Segretariato Generale

Direzione Generale della Ricerca

PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – Bando 2022 PNRR
Prot. P2022TXJX8

PART A

1. Line of intervention

Main line/Linea Principale

2. Research project title

NOrCa - Not Ordinary Cannabis - Exploring the chemical space around hemp (Cannabis sativa L.) waste and by-products from a circular economy perspective

3. Duration of the project (months)

24 months

4. Strategic emerging Topics - 5. Related Cluster

Strategic emerging topic: SUSTAINABILITY AND PROTECTION OF NATURAL RESOURCES
Cluster: Food, Bioeconomy, Natural Resources, Agriculture and Environment
Sub Cluster: 3.Sustainable and circular management and use of natural resources as well as prevention and removal of pollution are mainstreamed, unlocking the potential of the bio economy, boosting competitiveness and guaranteeing healthy soil, freshwater, seas and air for all, through better understanding of planetary boundaries and deployment of innovative technologies and other solutions, notably in primary production, forestry and bio-based systems.

6. Main ERC field

LS - Life Sciences

7. Other ERC field

8. ERC subfields

1.	LS9_8 Applied plant sciences, plant breeding, agroecology and soil biology
2.	LS9_11 Biomass production and utilisation, biofuels
3.	

9. Keywords

nº	Testo inglese
1.	Circular economy
2.	Cannabis sativa L.
3.	Hemp
4.	By-products
5.	Waste material
6.	Bioactive compounds

10. Principal Investigator

SACCHETTI (Surname)	**GIANNI** (Name)
Professore Ordinario (L. 240/10) (Qualification)	
02/05/1967 (Date of birth)	**SCCGNN67E02D548D** (Personal identification code)
Università degli Studi di FERRARA (Organization)	
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Declarations

☑ I declare that I have not participated as PI in PRIN 2022 call (n. 104 02/02/2022)

☑ I declare that I have participated as associated PI in PRIN 2022 call (n. 104 02/02/2022)

Current funding and applications submitted

Age limits derogation

The principal investigator and or the substitute are over 40 at the time of the publication of the call. They do not intend to benefit from the derogations to the age limits for the amount allocated to under 40 PI;

11. List of research units (RU)

nº	Associated Investigator	Qualification	University/ Research Institution	Registered office (address)	e-mail address
1.	SACCHETTI Gianni	Professore Ordinario (L. 240/10)	Università degli Studi di FERRARA	Ex Convento di S.Lucia-v.Ariosto 35 - FERRARA (FE)	scg@unife.it
2.	POLLASTRO Federica	Professore Associato (L. 240/10)	Università degli Studi del PIEMONTE ORIENTALE "Amedeo Avogadro"-Vercelli	Via Duomo, 6 - VERCELLI (VC)	federica.pollastro@uniupo.it
3.	MERLI Daniele	Professore Associato (L. 240/10)	Università degli Studi di PAVIA	Corso Strada Nuova, 65 - PAVIA (PV)	daniele.merli@unipv.it
4.	PELLATI Federica	Professore Associato (L. 240/10)	Università degli Studi di MODENA e REGGIO EMILIA	Via Universita', 4 - MODENA (MO)	federica.pellati@unimore.it

12 - Substitute Principal Investigator (PI) (To be identified among one of the associated PIs participating in the project).*

POLLASTRO (Surname)	**FEDERICA** (Name)
Professore Associato (L. 240/10) (Qualification)	
08/06/1976 (Date of birth)	**PLLFRC76H48F952C** (Personal identification code)
Università degli Studi del PIEMONTE ORIENTALE "Amedeo Avogadro"-Vercelli (Organization)	
(Phone number)	**federica.pollastro@uniupo.it** (E-mail address)

13. Brief description of the proposal

In recent years, the hemp (non-psychotropic Cannabis sativa L.) market exhibited incredible growth and it is expected to increase at a compound annual growth rate of 16.8% from 2022 to 2030 (https://www.hempbenchmarks.com/hemp-market-insider/hemp-waste/). At the same time, the hemp waste processing industry is in its infancy, providing limited answers to an urgent question: what can be done with the millions of tons of post-extraction material generated by companies? Currently, hemp waste is often used as biomass instead of recycled. The value of this residual material could go well beyond the current use, transforming itself into a source of new products. Leaves, industrial residues from inflorescence extraction processes, waxes, and lipids leave behind more than 400 molecules in an unexplored chemical space that finally assumed the form of waste (Atakan et al., 2012). Considering this biomass as a novel source of bioactive compounds is the aim of the project in the current genomic era, in which tens of thousands of potential drug targets have been identified. It is well known that the challenge of success in drug discovery lies in the number of small molecules that can be used. This project addresses such a challenging goal by looking forward to discovering the incredibly underrated value of hemp waste and by-products from a circular economy perspective. To this purpose, we propose a holistic approach that includes a comprehensive study of hemp waste and by-products by looking for uncommon cannabinoids that are considered minor not for importance but for concentration (Hanuš et al.; 2016), and additional unique molecules, including non-cannabinoids phenolic compounds and terpenic components (Pollastro et al., 2018; Isidore et al., 2021).
This project will follow novel approaches to: I) set environmentally friendly extraction protocols, according to the green chemistry, easily scalable, and cost-effective for an industrial level, following the Do No Significant Harm (DNSH) principle; 2) develop analytical methods to identify metabolites in hemp waste that could be valuable resources using advanced analytical methods based on untargeted and targeted metabolomics; 3) evaluate the biological activities of molecules by using a full panel of in vitro assays; 4) promote scientific as well as public dissemination with free conferences, workshops, in addition to scientific and informative journals and social networks.
The results of the project will find a concrete application in different ways: deep investigation of the chemical space around hemp waste in a circular economy perspective with the consequent: 1) production of molecular probes to better investigate the physiopathology of the endocannabinoid system, 2) disclosure of new hit/lead compounds with a good in vitro activity against the models applied, and which future synthesis could be proposed, 3) development of new analytical standards to certify the composition of hemp-derived products.

14. Total cost of the research project identified by items

Associated Investigator	item A.1	item A.2	item B	item C	item D	item E	item F	Total
SACCHETTI Gianni	21.257	56.101	0	0	11.604	6.549	3.000	**98.511**
POLLASTRO Federica	36.000	0	11.000	0	5.400	7.936	6.664	**67.000**
MERLI Daniele	48.250	0	0	0	7.238	7.000	5.000	**67.488**
PELLATI Federica	43.000	0	0	0	6.450	13.550	4.000	**67.000**
Total	**148.507**	**56.101**	**11.000**	**0**	**30.692**	**35.035**	**18.664**	**299.999**

N.B. The Item D and TOTAL columns will be filled in automatically

- item A.1: enhancement of months/person of permanent and temporary employees
- item A.2: cost of contracts of non-employees, specifically to recruit
- item B: cost of equipment and tools
- item C: cost of consulting and other services
- item D: overhead
- item E: materials cost
- item F: other costs

