properties, thus reducing the requirement for artificial preservatives (Arias et al., 2022a, 2022b, 2022c). Some of the research reports that have delved on the use of chitosan and quercetin are included in Table 1.

Based on previous results, the production of a biodegradable biopolymer with improved antioxidant and antimicrobial properties will enhance its potential application in various sectors due to its increased solubility, stabilization of quercetin and the mechanical strength of chitosan. But even with this promising function, it is necessary to assess whether this grafting process conforms to the principles of environmental sustainability and green chemistry. In this context, this research explores the environmental assessment of the grafting process using the Life Cycle Assessment (LCA) methodology, a recognized and standardized assessment framework in ISO 14040 (Finkbeiner et al., 2006; ISO, 2006), alongside an evaluation of the product score based on Green Chemistry principles through the Greenness Grid method (Pinto et al., 2020). The aim is to provide an overview of the environmental footprint potential of the grafted biopolymer and to ensure that this production process aligns with the development of safer, more efficient, and less

Table 1
Research reports on chitosan and quercetin.

Reference	Year	Function	Description	Sector
Sharma et al., 2024	2024	Tissue regeneration	Chitosan hydrogel films loaded with quercetin and reinforced with cellulose nanoparticles	Biomedical / Cosmetic
Mu et al., 2024	2024	Treatment of allergic rhinitis	Quercetin-crosslinked chitosan nanoparticles	Biomedical
Zhang et al., 2024a, 2024b	2024	Improve functionality	Covalent oxidized complex of rice bran, chitosan and quercetin	Food
Ma et al., 2024	2024	Drug delivery	Microencapsulation using coacervation reaction of Zein and chitosan with quercetin	Biomedical/ Nutraceutical
Wang et al., 2024	2024	Drug delivery	Nanoparticles by crosslinking modified chitosan with quercetin	Biomedical
Govindarajan and Muthuraman, 2023	2023	Quercetin purification	Covalent crosslinking of quercetin with chitosan	Biomedical
Soliman et al., 2023	2023	Drug delivery to treat cardiotoxicity	Nanoparticles of chitosan loaded with quercetin by inotropic gelation technique	Biomedical
Al-Musawi et al., 2023	2023	Bone tissue engineering	Hydrogel containing quercetin and chitosan, with also basil seed gum and zein microsphere	Biomedical
Kaboli et al., 2023	2023	Drug delivery for Alzheimer	Polymeric chitosan based nanocarriers for co-delivering quercetin and rivastigmine	Biomedical
Sela et al., 2023	2023	Food preservation	Carboxymethyl chitosan-quercetin conjugate using Schiff base chemistry	Food
Zhang et al., 2024a, 2024b	2023	Adsorption of dyes	Tetrafluoroterephthalonitrile crosslinked with quercetin chitosan as adsorbent	Wastewater treatment
Kamyabi et al., 2023	2023	Drug delivery	Quercetin encapsulation in chitosan nanoparticles	Biomedical
Niazi and Ashjari, 2023	2023	Drug delivery	Hybrid quercetin-silica-chitosan complex crosslinked with gelatine-folate	Biomedical
Gonta et al., 2023	2023	Oxidation of organic substrates	Copolymer by functionalization of chitosan and covalent grafting of quercetin	Cosmetic / food / biomedical
Ren et al., 2023	2023	Drug delivery	Encapsulation of quercetin and caffeic acid by grafting with chitosan copolymer	Biomedical
Min et al., 2022	2022	Bone tissue engineering	Synthesis of chitosan-cysteine complex with amino-based nanoparticles and quercetin	Biomedical
Yong et al., 2022	2022	Edible coating	Chitosan grafted with quercetin by horseradish peroxidase catalysis	Food
Roy and Rhim, 2021a, 2021b	2022	Functional films	Chitosan-gelatine complex crosslinked with quercetin and essential oil	Food
Shebis et al., 2022	2022	Active film	Quercetin-chitosan polysaccharide synthetized using L-valine-quercetin as precursor	Food
Wiggers et al., 2022	2022	Drug delivery	Crosslinking of chitosan with quercetin for antibacterial drug delivery	Biomedical
Roy and Rhim, 2021a, 2021b	2021	Functional films	Quercetin-chitosan biopolymer by chemical reaction	Food
Shen et al., 2020	2020	Bio-functional products	Polymeric reaction of lipoic acid and chitosan as nanocarrier for quercetin encapsulation	Food
Diao et al., 2020	2020	Functional films	Free-radical grafting of chitosan and quercetin	Food and biomedical
George et al., 2019	2019	Drug delivery	Hydrogel matrices of chitosan, cellulose, zinc-oxide nanoparticles loaded with quercetin	Biomedical
Li et al., 2018	2018	Drug delivery	Ionic gelation reaction for a chitosan nanoparticle loaded with quercetin and catechin	Biomedical
Zhou et al., 2013	2013	Drug delivery	Microspheres of chitosan and quercetin used as carrier	Biomedical
Torres et al., 2012	2012	Edible films	Enzymatic grafting of chitosan and quercetin for antioxidant properties	Food
Torres et al., 2012	2012	Edible films	Grafting of chitosan and quercetin by enzymatic oxidation of chitosan and chemical attach of quercetin and rutin	Food

hazardous production schemes.

This research article introduces a novel approach to developing bioactive biopolymers by the enzymatic oxidation of quercetin and it's grafting it onto chitosan, creating a sustainable material with enhanced functional properties. Unlike conventional methods, the proposed grafting process significantly improves the stability, solubility, and bioavailability of both quercetin and chitosan, enhancing their application potential in pharmaceuticals, cosmetics, and food sectors. Additionally, the integration of advanced modeling tools, such as SuperPro Designer® for operational data, combined with Life Cycle Assessment (LCA) and Greenness Grid (G2) evaluations, offers an innovative approach that aligns process modeling, green chemistry principles and environmental assessment. The proposed production scheme also addresses key environmental hotspots by recommending the use of renewable electricity, setting a benchmark for more sustainable bio-based materials and production schemes.