PART B

B.1

1. State of the art

Hemp (non-psychoactive C. sativa) is one of the oldest cultivated crops, dating back to around 3000 a. C. (Attard et al., 2018), with the industrial one belonging to the same species of narcotic and medicinal cannabis. So far, the efforts in breeding and cultivation led to the division of C. sativa into five different recognized chemotypes (chemical types). Based on the major cannabinoid content, the chemotypes are classified as: I) recreational and medical-type (narcotic) with a high content of the psychotropic Δ9-tetrahydrocannabinol (Δ9-THC); II) medicinal cannabis with Δ9-THC/CBD 1:1; III) industrial fiber hemp that has CBD (cannabidiol) as predominant and a minimum content of Δ9-THC (0.2% w/w); IV) fiber-type that contains cannabigerol (CBG) as the main cannabinoid; and V) fiber-type with almost no cannabinoids (Aizpurua-Olaizola et al.; 2022). Around 35% of hemp cultivation is intended for edible oil production. Hemp straw provides fiber and two main by-products: hurds (55% of straw), applicable as animal bedding, fillers in plastic composites and also as a building material, and hemp dust (10-20% of straw) (Candy et al., 2017). Recently, the main non-psychotropic cannabinoids, including cannabidiol (CBD) and cannabigerol (CBG), have been included in the Cosmetic ingredients by the EU and they are considered for their therapeutic potential. These cannabinoids are the predominant ones in hemp (chemotypes III and IV), and they are concentrated in female inflorescences. By looking at this panorama, it is clear that harvesting and processing of hemp generate vast amounts of waste products, mainly identifiable in 1) straw dust, 2) leafy parts, and 3) plant residues after solvent extraction and wastewater, that still contain substantial amounts of important compounds. Therefore, there is an obvious scientific and industrial interest in more efficient applications of both these by-products to convert them into higher-benefit functional ingredients with specific innovative green technologies in a One Health holistic approach for a global health benefit aim. Cannabinoids do not accumulate in straw dust. However, this latter by-product and the winterization process could provide crude fractions rich in high-value-added lipophilic molecules, including sterols, policosanols, triterpene alcohols, and squalene. C. sativa is a prolific producer of cannabinoids and more than 150 structurally different compounds belonging to this class have been described up to now (Hanuš et al.; 2016). Nevertheless, both the chemical and biological space has so far been systematically investigated only around the major constituents of the plant. This includes the so-called main four cannabinoids, such as Δ9-THC, CBD, CBG, and cannabichromene (CBC), and mostly in the context of a single end-point: the endocannabinoid system (CB1 and CB2). Different macromolecular end-points have been identified for cannabinoids (metabotropic receptors, ion channels, transcription factors, enzymes), qualifying them as a privileged structure for multitarget bioactivity assessment (Hanuš et al.; 2016). More recently, the interest in hemp has remarkably increased, due to the presence of specific phytochemicals in its leaves, a harvesting by-product of cannabinoid extraction completely neglected because of its quite low cannabinoid content (1-2%) and legally not foody. Leafy anatomical parts of hemp are, indeed, the richest ones in terms of flavonoids (0.34-0.44% in leaves and 0.07-0.14% in inflorescence for a total amount of 1% in cannabis with cannflavins being unique in C. sativa species) and with a different concentration between chemotypes, which are significantly higher in chemotype III (0.40%) than in II (0.14%) and I (0.07%) (Jin et al.; 2020). No information has been found regarding the other hemp chemotypes. Other phytochemicals with declared or potential interest are stilbenoids, which can be divided into phenanthrenes, dihydrostilbenes, and spiroindans. Between phenanthrene derivatives, denbinobin deserves particular consideration for its interesting biological activity and its extremely rare recurrence. Denbinobin, typical of orchidaceous plants, has been identified in the IV chemotype of fiber-hemp (Pollastro et al.; 2018). Eight dihydrostilbenes have been reported from cannabis, and some of them are ubiquitous in plants except for canniprene and hemp spiroindans which are still an open field of chemical and biological exploration (Pollastro et al.; 2018). Industrial practices are nowadays increasingly directed towards manufacturing procedures with higher sustainability to minimize waste generation, improve cost-effectiveness, and meet customer demand in a circular economy context. To achieve these goals, by-product valorization and recycling represent a great opportunity, which has attracted impressive attention over the past few years, under the recognition of innovative strategies based on green and environmentally friendly processes.

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2. Detailed description of the project: methodologies, objectives, and results that the project aims to achieve; indicate deliverables and milestones outlining the project coherence as to the strategic themes, indicating clear and innovative objectives, setting out the project sector relevance and its positioning with reference to the state of art, describing the role and contribution of each research unit

The present project, specifically named “Not Ordinary Cannabis (NOrCa)”, has a clear hypothesis that consists of transforming the underutilized hemp material (Fig. 1) into a concrete circular economy opportunity.

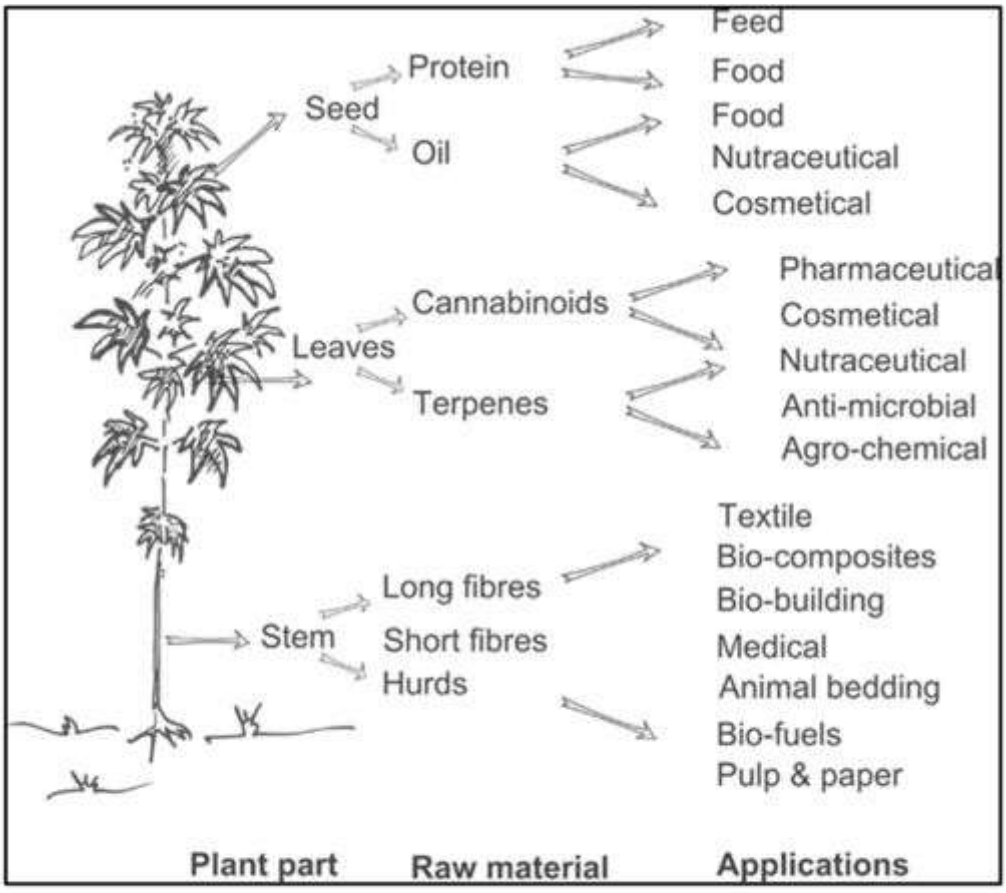


Fig.1 Actual and potential end-use application from the hemp plant

This will be done by exploring the vast area of the hemp waste and by-products chemical space to develop high-value applications based on its natural richness in potentially bioactive compounds. The project focuses on the investigation and isolation of different classes of compounds (from native cannabinoid esters and minor cannabinoids to phenolic compounds, terpenes, and other lipophilic constituents, and also bioactive peptides) left behind as by-products with the intent to construct a library since structural molecular point mutations can redirect their bioactivity (De Petrocellis et al.; 2011). This library could find applications in different areas and could be a useful tool to provide: 1) new analytical methods with appropriate standards for the chemical analysis required by industrial and pharmaceutical production of C. sativa-derived products; 2) new natural entities as molecular probes to deeply evaluate the hidden potential of C. sativa and generate new knowledge;
3) new hit/lead compounds for structure-activity relationship studies to improve the therapeutic outcomes; 4) new ingredients for nutraceutical and cosmetic products as companies are interested in plant-based ingredients with a growing concern for the environment (Martins et al.; 2022). Access to these compounds will involve suitable methods for extraction and analysis, bioassay-guided fractionation, isolation, and full structural characterization. Moreover, this project will benefit the team's experience in novel isolation protocol, structural elucidation, and optimized semisynthesis of secondary metabolites from C. sativa L. since 2004 with the identification of the new forefather of minor cannabinoids, namely the sesqui-CBG (Pollastro et al., 2011). The team also has deep expertise in targeted and untargeted metabolomics of hemp constituents using chromatographic methods coupled with mass spectrometry (Protti et al., 2019; Brighenti et al., 2021). The project will engage in a whole chain of research on hemp residue aiming at full characterization, identification, and assessment of high-value targets for end-use applications. This will be achieved by developing the “green factory” concept, harnessing the natural potential of these plant by-products to deliver high-quality raw materials. In addition, an integrated processing system to obtain maximal value from the waste in a sustainable manner will be developed, according to Agenda2030 goals 3 and 12. The knowledge generated during the project will be subjected to widespread dissemination to obtain the maximum benefit to the bioeconomy. Activities will be promoted not only to the scientific community but also to involve local grower associations and industries to demonstrate the feasibility of the production strategy targeted in this project. The project activities are organized in 6 integrated working packages (WPs), dealing with the collection and extraction of hemp waste and by-products (WP1), followed by the isolation of compounds (WP2), full chemical analysis of the extracted molecules with the creation of a data-library (WP3), and biological activity for innovative applications of hemp extracts and pure molecules (WP4). A continuous flow of information among the participants is guaranteed by the integrated design of the project and by the establishment of a communication platform (WP5). In the frame of WP5, the results of the project will be further elaborated to feed dissemination activities (WP6) for the community, and stakeholders. The main objectives of the project are shown in Table 1, together with their coherence as to the PNRR strategic themes.