2. Methodology

2.1. Process description

The production model considered for environmental assessment and potential compliance with green chemistry principles was developed by Torres et al. (2012). According to the process description, the process consists of three main steps: oxidation of quercetin with chloroperoxidase, grafting of quercetin onto chitosan, and downstream processes for separation of the functionalized biopolymer and recovery of the chemicals for reuse in the process (Fig. 1). The flow diagram shows a process model for an annual production of 273 kg of grafted chitosan-quercetin per year. The process combines batch steps of enzymatic oxidation of quercetin with chloroperoxidase enzyme and grafting of chitosan, scheduled to ensure optimization of production and minimum downtime of downstream equipment. Stochastic variations in production yield are assumed to be negligible. The cycle time for each of these units is 12 h, including start-up, reaction, discharge, cleaning, and replenishment time.

After the reaction stages, a holding tank for the mixture is considered prior to separation of the solids. Next, several filtration units are required to operate sequentially, namely two units; cloth filtration followed by microfiltration, each requiring 4 h of run time.

The conceptual design of the process was modeled in SuperPro Designer®. The process modeling included not only the main units, but also the auxiliary equipment for pumping, chemical dosing, and temperature control.

The enzymatic oxidation of quercetin, specifically of the flavonoid compounds present in its molecular structure, is carried out in a conventional stirred tank reactor, requiring as operating conditions a volume of 140 L and room temperature. A solution of quercetin is dissolved in 20 % isopropanol and 80 % water (with 0.36 % acetic acid), and 125 L of this solution is required to graft 1 kg of chitosan. The enzyme chloroperoxidase (100 pM) is added in combination with 1 mM H2O2 and 20 mM KCl, corresponding to the conditions at which the enzyme activity is maximal (Torres et al., 2012). Constant agitation and room temperature are required during this process.

The next step is to graft the oxidized quercetin with chitosan. This step begins by increasing the concentration of acetic acid to 1 % to ensure the dissolution of chitosan (Torres et al., 2012). This process aims to immobilize quercetin on the chitosan matrix (Torres et al., 2012). After 24 h, 1 M NaOH is added to raise the pH to 7 to promote the precipitation of the quercetin-grafted chitosan biopolymer (Jančič et al., 2021). Once the grafting reaction of quercetin onto chitosan is completed, the medium is transferred to a holding tank to allow cleaning of the reactor to prepare it for the next cycle and to ensure a stable flow entering the separation process.

The contents of the reactor are transferred to several filtration units where the polymer is separated from the unreacted reaction medium, which can be recycled to the enzymatic stages after lowering the pH. The product obtained is 1.54 kg of ground chitosan-quercetin per batch process, with 28.6 % wet content, so that 1.1 kg of product in dry weight consists of 1 kg of chitosan functionalized with 0.1 kg of quercetin. The batch processing time is 24 h for the enzymatic reactions (quercetin oxidation and chitosan-quercetin grafting) and 8 h in total for the two filtration units, for a total batch processing time of 32 h. Taking this into account and considering 330 days per year as operating time, the total number of batches per year is 247.

2.2. Life Cycle Assessment (LCA)

LCA is a widely used systematic methodology for the environmental assessment of established and emerging technologies, production systems, and products, covering all phases of the life cycle, from raw materials to final disposal (Lago-Olveira et al., 2024; Briassoulis et al., 2023). The main objective of LCA is to analyze the quality of the environmental performance of a product or process under assessment, as well as to identify which of the elements of the study under analysis are those that imply the higher environmental contributions (Ubando et al., 2019). It could be used as a decision-making tool for sustainable development and efficient bioeconomy (Sinkko et al., 2023; Pryshlakivsky and Searcy, 2021).

This methodology is standardized by ISO 14040 and ISO 14044 and consists of four main steps (Finkbeiner et al., 2006): goal and scope definition, in which the functional unit is selected, defined as the reference to which the inputs and outputs related to the process or product are standardized; life cycle inventory (LCI) definition, in which all the relevant inputs and outputs related to the life cycle of the product or process are collected, this being one of the most important stages of the LCA, as the results depend directly on the LCI values; impact assessment, in which the environmental burdens are quantified by selecting a calculation methodology; and interpretation phase, the final step, which includes the analysis of the results obtained and the proposal

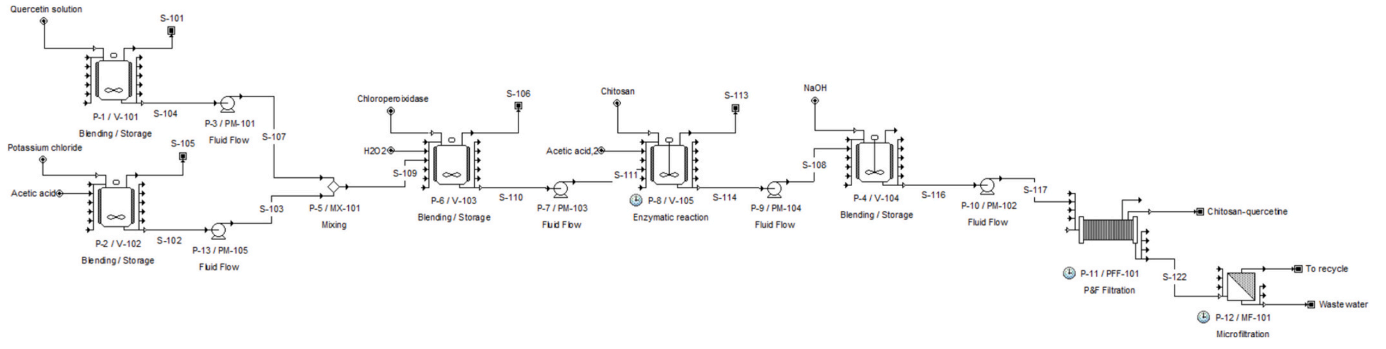

Fig. 1. SuperPro Designer model.

of sensitivity assessments.

In particular, for the evaluation of the chitosan-quercetin functionalized biopolymer, a gate-to-gate approach was considered (Fig. 2), thus considering all process steps from the extraction of raw materials to the factory gate (until the biopolymer is produced in the plant) (Russell-Smith and Lepech, 2015). With respect to the functional unit, 1 semi-batch process, which is the same as considering the production of 1.54 kg of chitosan quercetin biopolymer, has been considered. Ecoinvent v3.8 has been used as database for the life cycle inventory background activities, using as software SimaPro v9.6.0.1.

Regarding the characterization methodologies, Environmental Footprint v3.0 and ReCiPe 2016 Endpoint (H) V1.07/World (2010) H/H have been selected. The impact categories selected for assessment are depicted on Table 2. In addition to the environmental profile, a Monte Carlo simulation was conducted to analyze the uncertainty range in the environmental impact results, assuming a lognormal distribution. The simulation was performed with 2000 iterations and a 95 % confidence level, following the approach used by other authors (Bello et al., 2021).

2.3. Greenness Grid methodology

In the development of new bio-based production models and products, it is important to have in mind its adequacy to reduce or eliminate the hazardous effects to the human health and the environment. These are the goals of the Green Chemistry, also called as sustainable chemistry, a concept that emerged with the objective of encouraging process designs and products following a series of principles, concretely 12, that enhances the minimization of toxic compounds, the use of renewable energy and the reduction of waste production, among others (Anastas and Zimmerman, 2003). The definition of each principle is depicted on Table 3 including also 3 more principles, as considered by Pinto et al. (2020), which developed a scoring tool to assess products and process under the concept of Green Chemistry.

Lastly, with regard to the scoring and classification of each of the principles, as well as the total score obtained, the scale proposed by Pinto et al. (2020) has been used, in which each of the metrics has the same relative importance on the overall score obtained. The methodology consider the use of various equations and functions, as well as graphic models, to obtain numerical values that are subsequently normalized between 0 and 1. The final score is then obtained by adding up the individual scores for each of the 15 principles, thus obtaining a value between 0 and 15: ZBar Cap and color bar. The scales possible values and quantifications are depicted on Table 4.

Table 2
EF and ReCiPe Endpoint impact categories selected for assessment.

EF categories	Acronym	Unit
Climate Change	CC	kg CO_2 eq
Ozone depletion	OD	kg CFC11 eq
Ionizing radiation	IR	kg U-235 eq
Photochemical Ozone Formation	POF	kg NMVOC eq
Particulate Matter	PM	Disease inc.
Human toxicity, non-cancer	HTNC	CTUh
Human toxicity, cancer	HTC	CTUh
Acidification	AC	mol H+ eq
Eutrophication, freshwater	EF	kg P eq
Eutrophication, marine	EM	kg N eq
Eutrophication terrestrial	ET	mol N eq
Ecotoxicity, freshwater	ETF	CTUe
Land use	LU	Pt
Water use	WU	m^3 depriv.
Resource use, fossils	RF	MJ
Resource use, minerals and metals	MRS	kg Sb eq
ReCiPe EndPoint categories	Acronym	Unit
Resources	RES	mPt
Human health	HH	mPt
Ecosystems	EC	mPt

Table 3
Green Chemistry principles and metrics according to G2 scoring tool. Definitions of the principles and metrics available at: [1] Pinto et al. (2020), [2]Anastas and Zimmerman, 2003.

Principle (P)	Metric
P1. Prevent waste[2]	1. *E*-factor[1]
P2. Atom economy[2]	2. Atom economy[1]
P3. Less hazardous synthesis[2]	3. Hazard index - reactives[1]
P4. Design safer chemicals[2]	4. Hazard index - products[1]
P5. Safer solvents and auxiliaries[2]	5. Hazard index - auxiliaries[1]
P6. Design for energy efficiency[2]	6. Energy index[1]
P7. Use of renewable feedstocks[2]	7. Feedstock risk[1]
P8. Reduce derivatives[2]	8. Derivatives[1]
P9. Catalysis[2]	9. Use of catalyst[1]
P10. Design for degradation[2]	10. Half-life index[1]
P11. Real time analysis for pollution prevention[2]	11. Total hazard index[1]
P12. Inherently benign chemistry - accident prevention[2]	12. Accident Prevention[1]
*P13. Carbon efficiency[1]	13. Carbon efficiency[1]
*P14. Reaction efficiency[1]	14. Curzons ME[1]
*P15. Process productivity[1]	15. Mass productivity[1]

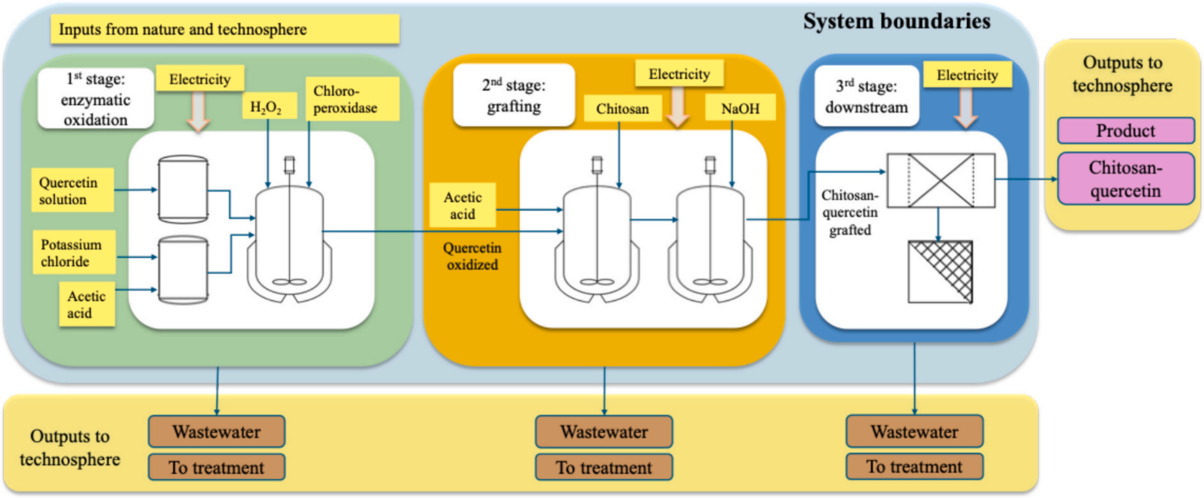

Fig. 2. System boundaries and process stages.

Table 4
Quantitative and qualitative classification for the Greenness Grid method.

Color code					
Meaning	Unsustainable	Critical	On path	Potential	Sustainable
Score per metric [0–1]	[0–0.2]	[0.2–0.4]	[0.4–0.6]	[0.6–0.8]	[0.8–1]
Total index score [0–15]	[0–3]	[3–6]	[6–9]	[9–12]	[12–15]

3. Results

3.1. Modeling results – Life Cycle inventory

With the mass and energy balances obtained from the SuperPro Designer simulation, the life cycle inventory is obtained (Table 5). The use of the 2-propanol is required to solubilize the quercetin and make it more accessible to be oxidized by the enzyme. Given this, a solution of 2-propanol-quercetine is used as input material. As for acetic acid, potassium chloride (not shown in the LCI because it is recycled) and hydrogen peroxide are necessary to maintain the most suitable reaction conditions for the enzymatic oxidation of quercetin by chloroperoxidase. Grafting of the oxidized quercetin onto chitosan involves the addition of acetic acid for solubilization of the biopolymer and, finally, sodium hydroxide is used to precipitate the grafted chitosan.