Table 1: Project Work Packages (WPs), their objectives, coherence with PNRR topics and expected results

WP	WP Title	Objectives, coherence with PNRR topics and expected results
1	Developing of new green methods for the extraction of hemp waste and by products	**Object**: Valorization of hemp industrial waste (leaves and dust) and by products (plant residual material and wastewater after cannabinoid extraction) by deep investigation of their undiscovered potential **Coherence with PNRR**: Sectors 5.6.1 art. 4 and 5.6.3 Art. 2.b **Expected result**: development of at least 3 new extraction methods following the concept of green chemistry.
2	Exploring hemp biodiversity to isolate novel high value bioactive compounds	**Object**: Isolation of lipophilic compounds from hemp dust to be defined for pharmaceutical/nutraceutical/cosmetic applications. Isolation and characterisation of compounds (cannabinoids esters, minor cannabinoids, phenolic compounds, terpenes and and small peptides) from hemp leaves and extraction waste to discover new hit/lead compounds for multi-purpose application and scale up process or synthesis. Synthetic alternatives to produces less abundant cannabinoids and their derivatives in an appropriate amount for bioassays. **Coherence with PNRR**: Sector 5.1.2 art.3, art. 6 **Expected result**: fractionation of at least 6 new enriched mixtures from hemp waste and by-products; development of at least 1 new method for the synthesis of less abundant cannabinoids or derivatives.
3	Chemical analysis and compound data library	**Object**: Full chemical analysis of recovered materials and compounds using advanced chromatographic methods. Construction of a GC-MS and UHPLC-HRMS library that allows for the identification of compounds in non-characterized Cannabis waste and to follow their enrichment in the extraction steps. Purification of compounds from mixtures of congeners from WP1 by micro-scale techniques (e.g., preparative LC) to be submitted to the biological characterization (WP3). Characterization of the photochemical and thermal stability of the isolated compounds. **Coherence with PNRR**: Sector 5.1.2 art.3, art. 6 **Expected result**: development of at least 1 new analytical method based on GC-MS and 1 new analytical method based on UHPLC-HRMS; purification and chemical characterization of at least 3 new compound from the mixtures under investigation.
4	Assessing the bioactivity compounds from hemp waste	**Object**: Evaluation of the antioxidant properties of extracts and compounds obtained in WP1-2 in chemical systems and cell cultures. Determination of the neuroprotective activity of extracts compounds obtained in WP1-2 in cell cultures. Assessment of the antiproliferative properties of extracts and compounds obtained in WP1-2 by exploring the effects on cell viability and proliferation, induction of apoptosis and other mechanism/s of action. Screening of extracts and compounds obtained in WP1-2 for their antimicrobial properties, to discover new anti-infective agents for the support of both human and plant health. Determination of the safety profile and bioavailability of bioactive metabolites in cell culture for potential pharmaceutical, nutraceutical and cosmetic applications. **Coherence with PNRR**: 5.1.3 art 3 and 5.6.4 art. 3 **Expected result**: reliable *in vitro* biological data on the extracts and isolated compounds from previous WP; identification of at least 1 extract and/or 1 pure compound with promising application in the pharmaceutical/nutraceutical/cosmetic fields.
5	Project management and coordination	**Object**: Coordination of the participants actions and progress monitoring; reporting of consortium activities and achievements; financial and administrative management; management and coordination of the EAB. **Expected result**: 12 meetings with the RUs; mid-term and final reports
6	Dissemination and exploitation	**Object**: Dissemination of the generated know-how on various levels, exploitation of the generated know-how and evaluation of options to protect it. Definition of the exploitation roadmap for the project results. **Expected result**: website and social media dissemination; mid-term workshop; final workshop; at least 6 scientific papers in international scientific journals with high impact factor and/or in the Q1 ranking (open-access); at least 4 oral communications in international/national congresses/symposia; at least 4 poster presentations in international/national congresses/symposia; at least 4 divulgative meetings.

The deliverables and the milestones are shown in section 7 of the proposal. The novelties in comparison with the state-of-the-art are shown in Table 2.

Table 2: Novelty statement

Topic	State-of-the-Art (SoA)	NOrCa
Explore hemp biodiversity to identify novel high value applications	- Hemp wastes used for animal breeding or disposed of as useless - Wastes from cannabinoid extraction (mother liquors, exhausted vegetal material) are disposed off	- Design of green extraction procedures to valorize hemp extraction waste and by products to recover bioactive compounds
Characterization of secondary hemp metabolites	- Lack of analytical data on most Cannabis secondary metabolites - Lack of chromatographic and mass spectrometric data to identify the metabolites in hemp	- Use of the isolated compound as analytical standards to characterize hemp chemotypes and wastes - Creation of a chromatographic and mass spectrometry database - Identification of new secondary metabolites
Biological characterization of secondary hemp metabolites	- Biological data limited to principal metabolites (CBG, CBD, THC, CBC, CBN)	- Study of the biological activities of extracts and pure compounds from the matrices under investigation
Sustainability and final assessment	- Extraction procedures for secondary metabolites does not comply with green chemistry principles	- Extraction protocols will comply with green chemistry principles (Do No Significant Harm, DNSH), easily scalable and economically advantageous on and industrial level
Dissemination	- Cannabis sativa L. perceived as a source of THC, CBD and CBG for medical and recreational use	- Fact-checking information about the possibility of using Cannabis sativa L. as a source of multiple valuable compounds for the pharmaceutical/nutraceutical and cosmetic fields

The specific role and contributions of each research unit are summarized in Table 3.

Table 3: Specific role and contribution of each research unit (RU)

RU	Organization	Main role in the project
1	University of Ferrara (UNIFE)	**G. Sacchetti** (PI). Responsible for scientific and economic reporting (drafting the mid-term and final report) as well as for the management of the RUs (WP5). Dissemination (WP6). Tutoring the PhD candidate. **M. Tacchini** (Unit member). Developing and optimizing extraction processes with a low environmental impact (WP1). Evaluate their phytotherapeutic and phytosanitary activity (WP4). Tutoring the PhD candidate.
2	University of Piemonte Orientale (UPO)	**F. Pollastro** (Associated PI). Fractionation, purification and structural characterization of compounds from hemp waste and by products (WP2). Development of appropriate methods for the synthesis of derivatives (WP2). Project exploitation and management (WP5). Dissemination (WP6).
3	University of Pavia (UNIPV)	**D. Merli** (Associated PI): Purification of compounds from complex mixtures from the extraction procedures (WP2). Final characterization of the isolated compounds and creation of a mass spectrometry library (WP3). Characterization of the photochemical and thermal stability of the isolated compounds (WP3). Project exploitation and management (WP5). Dissemination (WP6). **A. Bonanni** (Unit member): Chemometrics. Environmental impact of the extraction procedure. Development of electroanalytical methods for the analysis of secondary metabolites in crude extracts and vegetable material (WP3). **A. Profumo** (Unit member): Final characterization of the isolated compounds and creation of a mass spectrometry library (WP2).
4	University of Modena and Reggio Emilia (UNIMORE)	**F. Pellati** (Associated PI): Development of new highly efficient and green methods for the extraction of bioactive compounds from hemp waste and by products (WP1). Purification of compounds by preparative LC (WP2). Development of untargeted and targeted metabolomics for the study of the composition of the extracts (WP3). Final characterization of the isolated compounds and creation of a mass spectrometry library (WP3). Project exploitation and management (WP5). Dissemination (WP6). **D. Tagliazucchi** (Unit member): Extraction and purification of peptides from the matrices under investigation (WP1). Assessment of the antioxidant properties of extracts and isolated compounds (WP4). Determination of the safety profile and bioavailability of the isolated compounds (WP4). **G. Biagini** (Unit member): Assessment of the neuroprotective properties of extracts and isolated compounds using cell cultures (WP4). **L. Corsi** (Unit member): Assessment of the antiproliferative activity of extracts and isolated compounds and study of the mechanim/s of action involving apoptosis (WP4). Determination of the safety profile and bioavailability of the isolated compounds (WP4).