On the other hand, the energy needs, which amount to 43.51 kWh, are derived from the needs of constant agitation and the downstream filtration units. Specifically, 25.52 % of the total energy consumed corresponds to the first and second stages, while 74.18 % corresponds to the downstream process.

3.2. Environmental assessment

This section includes the analysis of the environmental profile, the identification of the main contributors to environmental burdens, as well as the proposal of sensitivity assessments.

Table 6 includes the inventory database used for the performance of the environmental assessment, considering Ecoinvent v3.8 as the database. It should be noted that Spain's electricity mix, according to EcoInvent database in 2024, comprises 42.92 % oil, 22.48 % natural gas, 13.20 % nuclear energy, 9.73 % wind energy, 7.38 % biofuels, 2.38 % coal and 1.91 % hydropower.

Table 5
Life Cycle Inventory. Functional unit: 1 batch process production of 1.54 kg of chitosan-quercetin/batch.

INPUTS			**OUTPUTS**		
Material	**Amount**	**Unit**	**Material**	**Amount**	**Unit**
Quercetin	0.13	kg	Chitosan quercetin	1.54	kg
2-propanol	0.49	kg	Chitosan quercetin- dry	1.1	kg
Acetic acid	1.23	kg	Quercetin oxidized	$1.84 \cdot 10^{-2}$	kg
Chloroperoxidase	$6.63 \cdot 10^{-4}$	kg			
Hydrogen peroxide	$4.25 \cdot 10^{-3}$	kg	**Waste to treatment (Wastewater)**		
Chitosan	1.00	kg	Wastewater	36.63	L
Sodium hydroxide	0.11	kg	2-propanol	0.625	L
Water	35.64	kg	NaCl	0.16	g
			HCl	0.09	g
Energy	**Amount**	**Unit**	Water	36.01	kg
Electricity	43.51	kWh	Chloroperoxidase	$6.63 \cdot 10^{-4}$	kg

Table 6
Ecoinvent v3.8 database used for the environmental assessment.

Item	Database used
2-propanol	1-propanol {GLO}| market for | Cut-off, U
Acetic acid	Acetic acid, without water, in 98 % solution state {GLO}| market for | Cut-off, U
Chloroperoxidase	Enzymes {GLO}| market for enzymes | Cut-off, U
Hydrogen peroxide	Hydrogen peroxide, without water, in 50 % solution state {RER}| market for hydrogen peroxide, without water, in 50 % solution state | Cut-off, U
Sodium hydroxide	Sodium hydroxide, without water, in 50 % solution state {GLO}| market for | Cut-off, U
Water	Tap water {Europe without Switzerland}| market for | Cut-off, U
Electricity	Electricity, medium voltage {ES}| market group for | Cut-off, U
Wastewater	Wastewater, average {Europe without Switzerland}| market for wastewater, average | Cut-off, U

3.2.1. Environmental profile

The environmental contribution of the elements considered in the life cycle inventory is represented in Fig. 3, while the impact scores are shown in Table 6. As can be seen, energy requirements are the main hotspot in all the impact categories ranging from 19.76 % in the MRS impact category to a maximum of 96.09 % in the IR one, with an average value of 66.19 %. On the other hand, significant loads are also observed for the use of 2-propanol, required to dissolve quercetin, reaching its maximum contribution in the MRS impact category, amounting to 52.39 %, followed by a load of 34.65 % and 30.42 % for POF and PM impact categories, respectively. In the case of the acetic acid, the large environmental contributions are observed on WU and MRS impact categories: 27.38 % and 25.98 %, respectively. Finally, the highest contribution of sodium hydroxide is observed in the OD impact category, amounting to 5.47 %, thus being not significant.

On the other hand, the scores obtained per impact category, for both EF and ReCiPe EndPoint approaches, are depicted in Table 7, while the uncertainty values are depicted on Table 8. Monte Carlo analysis was used to assess the level of uncertainty in the environmental results obtained through both methodologies. While Table 8 shows the scores, the graphs from the simulation are included in the **Supplementary Material** of this manuscript. The highest level of uncertainty was observed in the ETF impact category, where the difference between the minimum and maximum values reached 4320 CTUe. The final score achieved for this category, 235 CTUe, is closer to the minimum score obtained. An examination of the ETF graph in the Supplementary Material shows that, across the 2000 iterations (yielding 49 different score values), only three scores fall outside the range, while the rest remain close to the minimum score. Therefore, despite the high uncertainty, the final score obtained for the ETF impact category is considered both adequate and reliable. (See Table 8)

The next category with significant uncertainty is WU, with values ranging from −1231 m^3 depriv. as the minimum value to 977 m^3 depriv. as the maximum. In contrast to the ETF impact category, the values obtained from the 2000 iterations for WU follow a normal distribution, with most impact values clustering around the mean. Consequently, the final score in the environmental profile, 7.64 m^3 depriv., is deemed representative, as it aligns closely with the mean from the uncertainty analysis.

Finally, notable variation was also observed in the RF impact category, with values ranging from 342.30 MJ to 977 MJ. This category also exhibited a normal distribution, slightly skewed toward lower values, with greater dispersion in the mid-to-maximum range. Given this distribution, the score for the RF impact category, 464.81 MJ, is considered representative and has a lower level of uncertainty.

In terms of the EndPoint areas of protection, "human health" has the highest damage potential, amounting to 622 mPt. It is worth mentioning that this area of protection has the highest number of damage pathways. On the other hand, the "ecosystem" area of protection, being the second

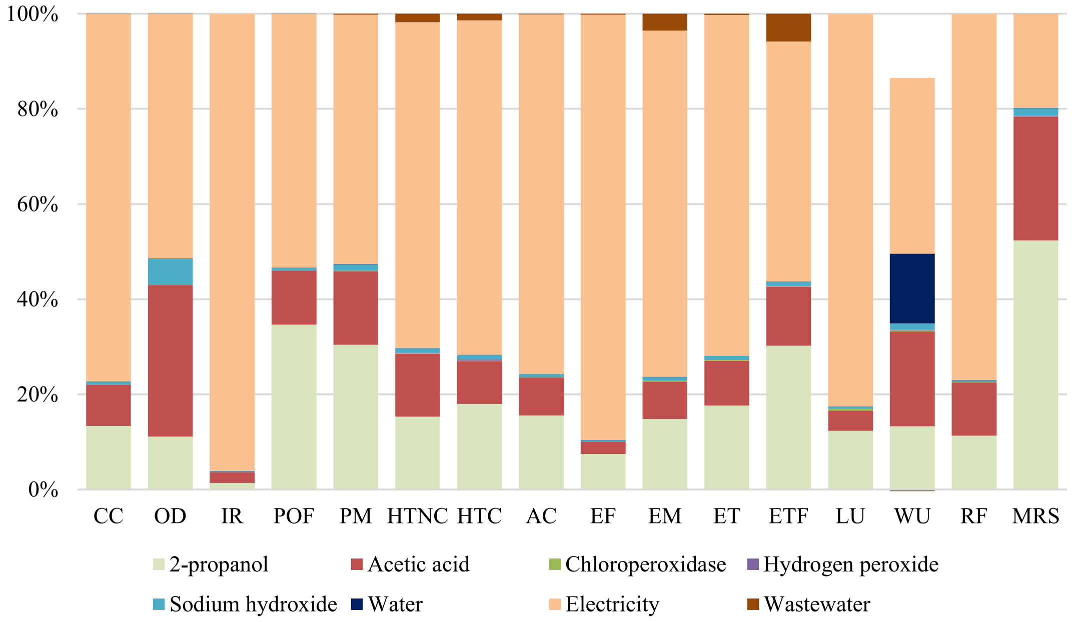

Fig. 3. Environmental profile of the process considering EF 3.0 methodology.

Table 7
EF and EndPoint impact scores values.

Acronym	Value	Unit	ReCiPe EndPoint	
CC	21.69	kg CO_2 eq		
OD	$1.57 \cdot 10^{-6}$	kg CFC11 eq		
IR	10.25	kg U-235 eq	RES	16.5 mPt
POF	0.07	kg NMVOC eq		
PM	$4.33 \cdot 10^{-7}$	Disease inc.		
HTNC	$1.90 \cdot 10^{-7}$	CTUh		
HTC	$3.84 \cdot 10^{-9}$	CTUh		
AC	0.12	mol H+ eq	HH	622 mPt
EF	0.02	kg P eq		
EM	0.02	kg N eq		
ET	0.18	mol N eq		
ETF	248.07	CTUe		
LU	54.11	Pt		
WU	7.64	m^3 depriv.	EC	28 mPt
RF	464.81	MJ		
MRS	$4.61 \cdot 10^{-6}$	kg Sb eq		

highest damage category with a value of 28 mPt, encompasses damage to freshwater species, terrestrial species and marine species. Although the number of MidPoint categories affected is higher, the impact categories related to toxicity scored significantly lower than those affecting the "human health" area of protection. Lastly, in the case of the "resources" area of protection, with the aim of representing the potential for damage to resource availability, the lower damage potential has been observed, amounting to 16.5 mPt.

3.2.2. *Sensitivity assessment*

After identifying the critical points, sensitivity analyses were conducted to enhance the sustainability potential. The following evaluations were carried out: (1) the use of renewable electricity, as electricity is the primary hotspot in the environmental profile; (2) a 20 % reduction in the acetic acid dose to assess whether optimizing the acetic acid dose would yield an environmental benefit, given its moderate impact on the environmental profile; (3) a 20 % reduction in the use of 2-propanol in the quercetin solution, following similar reasoning as in (2); and (4) the use of bioethanol instead of 2-propanol, as this substitution minimally affects the efficiency of the enzymatic reaction and grafting process, using "Ethanol, without water, in 99.7% solution state, from fermentation {GLO}| market for | Cut-off, U" from the Ecoinvent v3.8 database.

The results obtained by considering the use of renewable electricity (RE) are depicted on Fig. 4, compared to the baseline scenario (BC). As can be seen, a significant impact reduction is observed in almost all assessed impact categories, amounting to an average reduction of 47.48 %. Two exceptions are observed, concretely WU and LU, which were expected given the fact that renewable energy implies the use of, for example, energy coming from the forest resources, which implies extensive land use, and hydroenergy, which requires the use of water for energy production. The highest environmental load reduction is observed for the IR impact category with 92.41 %, followed by EF, amounting to 88.32 %, and CC, with 72.25 % of impact reduction. In the case of the impact category of FRS, the reduction percentage amounts to 74.03 %. This significant reduction in environmental loads is comparable to those reported in other research studies. Although different impact assessment methodologies can be used, the primary conclusion remains consistent: renewable electricity can substantially enhance sustainability potential. For instance, Arias et al. (2023) report environmental load reductions ranging from 6 % to 84 % with renewable electricity; Rebolledo-Leiva et al. (2023) report reductions exceeding 50 % in impact categories such as PM, EF, and CC, though with slight increase in LU and WU as reported here; Estévez et al. (2024) reported impact reductions of up to 85 % with renewable energy.

On the other hand, regarding the other alternative sensitivity assessment proposed, the comparison between the results obtained is depicted in Fig. 5**.** As observed, the use of renewable electricity is by far the sensitivity scenario with the best environmental profile, while the other options for optimization achieve reductions in environmental loads are, for the acetic acid sensitivity analysis, in the range of 0.46 %, in the case of IR impact category, and 55.53 % in the case of WU, achieving an average reduction value of 14.04 %. When analyzing the reduction of 2-propanol, the minimum reduction value has been achieved for IR impact category, as the case of acetic acid, with only 0.27 %, while for HTC a 47.52 % of environmental load reduction was obtained, with an average reduction value that amounts to 15.25 %, slightly higher compared to acetic acid sensitivity analysis. For the last case, the substation of 2-propanol by bioethanol, the average reduction value obtained amounts to 10.24 %, but in 6 out of 16 impact categories an increase on the environmental load has been obtained, as a result of the use of a fermentative process for the production of the bioethanol, which implies higher production times with constant agitation and temperature maintenance, which results in higher energy demand, and also the

Table 8
Monte Carlo assessment values per PEF impact category.