WP1. Developing new green methods for the extraction of hemp waste and by-products

This WP will involve the extraction of different hemp wastes and by-products, and it will be performed by the University of Ferrara (UNIFE) and the University of Modena and Reggio Emilia (UNIMORE). Minor cannabinoids, phenols, peptides, and terpenes will be extracted from leaves, and residual plant material after the extraction and wastewater of cannabinoids extraction (Pellati et al., 2018; Ternelli et al., 2020; Samaei et al., 2021). Hemp dust, instead, will be a source of waxes, policosanols, polyunsaturated fatty acids, and phytosterols (Venturelli et al., 2019). The by-products and waste material, objects of our research, will be provided by specialized companies (Canvasalus, Assocanapa, Linnea, and Indena), already involved in collaborations with the University of Eastern Piedmont (UNIUPO). The extraction strategies will be characterized by a green-chemistry approach, aimed to minimize the use of organic solvents and optimize the final yield and selectivity (Guerrini et al., 2020). Specifically, different methods with

increasing polarities will be explored, including supercritical CO2 extraction, steam distillation (for the essential oil), ultrasound and microwave-assisted extraction, pressurized fluid extraction, using hydroalcoholic solvents and Natural Deep Eutectic Solvents, which are a new alternative to toxic organic solvents, being them composed of non-toxic, biocompatible and highly sustainable chemicals. Moreover, these extraction methods will be optimized by using chemometric approaches (design of experiment, DoE) by the University of Pavia (UNIPV), which represent a systematic, efficient method to study the relationship between multiple variables and key output.

WP2. Exploring hemp biodiversity to isolate novel high-value bioactive compounds

After having developed the appropriate procedure for the extraction of the compounds of interest, this WP will focus on the fractionation and isolation of compounds from the raw extracts.

Task 2.1 Lipophilic compounds from hemp dust

Starting from hemp dust lipophilic extracts obtained in WP1, a preliminary separation between the saturated fraction (saturated fatty acids and waxes esters) from the unsaturated one (polyunsaturated fatty acids, policosanols, sterols, and triterpenoids) will be provided by UNIUPO by a winterization procedure.

Task 2.2 Secondary metabolites from hemp leaves and wastewater

Starting from crude extracts from WP1, the isolation performed by UNIUPO will be focused on phenolics, peptides, terpenes, CBD, CBG, relative pre-cannabinoids CBDA and CBGA, and minor cannabinoids. The unused leaves from the collection of inflorescences or seeds could be considered as an optimal source of phenolic compounds (ranging between 0.34-0.44%), and cannabinoids (1.10-2.10%) (Jin et al.; 2020), while we expect to isolate minor cannabinoids from the wastewater of the plant extraction. Previous studies focused on the V chemotype (without cannabinoids) of C. sativa at the UNIUPO group in collaboration with Canvasalus (Dr. Grassi), which led to the discovery of two new dihydrophenanthrenoids and a new derivative of denbinobine with interesting biological activity (Salamone et al.; 2022).

Task 2.3 Optimization of the isolation procedures

The mixture of closely related molecules obtained from previous tasks will undergo further purification strategies to isolate pure compounds by UNIPV and UNIMORE, which will be fully characterized for their chromatographic and spectroscopic features in WP3, and further submitted to WP4 for biological assays. In this step, high-performance preparative techniques will be adopted for the purification. In detail, automated flash-column chromatography will be the technique of choice, both with normal (silica, alumina, Florisil) phase, reverse phase (RP) C-18, and size exclusion (Sephadex-LH-20) stationary phases (Radwan et al.; 2021). Preparative HPLC (RP) will be proposed to obtain pure samples to be submitted to WP4 for the biological assay if low-pressure column chromatography would lead to poor results.

Task 2.4 Overcoming the availability challenge by synthetic methods

The challenges of the availability of less abundant cannabinoids and their derivatives will be addressed by developing a general synthesis of pre-cannabinoid terpenyl esters (Hanuš et al.; 2016). The synthesis of terpenyl pre-cannabinoids is complicated by the decarboxylation of the activated carboxylic group under coupling conditions, a problem not uncommon in polyphenolic acids (Appendino et al.; 2002). Despite this issue, the proponents have obtained preliminary evidence that coupling is possible under Keck-type conditions (Fig. 2).

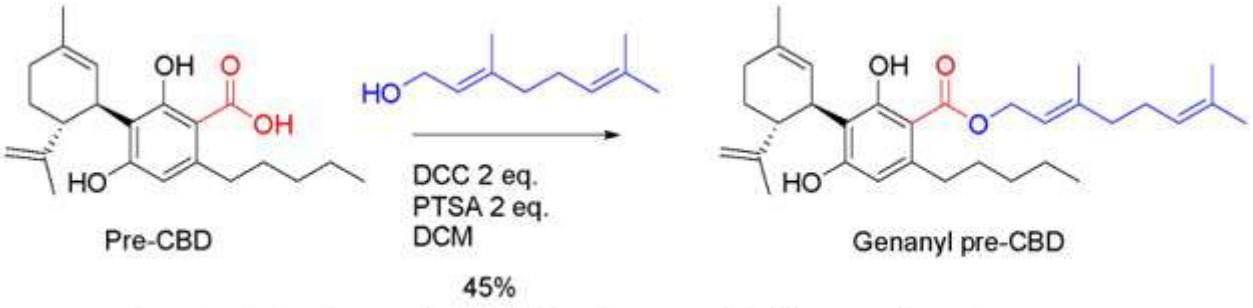


Fig. 2: Synthesis of terpenyl pre-cannabinoids as exemplified by geranyl pre-CBD

O-methylated cannabinoids are typical of some cannabis strains (Hanuš et al.; 2016). Apart from the lack of activity on CB1, little is known about the biological significance of the O-methylation of cannabinoids. The reaction gives mixtures of mono-and di-methyl derivatives, but the issue could be solved with a protecting group, as shown in Fig. 3.

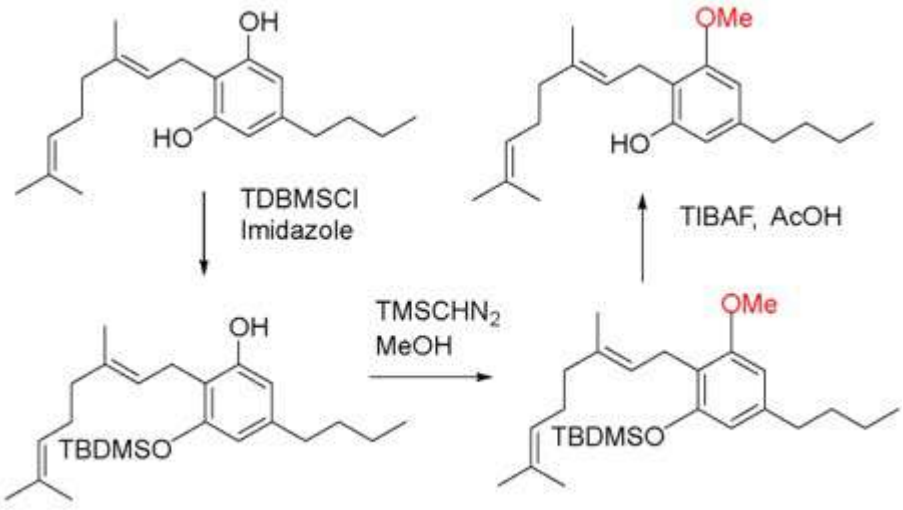


Fig. 3: Semisynthesis of *O*-methyl cannabinoids as planned with CBG

The CBG derivatives, cannabinerol (CBNR) and sesqui-CBG, typical of CBG-rich chemotype (CARMA) will be obtained with an easy synthetic protocol as described in Fig. 4.

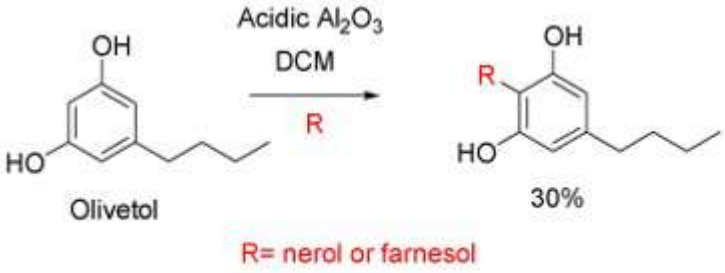
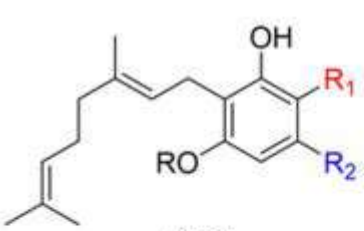
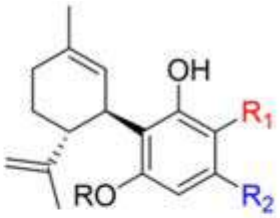


Fig. 4: Synthesis of CBGNR and Sesqui-CBG

The isolation of multi-gram amounts of the most abundant cannabinoids in hemp waste cannabis (CBD, CBG), in the form of their corresponding pre-cannabinoids (CBDA, CBGA), will be the starting point to proceed with the synthesis of derivatives that, together with the isolation of their lower homologs (viridins CBGV and CBDV) and phenolics compounds, will provide the molecules needed for the further steps of the project (Fig. 5). This task will be performed by UNIUPO.



CBG



CBD

	R	R_1	R_2
CBG	H	H	C_5H_{11}
CBGV	H	H	C_3H_7
CBG-OMe	CH_3	H	C_5H_{11}
CBGA-terpenyl ester	H	monoterpene	C_5H_{11}

	R	R_1	R_2
CBD	H	H	C_5H_{11}
CBDV	H	H	C_3H_7
CBD-OMe	CH_3	H	C_5H_{11}
CBDA-terpenyl ester	H	monoterpene	C_5H_{11}

Fig. 5: Database of cannabinoids available by isolation or synthesis in sufficient amount to sustain biological studies

WP3. Chemical analysis and compound data library

WP3 will be focused on the full characterization of the extracts and compounds obtained from WP1 and WP2, as well as on the study of the photo and thermal stability/degradation of the recovered compounds.

Task 3.1 Chemical characterization of the extract and isolated compounds

Full characterization of the extracts and pure compounds obtained from WP1 and WP2 will be the focus of this task, which is addressed in the development of advanced analytical methods, selected based on the chemical structures of the molecules to be investigated (Iseppi et al., 2019; Protti et al., 2019; Brighenti et al., 2021; Samaei et al., 2021; Seccamani et al.; 2021; Franco et al.; 2022). In this task, untargeted and targeted metabolomics and peptidomics will be deeply applied by UNIMORE and UNIPV to monitor the composition of the extracts and check the purity of pure compounds. The exact mass value and fragmentation pattern, arising from HR-GC-MS and UHPLC-HRMS, along with NMR (1D and 2D) experiments, polarimetry, and X-ray diffraction will provide key information on the structure of the examined compounds. This data obtained by UNIMORE and UNIPV will allow the creation of a library of information containing all chromatographic and mass spectrometry data (Seccamani et al.; 2021), that will facilitate the identification of the components of the scraps during the analysis and extraction procedures. The library would be useful also to characterize unsorted scraps from Cannabis whose genome is unknown and to establish an optimized purification protocol according to the nature and abundance of the compounds found. The availability of different cannabinoid standards obtained in previous work and during the present project (Seccamani et al.; 2021; Franco et al.; 2022) would also lead to the detection and the quantification of different degradation products, including minor cannabinoids and potentially psychoactive and/or regulated substances (e.g. Δ9-THC derivatives), whose presence should be monitored step by step during the project. In addition to the above-cited techniques, an electrochemical characterization of the extracted compounds will be carried out by UNIPV for the identification and quantification of the isolated compounds before and after the separation/purification from the original mixtures.

Task 3.2 Characterization of the photochemical and thermal stability of the isolated compounds

Experimental analyses carried out on the fractions obtained using the separation protocol will provide information about the thermal and photostability of the compounds, with the compounds undergoing different stressing conditions. In the case of compounds showing a significant biological activity (WP4), detailed stability studies of the substance will be performed by UNIPV, given the fate of the substance when included in a suitable vehicle for human use (Seccamani et al.; 2021). In particular, the compounds solubilized in suitable media (ethanol, ethers, glycols) will be irradiated with different wavelengths to prove their stability. In parallel, solutions of the compounds will be subjected to thermal decomposition tests also using MW-induced thermal treatments. The decomposition process would be studied also in the presence of catalysts to verify their effect, as organic acids can contaminate the extracts and some cannabinoids in these conditions can cyclize forming psychoactive substances (i.e., CBD can be partially

converted in Δ9-THC) (Franco et al.; 2022). Data obtained from task 3.2 will be particularly useful in this regard to help in the synthesis of compounds that would confirm the presence of presumptive compounds that are not available in pure form.

WP4. Assessing the bioactivity of compounds from hemp waste

The scientific activity of WP4 will focus on the evaluation of the biological activities of extracts/fractions/compounds isolated from the hemp waste using in vitro assays, to identify new bioactive compounds for potential applications.

Task 4.1 Evaluation of the antioxidant properties of extracts and isolated compounds

The antioxidant activity of the extracts obtained in WP1 will be preliminarily evaluated by UNIFE using bioautographic assay on HPTLC. This will highlight the most active fractions and will guide the isolation of the most active molecules (Tacchini et al., 2019). Afterward, compounds with marked antioxidant activity in chemical systems will be tested by UNIMORE for their ability to inhibit oxidative stress in the murine HeLa human keratinocytes cell line. The protective effect of isolated compounds will be evaluated against the cell oxidative stress induced by oxidizing compounds, such as hydrogen peroxide H_2O_2 or menadione. The antioxidant activity of the molecules will be evaluated as the ability to reduce the oxidant-induced generation of ROS, and through the induction of Nrf2 transduction signal. The determination of the toxicity range of isolated molecules in cells will also be performed, to find the concentration range suitable for the assessment of antioxidant activity.

Task 4.2. Evaluation of the neuroprotective activity of extracts and isolated compounds

Immortalized human HMC3 microglia, human SVGp12 astrocytes, and human (HN-h) hippocampal neurons will be used in these experiments. The protocol will consist of two distinct steps: pre-treatment and treatment. Cells will be divided into different groups: i) control group, administered only medium; ii) lipopolysaccharide (LPS) group, administered LPS alone at 250 ng/mL for 24 h; iii) extracts (and, alternatively, pure compounds) + LPS. In the first step, pre-treatment with extracts and isolated compounds will be performed 4 h before. After treatments, immunocytochemical techniques (i.e., labeling the nucleus with DAPI, and microglial activation with MHC-II and CD68 markers) will be used, together with a confocal microscope to assess the cell activation state. The LPS-induced microglial activation should induce upregulation of pro-inflammatory cytokines IL-6, IL-1β, and TNF-α, which may be determined by non-competitive sandwich ELISA. In the second step, the conditioned media of HMC3 and/or SVGp12 cell supernatants, treated according to the above-mentioned scheme, will be used to create indirect co-culture conditions, as they will be added to HN-h cells. In this regard, we will primarily evaluate: i) the viability of HN-h cells by the 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide (MTT) test; ii) the oxygen radical species (ROS) production in HN-h cells, by using 2,7-dichlorofluorescin diacetate probe and plate fluorimetry. In addition to this, the conditioned media of HMC3 and/or SVGp12 cell supernatants treated with LPS will be added to the BBB hCMEC/D3 cell line after the pre-treatment with the extracts and pure compounds. After the pro-inflammatory response, changes in the HMC3 and/or SVGp12 cell supernatants treated with LPS will be introduced to the BBB hCMEC/D3 cell line and will be assessed in all treatment groups using immunoblotting techniques.