	CC	OD	IR	POF	PMF	HTNC	HTC
Impact score	*21.69*	*$1.57\cdot10^{-6}$*	*10.25*	*0.07*	*$4.33\cdot10^{-7}$*	*$1.90\cdot10^{-7}$*	*$3.84\cdot10^{-9}$*
Minimum	19.65	$1.05\cdot10^{-6}$	3.30	$5.75\cdot10^{-2}$	$3.34\cdot10^{-7}$	$-2.07\cdot10^{-6}$	$-1.54\cdot10^{-8}$
Median	22.05	$2.72\cdot10^{-6}$	56.10	$6.66\cdot10^{-2}$	$6.22\cdot10^{-7}$	$2.79\cdot10^{-7}$	$4.87\cdot10^{-9}$
Maximum	24.45	$4.39\cdot10^{-6}$	108.9	$7.57\cdot10^{-2}$	$9.10\cdot10^{-7}$	$2.63\cdot10^{-6}$	$2.52\cdot10^{-8}$
Mean	22	$2.72\cdot10^{-6}$	56.00	$6.66\cdot10^{-2}$	$6.22\cdot10^{-7}$	$2.79\cdot10^{-7}$	$4.87\cdot10^{-9}$
Standard deviation	1.43	$9.92\cdot10^{-7}$	31.44	$5.43\cdot10^{-3}$	$1.71\cdot10^{-7}$	$1.40\cdot10^{-6}$	$1.21\cdot10^{-8}$
Percentile 2.50 %	19.68	$1.07\cdot10^{-6}$	3.85	$5.76\cdot10^{-2}$	$3.37\cdot10^{-7}$	$-2.05\cdot10^{-6}$	$-1.52\cdot10^{-8}$
Percentile 97.50 %	24.43	$4.37\cdot10^{-6}$	108.35	$7.56\cdot10^{-2}$	$9.07\cdot10^{-7}$	$2.61\cdot10^{-6}$	$2.50\cdot10^{-8}$

	AC	EF	EM	ET	ETF	LU
Impact score	*0.12*	*0.02*	*0.02*	*0.18*	*248.07*	*54.11*
Minimum	$1.04\cdot10^{-1}$	$7.64\cdot10^{-3}$	$1.81\cdot10^{-2}$	$1.58\cdot10^{-1}$	235	35.19
Median	$1.17\cdot10^{-1}$	$9.79\cdot10^{-2}$	$2.11\cdot10^{-2}$	$1.85\cdot10^{-1}$	2395	62.16
Maximum	$1.30\cdot10^{-1}$	$1.88\cdot10^{-1}$	$2.41\cdot10^{-2}$	$2.11\cdot10^{-1}$	4555	89.14
Mean	$1.17\cdot10^{-1}$	$9.79\cdot10^{-2}$	$2.11\cdot10^{-2}$	$1.85\cdot10^{-1}$	2395	62.16
Standard deviation	$7.72\cdot10^{-3}$	$5.37\cdot10^{-2}$	$1.80\cdot10^{-3}$	$1.60\cdot10^{-2}$	1285.98	16.06
Percentile 2.50 %	$1.04\cdot10^{-1}$	$8.58\cdot10^{-3}$	$1.81\cdot10^{-2}$	$1.58\cdot10^{-1}$	257.50	35.47
Percentile 97.50 %	$1.30\cdot10^{-1}$	$1.87\cdot10^{-1}$	$2.41\cdot10^{-2}$	$2.11\cdot10^{-1}$	4532.50	88.86

	WU	FR	MRS
Impact score	*7.64*	*464.81*	*$4.61\cdot10^{-6}$*
Minimum	−1231.00	342.30	$3.51\cdot10^{-6}$
Median	−127.00	539.10	$4.94\cdot10^{-6}$
Maximum	977.00	735.90	$6.37\cdot10^{-6}$
Mean	−127.00	539.10	$4.94\cdot10^{-6}$
Standard deviation	657.28	117.17	$8.52\cdot10^{-7}$
Percentile 2.50 %	−1219.50	344.35	$3.52\cdot10^{-6}$
Percentile 97.50 %	965.50	733.85	$6.36\cdot10^{-6}$

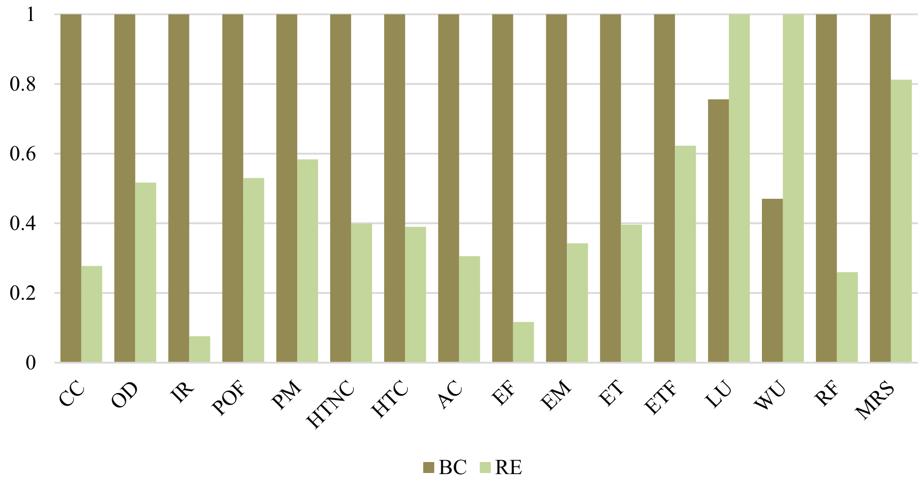

Fig. 4. Comparison between environmental loads of base case scenario (BC) and sensitivity analysis considering renewable electricity (RE).

use of enzymes, which also have an important effect over the environmental loads obtained. Given the results obtained, the better alternative in trying to improve the environmental sustainability potential is considering the use of renewable electricity as well as the optimization of the use of chemicals along the process. On the other hand, a combined sensitivity analysis, referred to as “Combined”, has also been presented. This analysis considers a 20 % reduction in the dosages of citric acid and 2-propanol, as well as the use of renewable electricity to meet energy requirements, resulting in an improved environmental profile with an average reduction of 61.64 %.

The results obtained when analyzing the impact values at the End Point are analogous to those of the EF calculation methodology, as it is also observed that the largest contributor to the environmental profile is electricity. This contribution is almost entirely reduced when renewable energies are considered, as can be seen in Fig. 6, reaching around 72 % reduction of the damage potential. In the case of the other main contributors to the environmental impact, their reduction by 20 % is 11.46 mPt in the case of acetic acid and 18.12 mPt for 2-propanol, while for bioethanol, the reduction achieved is higher compared to the 20 % reduction of 2-propanol use, with 66.69 mPt. But all these values are much lower than what can be reduced by relying on the renewability of electrical energy, which amounts to a reduction of 476.64 mPt. On the other hand, the combination of the three proposed sensitivity analyses contributes to an overall reduction of 398.54 mPt with respect to the base case.