Task 4.3 Evaluation of the antiproliferative activity of extracts and isolated compounds

Considering that the antiproliferative activity of many phenolics and terpenes is related to their ability to affect cancer cell viability and proliferation, the isolated molecules will be tested in cancer cells (human glioblastoma cell line U87MG, human hepatic carcinoma HepG2, and human colon carcinoma HT-29), using the CCK and ELISA BrdU methods for a preliminary assessment of antiproliferative effects by UNIMORE (Anceschi et al., 2022). In parallel, the cytotoxic activity will be assessed on non-cancer cells. It is well known that the antiproliferative properties of many phenolic compounds are closely related to their ability to induce cell cycle arrest and trigger apoptosis. To quantify any antiproliferative mechanisms (induction of apoptosis) in cancer cells due to the treatment with the selected molecules, immunochemical experiments and flow cytometry analyses will be performed. In particular, the cell cycle will be analyzed using Annexin V and Propidium Iodide staining with the Cytofluorometer Coulter Epics XL MCL. The molecular mechanism of apoptosis will be determined by the assessment of the protein expression such as Bcl-xl, p53, p21, bax, caspse 3/7/8/9, and cyclins and/or cyclin-dependent kinase involved in the cell cycle. The molecules isolated from the waste material will also be tested in cancer cells to evaluate their modulatory effects on lipid metabolism (nowadays a promising target for anticancer drugs), and various lipophilic or amphiphilic molecules. This will act through modification of the organization and general structure of the lipids of biological membranes, which is due to the inhibition of the expression of cellular enzymes. The ability of the selected compounds to modify, at non-cytotoxic concentrations, the profile of cellular lipid components (phospholipids, cholesterol, and fatty acids), in cancer cells (U87MG, HepG2, HT-29) will be evaluated by metabolomic techniques (UHPLC-HRMS).

Task 4.4 Evaluation of the antimicrobial activity of extracts and isolated compounds against human and plant pathogens

The search for new molecules with antibacterial activity is a pressing topic of worldwide interest and involves both human and plant health. This phenomenon is embodied both by the rise of the antibacterial resistance phenomenon and by the extreme fragility of plant individuals towards phytopathogenic attacks. Flavonoids, terpenes, and stilbenes, for example, could exert antibacterial effects by various mechanisms of action: the direct killing of bacteria, the synergistic activation of antibiotics, or/and the attenuation of bacterial pathogenicity. Considering these premises and the green innovative technological strategies developed in WP1, the extracts and pure compounds will be tested by UNIFE for their antimicrobial activity (Guerrini et al., 2020). Bioautographic assay on a high-performance thin layer chromatography (HPTLC) plate and the assessment of the minimum inhibitory concentration (MIC) will be performed to evaluate antibacterial activity against Gram-negative Escherichia coli (ATCC 4350), Pseudomonas aeruginosa (ATCC 27853), Agrobacterium tumefaciens (DSM 30207), Agrobacterium vitis (DSM 6583), Pseudomonas syringae pv. syringae (DSM 10604) and Gram-positive Staphylococcus aureus (ATCC 29230), Staphylococcus epidermidis (ATCC 14990), Enterococcus faecalis (ATCC 29212), and Clavibacter michiganensis subsp. nebraskensis (DSM 20400).

Task 4.5 Determination of the safety profile and bioavailability of the isolated compounds

At this stage of the project, it will be important to evaluate which of the molecules isolated from the hemp waste material with biological activity are absorbed and/or metabolized at the cellular level. For this purpose, uptake studies will be carried out by UNIMORE for the bioactive molecules in CaCo-2 cells, as a model of intestinal epithelium, and the metabolic activity will be determined using HepG2 cell line (Ekbatan et al. 2018), also in co-culture. In addition, the metabolites (conditioned medium), coming from cell metabolic activity of either Caco2 and HepG2, in parallel to the “pure” compounds, will be assessed on 3T3 fibroblasts,

HaCat keratinocytes, and neuronal differentiated SHSY5Y to determine the toxicological profile. The absorption of molecules and the production of main cell metabolites will be evaluated by chromatographic techniques (UHPLC-HRMS), as described in WP3. The preliminary assessment of safety profile and bioavailability in cell cultures will furnish useful indications for the potential applicability of bioactive compounds in the pharmaceutical, nutraceutical, and cosmetic fields.

WP5. Project management and coordination

Task 5.1 Meeting and exploitation opportunities

The Principal Investigator (PI) will program and structure project meetings (every two months, in agreement with section 7 of the proposal) to monitor and validate the project progress and to provide inputs concerning industrial exploitation opportunities. Both face-to-face meetings (main industrial events or fairs) and virtual workshops will be organized.

Task 5.2 Quality assessment

Scientific and technical tasks within each WPs will be the responsibility of the WP leaders, but the PI will provide procedures for progress monitoring and reporting. Partners will publish their results in theses, conferences, peer-reviewed scientific journals, and eventually in patents.

The PI, together with the associated PIs, coordinates the quality assurance management. Timely awareness and reaction to potential problems are crucial for quality assurance management effectiveness. The WP leaders will implement the actions. The following activities will be realized:

1)Quality procedures: the 2-month periodicity for the PSC meeting is foreseen to perform an internal assessment of the project and assure the conformity and the quality of all project deliverables with the requirements; 2)Risk contingency management: the risk management process deals with project risks, making sure that the Consortium manages to fulfill the project goals on time and within budget. Project risks will be constantly assessed and evaluated within the whole project duration.

WP6. Dissemination and technological transfer

Dissemination activities will involve all the research units of the project and they will include the setup of a project web page that will be regularly updated and the creation of a logo for this project. The public pages will be used to disseminate project output to the general public. The Substitute Principal Investigator will be responsible for the social pages (Facebook and Instagram). In this way, suitable dissemination will be provided through these channels and on specific blogs (www.storiediunapiantaeroica.wordpress.com). These activities will provide clear mechanisms for feedback, opinion, and comments. Scientific dissemination of the results includes the submission of research articles to relevant Journals (with high IF and belonging to Q1 international journal ranking) and other awareness-raising academic activities, such as keynote lectures, and oral and poster communication at international and national scientific congresses. Dissemination will be focused also on the community trying to stimulate the public interest with free seminaries. Industrial and commercial exploitation and international dissemination of the results will be considered throughout the project to maximize the impact and market penetration of the metabolites in new applications. A final report on exploitation activities will be prepared. Potentially valuable intellectual property will be captured, evaluated, and protected by appropriate means.

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3. Detailed description of the project team and planning; indicating the research team components – PI and associated PIs - and their relative expertise/track record, gender equality of the composition, the interrelation and coherence of the team components. RUs- and the feasibility of the project, thus outlining the congruity between objectives, timing and costs

The research carried out in the frame of the project will be performed thanks to a deep integration between the research units (RUs) and facilities of UNIFE, UNIUPO, UNIPV, and UNIMORE, as shown in the PERT chart of Fig. 6. The project also promotes equality in the participation in scientific research of both women and men, thus favoring gender balance.

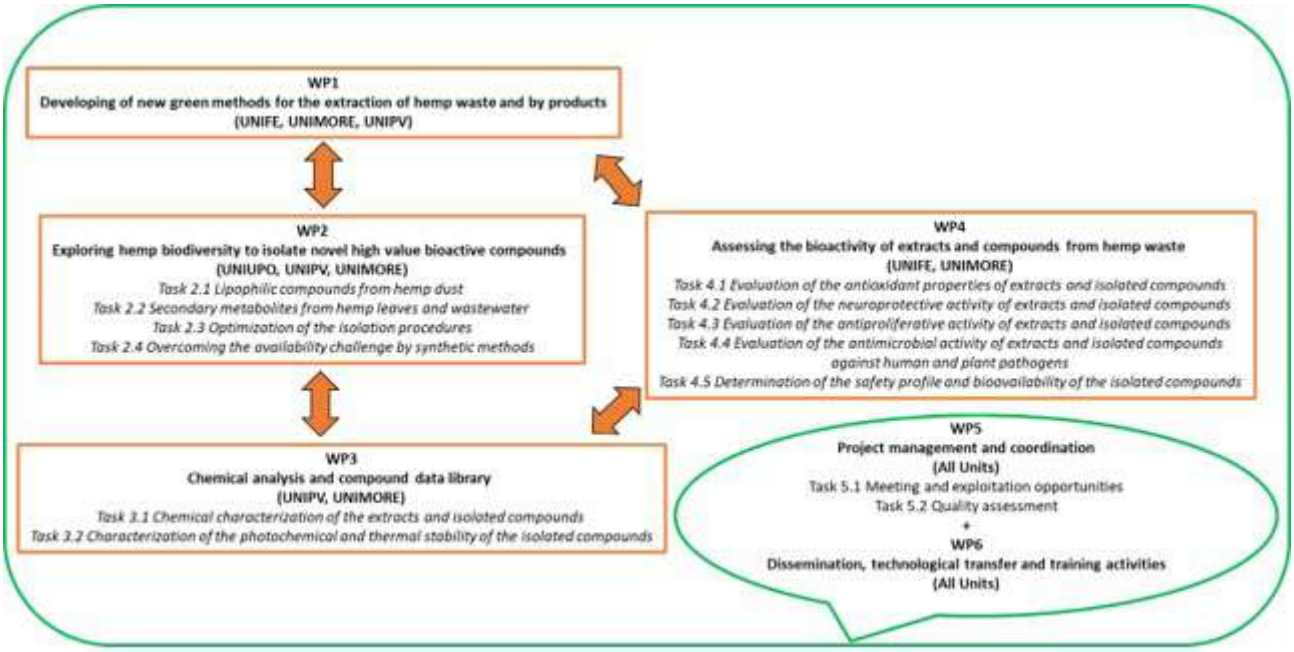

Fig. 6: Pert chart

RU 1: University of Ferrata (UNIFE). The research topics of the UNIFE unit concern the study of plants from a chemical and biological point of view. The PI (Prof. Gianni Sacchetti) is a pharmaceutical biologist with highly consolidated expertise on plant extracts and isolated compounds for possible applications as components of human health products (phytotherapeutics, nutraceuticals, cosmetics) and as new tools for organic and integrated agricultural treatments (phytoiatric products and biostimulants). The other member of the research unit has expertise in the same ambit. Optimizing extraction processes with a low environmental impact, including supercritical fluid extraction (SFE by Applied Separation, USA), ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), Naviglio pressurized fluid extraction (PFE), and steam distillation, has always been a key focus of the operating group research (e.g. Valsovit projects, http://www.valsovit.it/nqcontent.cfm?a_id=13622; and BIOFACE projects, https://www.unife.it/it/notizie/2021/scienza-cultura-e-ricerca/bioface), aiming to obtain new bioactive molecules, maximizing the utilization of the resources and converting waste materials into new marketable products. The experience gained over the years by the RU through these projects will ensure the congruity between the objectives, time, and cost of the work. In a general view of this project, the planning of the RU's work will be carried out by the PI in close contact with Dr. Massimo Tacchini (a further component of the RU) and supported by the successful PhD candidate. Going into detail, the most efficient extraction methods will be established according to the by-product considered, to obtain the best extraction yield and content of secondary metabolites. Once obtained, part of the extracts will be handed over to the other RUs to proceed with the purification and isolation of the main molecules and for the evaluation of biological activities. Moreover, the group can rely on the following equipment: high-performance thin-layer chromatography (HPTLC, Camag system with depositor, development, and densitometer), high-performance liquid chromatography system (HPLC-DAD Jasco), gas chromatography coupled by mass spectrometry and flame ionization detector (GC-MS/FID, Varian 4000 and Thermo), laminar flow hoods for sterile work and incubators for the bacterial growth.

RU 2: University of Eastern Piedmont (UNIUPO). The laboratories at UNIUPO are fully equipped for the phytochemical work requested by the project. The associated PI (Federica Pollastro) has deep expertise in the isolation, chemical characterization, and synthesis of naturally occurring compounds, in particular cannabinoids. The phytochemical laboratory space available is over 200 m2, and, apart from the basic phytochemical facilities (rotary evaporators, columns for gravity chromatography, sintered filters for vacuum chromatography, TLC plates, percolator, rotary extractor, special area for storing plant material), a pilot scale rotary evaporator (Buchi), a lyophilized (KNF), two automatic flash chromatography (Buchi and Biotage), one analytical- (Jasco) and two preparatives (Waters, Jasco) HPLC instruments, and an ultrasound system for extraction/reactions (CED) are available. The spectroscopic facilities include MS (Polaris Q ion trap mass spectrometer, Thermo Finnigan), HPLC-MS, GC-MS, 400 MHz NMR instrument (Jeol), IR, UV, and an automatic polarimeter. This allows for a) purification and spectroscopic characterization of new constituents, b) detection of their concentration in plant biomasses, and c) scale-up of their isolation in order to get sufficient material for biological evaluation. A library of C. sativa chemical constituents is available from previous work, and access to the ACS database of SciFinder will allow the quick dereplication of any compounds isolated and not yet present in the library, making it possible to focus the spectroscopic activities on new constituents.

RU 3: University of Pavia (UNIPV). The UNIPV research group is a dynamic and multidisciplinary team, engaged in important basic and applied research in several fields. The associated PI (Daniele Merli) and the other members of the research unit are analytical chemists who have been working extensively and gained relevant experience in the development of chromatography and electrochemical methods for the determination of drugs, food components, and pollutants. The research unit also has experience in chemometrics and experimental design, both of which will be used to optimize the experimental conditions of Cannabis extraction. The UNIPV research group is already working on the identification of degradation products and minor components of C. sativa, with a total of 4 master's degree theses completed or ongoing. The UNIPV unit has access to modern analytical apparatus for the detailed characterization of organic and inorganic products (NMR at 400 and 700 MHz, GC-MS, ICP), preparative HPLC, Karl-Fisher titration instruments, and has access to the “Centro Grandi Strumenti”, that allow the members to use HPLC-MS (TOF), high-resolution GC-MS apparatus, TEM, X-Ray diffractometer. Photochemical apparatus for quantum yield measurement, fluorescence and

phosphorescence spectroscopy, and time-resolved techniques (determination of emission lifetimes and characterization of short-lived intermediates and excited states via Laser Flash Photolysis) are available, as well as a wide range of photochemical reactors (multi-lamp apparatuses equipped by low-pressure Hg lamps, immersion well photoreactors, solar simulators, flow photochemical reactors) operating at different wavelengths (UV lamps, LEDs, sunlight as the light sources) and different temperatures. Finally, the members of the UNIPV units also have recognized skills in green metrics. This made UNIPV capable of optimizing the extraction procedure conditions in terms of the scale of productivity and sustainability. UNIPV and UNIUPO members are already working in the field of natural cannabinoids and have so far published two papers in peer-review journals.
RU 4: University of Modena and Reggio Emilia (UNIMORE). The UNIMORE group has strong and consolidated expertise in both chemical analysis as well as bioactivity assessment of plant-derived extracts and pure compounds in the field of drug discovery. The associated PI (Federica Pellati) is a medicinal chemist with deep expertise in the development of new extraction procedures and advanced analytical methods for the study of plant extracts and natural compounds as well as their bioactivity for pharmaceutical and nutraceutical applications. The other members of the research unit include a biochemist with expertise in the analysis and bioactivity (antioxidant) assessment of natural products, a physiologist with strong expertise in neuroprotection evaluation, and a pharmacologist with consolidated experience in the study of the antiproliferative activity of natural products. A multidisciplinary strategy is applied in the UNIMORE group to evaluate the biological activity of extracts of different medicinal plants (especially those rich in polyphenols, cannabinoids, and terpenes), to isolate and to characterize their components and to identify their mechanism (s) of action, making use of a competence integrated from chemistry with biochemistry and pharmacology. In the research activity of the laboratory, the interest is aimed in particular at the development and application of innovative chromatographic methods for the multi-component analysis of plant extracts, based on chromatographic techniques coupled with mass spectrometry in the so-called untargeted and targeted metabolomics. As for biological activity, the interest is particularly aimed at the discovery of natural compounds with antioxidant/neuroprotective/antiproliferative properties. The research activities also include peptide profiles from hemp by-products and waste and their potential bioactivity. The UNIMORE group has many scientific peer-review papers related to the extraction and analysis of bioactive compounds from non-psychoactive C. sativa as well as on the biological evaluation of plant extracts against cancer and Central Nervous System (CNS) pathologies. In this ambit, it is important to highlight the already existing collaboration with both UNIFE and UNIUPO, as demonstrated by three joint publications with each group. The research of the UNIMORE group is performed in strong collaboration with many researchers from other Italian and foreign Universities. The UNIMORE chemical laboratories are equipped with all the necessary tools for the extraction (UAE, MAE, steam distillation) and purification of natural active ingredients, for spectrophotometric and chromatographic analysis (HPLC-UV/DAD, HPLC-ELSD, GC-FID). The laboratory also makes use of the instrumentation available at the Centro Interdipartimentale Grandi Strumenti (CIGS) for HPLC systems coupled to different types of mass analyzers (ion trap, triple quadrupole, Orbitrap) and GC-MS. For the bioactivity assessment, the UNIMORE group has cell culture facilities, a spectrofluorometer and spectrophotometer, cytofluorimetric equipment, electrophoresis and western blot facilities, a microplate reader, and so on.
The summary of the roles of the RUs involved in the project is shown in Table 3 (Paragraph B.2)
As for the feasibility of the project, the proponents have identified possible risks related to the WPs and found appropriate solutions to all the possible issues, as shown in Table 4.