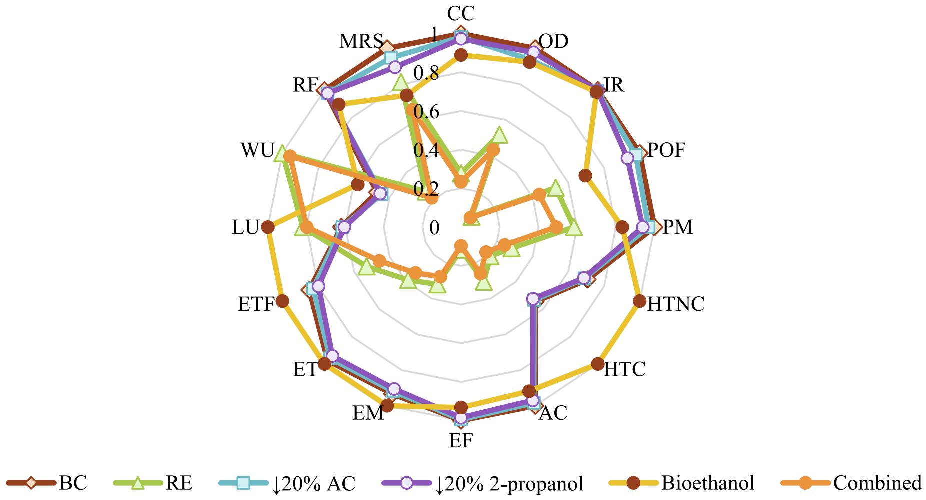

Fig. 5. Sensitivity assessment. Comparison between environmental loads reduction potential.

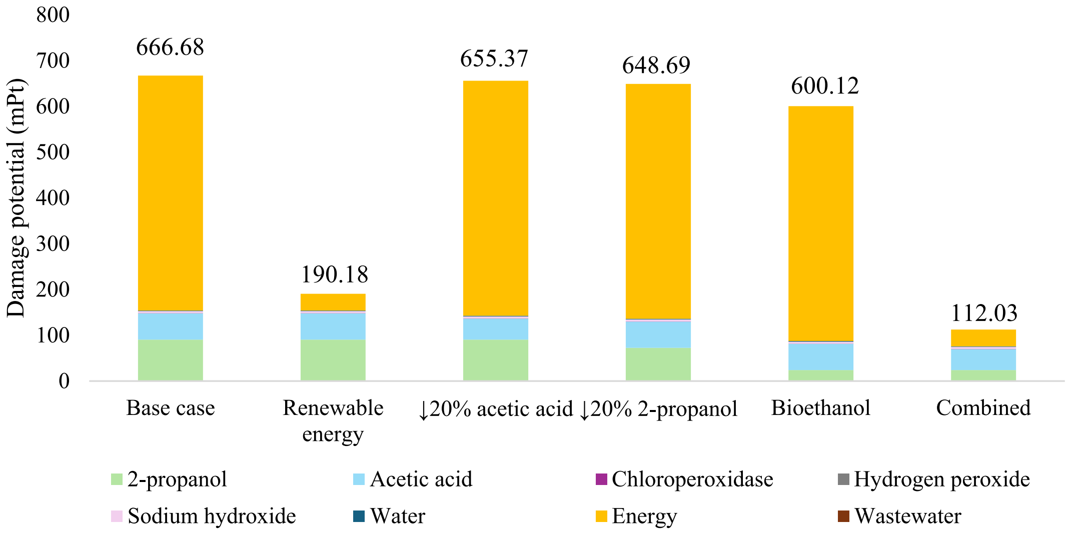

Fig. 6. EndPoint scores obtained for base case and sensitivity assessment scenarios proposed. *Combined mean that the score obtained is the result of considering renewable energy + reduction on 20 % of acetic acid + reduction on 20 % of 2-propanol.

3.2.3. *Green index*

The evaluation of the production model from the perspective of Green Chemistry, both the quantitative values obtained, and their qualitative significance are shown in Table 7. As can be seen, the metrics related to hazardousness, derivative production, biodegradability potential or atom economy have a high value, which implies its qualification as a sustainable model. The chemicals and products used in the process are considered safe according to their safety data sheets, and the fact that a biodegradable biopolymer is produced, and that most of the inputs required in the process can be recycled, also contribute to the increased sustainability of the proposed production model. However, there are also certain aspects that need to be partially improved, as in the case of waste prevention, in this case wastewater, or fully improved for those metrics for which a rating of "unsustainable" has been obtained. In this rating, the "energy index" stands out, which was to be expected given the results of the LCA, where electricity was a clear hotspot, and "mass productivity", as low yield of product is obtained compared to the consumption of inputs needed in the process.

However, the combination of all the metrics results in a classification of a "potentially sustainable" scenario and is therefore in an ideal position and its possibility of achieving a "sustainable" classification by increasing its TRL (Technology Readiness Level) to pilot and/or commercial plant is very high.

4. Discussions

4.1. *Research findings*

This manuscript focuses on evaluating the sustainability and green potential of a valorization model and, by extension, a wastewater treatment approach. This model aims, on one hand, to reduce the organic load of a highly polluted industrial wastewater stream and, on the other, to valorize this stream to produce a marketable, value-added product: a bio-based polymer with bioactive properties that can function as a biofilm. This valorization model enhances the functional activity of chitosan and quercetin, resulting in a biopolymer with improved bioactive properties due to the grafting of chitosan with quercetin. Experimental results have shown that this biopackaging extends shelf life, demonstrated in Opuntia ficus indica cladodes, where a reduction in enzymatic oxidation was observed after applying this biofilm (Torres et al., 2012). Other researchers, such as Roy and Rhim (2021a, 2021b), have also evaluated the use and functional properties of this biofilm, observing both antioxidant and antibacterial activities through the combination of chitosan and quercetin in a biofilm for food. Similarly, Valencia et al. (2021) found similar functionalities, specifically the elimination of DPPH and ABTS radicals when applying the chitosan-quercetin biofilm to several Gram-negative bacterial species. Furthermore, with respect to the benefits of quercetin grafting, Souza et al. (2014) observed not only an increase in the bioactive activity of the biofilm but also improvements in its physical and thermogravimetric properties, such as tensile strength, morphology, elongation, thickness, and stability.

However, despite the multiple benefits offered, it is important to assess the sustainability and safety of this biofilm. Therefore, a life cycle analysis and a green chemistry assessment were conducted, leading to the following conclusions: (1) the level of optimization is high, as the process has been scaled from laboratory to industrial production; (2) the use of renewable energy sources significantly reduces environmental impact; (3) optimizing chemical use in the process is crucial to minimizing environmental impact and improving alignment with green chemistry principles; (4) despite low process optimization, a green score of 11.55 was achieved, indicating a potentially sustainable process scenario with high market potential; and (5) as a valorization model that utilizes otherwise unusable waste resources, it promotes waste reduction and supports a more sustainable and circular water treatment system, with the potential to reduce the use of conventional plastics in the food sector in the future.

4.2. Analogy with the EU SSbD framework

This model could be considered within the scope of the Safe and Sustainable by Design (SSbD) framework, which aims to integrate safety, sustainability, and circularity from the early stages of design (Abbate et al., 2024; Caldeira et al., 2022). This assertion is supported by the fact that the Greenness Grid methodology effectively addresses the ‘safety’ aspects of the model, including assessments of the hazard indices of reactants, products, and auxiliary substances, as well as the ‘total hazard index’ and the ‘accident prevention’ principle. In terms of the ‘sustainability’ component of SSbD, this is addressed through the LCA methodology, which evaluates the environmental sustainability of the production model. Finally, regarding the ‘circularity’ aspects of SSbD, the Greenness Grid methodology analyzes principles such as ‘atom economy,’ ‘carbon efficiency,’ and ‘mass productivity,’ which relate to the circular (re-)use of inputs and outputs within the process.

4.3. Limitations and future framework

In the design and analysis of the valorization model, some limitations have been identified. The first one is the lack of development of this technology at pilot or industrial scale. Modeling the process from a laboratory scale involves lower optimization in the use of chemicals, energy, and processing time. Therefore, it would be advisable to conduct experiments at least at a pilot scale, as this would be a precursor to commercial-scale trials. At this stage, it would also be beneficial to consider the Green Chemistry Principles and Greenness Grid score analysis, where sectoral reference values have been applied for certain principles, such as Principle 12 (‘Accident Prevention’) and Principle 11 (‘Total Hazard Index’).

Secondly, it is important to note that for certain process inputs, analogous inventories were used in the LCA. For instance, 2-propanol was substituted with 1-propanol in the absence of a specific entry for 2-propanol in the Ecoinvent database. Although the environmental impacts are expected to be similar, results would be more precise if the actual compound were available. Similarly, for chloroperoxidase, a generic enzyme database was used, which may introduce some variability in the results. Another area for improvement in future studies would be a detailed physicochemical analysis of the wastewater generated by the valorization model. This would help determine the extent of organic load reduction and its environmental impact. In this study, a generic effluent was considered, but more accurate results would require an evaluation of each organic and inorganic component of this effluent and its potential environmental impact.

Although certain limitations have been identified in studying environmental and green chemistry principles, this analysis represents an initial step toward integrating this valorization and bioactive packaging production model into the market. Its high sustainability potential and low impact values, especially with renewable energy use, are promising in the development of alternative products to replace conventional fossil-based plastics used in the food industry and beyond. Furthermore, providing an active and functional bioplastic would reduce reliance on chemical-based food preservatives, which have been shown to affect food quality and organoleptic properties.

4.4. Policy implications

The results of this research, along with the proposal for a new valorization and wastewater treatment model to obtain a high-value market product capable of replacing conventional plastics in the food sector, are expected to positively impact EU policy objectives. First, this model supports the EU bio-economy strategy by developing a bio-based material that promotes circular resource use and potentially reduces high-organic-load residual waste with significant environmental impact. This aligns with the EU Circular Economy and Waste Reduction Action Plans, as it introduces a biodegradable biofilm, encouraging more sustainable end-of-life treatment and more efficient resource use.

Secondly, the model aligns with the European Green Deal objectives, particularly by promoting renewable energy sources for electricity, aiding the climate neutrality goals for 2050 by increasing the share of renewable energy in the European energy mix. Thirdly, producing a biofilm with bioactive and functional properties that can reduce or eliminate artificial preservatives represents a significant advancement for the food and pharmaceutical sectors, aligning with the goal of promoting safer products under the Pharmaceutical Strategy for Europe.

Additionally, the findings from this study could guide the development of new strategies, action plans, and policies for end-of-life treatment, industrial resource valorization, and bio-based products. However, it is essential to note that these production models are largely at the laboratory scale. Thus, it would be necessary for policymakers, governments, and stakeholders to focus their efforts on supporting their scale-up, for example, through green financing, tax reductions, or incentives for environmental certification.

5. Conclusions

In this report, a production model was proposed for the functionalization of chitosan with the flavonoid quercetin to obtain a biopolymer with bioactive functions, such as antioxidant and antimicrobial, and improved physicochemical properties, such as viscosity and mechanical resistance. Therefore, the model consisted of two enzymatic steps and a separation-purification step was proposed. The mass and energy balances obtained from its modeling in SuperPro Designer® were used to perform the environmental assessment. The results obtained showed that the energy demand is the main hotspot of the environmental profile, and that the choice of renewable energy could significantly reduce the environmental impact and the potential for damage, as also observed in the EndPoint assessment. On the other hand, the production model was also evaluated from the perspective of Green Chemistry principles, using the metrics proposed by the Greenness Grid (G2) tool. The final score obtained with this method was 11.55/15, indicating a “potential sustainability” rating. Given the high degree of optimization of the process, being an analysis based on primary laboratory data, it is considered that this model could be framed within what is considered sustainable, promoting the integration into the market of a bio-based product with improved bioactive properties and with high potential to be used in different sectors of the value chains: pharmaceutical, nutraceutical, cosmetic and/or food, among others.

CRediT authorship contribution statement

Ana Arias: Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Eduardo Torres:** Methodology, Investigation. **Gumersindo Feijoo:** Supervision, Writing – review & editing. **Maria Teresa Moreira:** Conceptualization, Validation, Supervision, Writing – review & editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eiar.2024.107754.

Data availability

Data will be made available on request.

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