Table 4: Risks and Mitigation Measures

WP	Risk	Probability	Mitigation Measures
1	**R1.1** Difficult optimization of the extraction conditions	Low-medium	Application of the Design of Experiment (DoE) approach
	R1.2 Low yield of extraction	Low-medium	Use of chemotype varieties selectively enriched in minor cannabinoids and phenols, making it possible to expedite their extraction from plant biomasses
2	**R2.1** Lack of isolation of compounds, due to the chemotype diversity	Low-medium	Use of specific hemp varieties, enriched in selected classes of chemical compounds
	R2.2 Low purity of the compounds delivered for the spectral characterization	Medium	Further purification by preparative LC
	R2.3 Low yield of the compounds delivered for the spectral characterization	Medium	Development of appropriate synthetic methods
3	**R3.1** Unable to definitively identify the isolated compounds	Low-medium	Total synthesis of the compounds to compare their chemical structures
	R3.2 Complex mixture obtained in the photo- and thermal- degradation studies	Medium-high	Isolation of the compounds from preparative-scale degradation experiments
	R3.3 Degradation of isolated compounds, due to their thermal/light instability.	Low-medium	Adoption of specific operative conditions (low experimental temperatures, protection from light exposure) to avoid degradation and assess bioactivity in proper conditions
4	**R 4.1** Low amount of isolated compound for the assessment of bioactivity.	Medium	Targeted screening of bioactivity using bioautograohic methods
	R 4.2 Low solubility of extracts/ compounds due, to precipitation in the experimental conditions.	Low-medium	Encapsulation within β-cyclodextrin to improve water-dispersibility and increase bioactivity
	R 4.3 Low bioactivity of extracts/isolated compounds	Medium	Assessment of the bioactivity of derivatives obtained by synthesis
5	**R5.1** Activities delivery delayed	Medium	Periodic meetings (2 months) and constant activity updates
	R 5.2 Disagreement on ownership rules	Low-medium	Continuous review and updates of the common and individual exploitation plans
	R 5.3 Weak exploitation	Low-medium	Continuous review and updates of the project exploitation plans
	R5.4 Know- how risks: there are leaks of confidential information	Low	IPR management of the project results and definition of the dissemination strategy

Based on the above-described information, it is possible to highlight that the four RUs possess the expertise, equipment, and person-months to develop the project with the timescale proposed and in full agreement with the financial aspects. This information is described in detail in sections 7 and 8 of the proposal, respectively, and in part B2 - section 4. The acquisition of one position of PhD by UNIFE will further reinforce this aspect, allowing a young researcher to develop her/his project in collaboration with the other RUs involved in the proposal in a multidisciplinary context.

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4. Detailed description of the Project impact, as such; indicating knowledge improvements, technological innovation and/or industrial applications, scientific community reinforcement, level of research internationalization, dissemination and exploitation of the results

As shown in Table 1 of Paragraph B.2, several innovations are proposed in the present project. No systematic study going beyond the determination of the Δ9-THC/CBD ratio has ever been carried out on the phytochemical profile of hemp, with the occurrence of the structurally unique hemp phenolics remaining completely overlooked, as well as that of the so-called “minor cannabinoids”.
As for the knowledge improvements, sustainable extraction protocols for minor hemp constituents from waste and by-products will be developed, following the Do No Significant Harm principle (DNSH). In this way, waste and by-products from hemp refining will be enhanced in an eco-sustainable protocol. This approach would also lead to the identification of hemp secondary metabolites, which are up to now unknown to the scientific community. The isolated compounds will be fully characterized and a chromatographic library will be set up based on HPLC and GC data, allowing for the identification of these constituents in raw hemp extracts and the enrichment during the extraction/purification protocols. The purified and completely characterized compounds will be submitted to biological evaluation tests when data present in the literature are lacking or unavailable, as is the case for most minor cannabinoids and other compounds derived from hemp.
The project will have significant scientific and technological outcomes of both academic and industrial relevance by rendering the natural bioactive molecules in hemp high-value specialty chemicals. Indeed, this research will build on a fundamental scientific understanding of the development of these bioactive molecules and apply innovations in agronomy, post-harvesting handling, and recycling to maximize their extraction and utilization in pharmaceutical, nutraceutical, cosmetic, and agrochemical applications.

Moreover, the knowledge from the ongoing industrial collaborations will complement that generated in NOrCa and hemp, for the first time, will simultaneously provide high-value products that complement its more traditional fiber-based products and amplify its intrinsic pharmaceutical potential closed around CB1 and CB2 receptors.
The knowledge generated within this project will result in significant environmental and economic benefits by increasing the use of high-value chemical products, while still providing biodegradable, eco-friendly biomaterials and biomass (exhausted plant). This project represents an additional link in the development of a highly competitive circular economy based on hemp. This integrated recycling strategy can help stimulate many sectors starting from the agro-rural economy to the pharmaceutical, nutraceutical, and cosmetic fields by the generation of jobs in the emerging sector of the bio-based circular economy. Ultimately, the high-value products of these multipurpose dedicated crops will be cheaper, readily accessible, and more environmentally friendly than the green-house grown plants or synthetic alternatives currently available. While there is an increasing demand for hemp fiber products in the markets, the use of hemp in other applications is still relatively limited, with plant residuals after the extraction and wastewater, dust, and leaves representing an urgent issue that requires attention especially if they could be reborn under the light of another product. The knowledge generated within this project will reinforce the possibility to implement successful hemp production from the harvesting to the recycling chains. Currently, in Italy, there is a flourishing interest in the cultivation of hemp and a relevant number of farmers associations and enterprises have been founded with the scope of transforming hemp, mainly into bio-building materials and for the commercialization of its seeds. The strategic relevance of the work is accentuated by the enterprises in the Italian landscape that work in the hemp field with targeted research and innovation, respectively related to extraction and development of cosmetic and nutra/pharmaceutical applications.
Dissemination will be carried out at the national and, especially, international level in order to facilitate effective exploitation of the outputs from the research and to create a joined-up network where the outputs of the work can move from the laboratory to the end product. The results of this project will be disseminated to the scientific community through research papers in international scientific journals with high impact factor and the Q1 ranking (in the open-access mode), after careful assessment of possible patenting of new chemical entities and/or their bioactivity. Scientific results will be presented during the annual conference of the European Industrial Hemp Association (EIHA), at the CanneX congress in Tel Aviv as well as at the symposia of the Cannabis Chemistry Subdivision (CANN) of the Division of Chemical Health and Safety (CHAS) of the American Chemical Society (ACS), organized twice per year. These are recognized as the largest meetings of experts on industrial hemp in Europe and worldwide.
The degree of internalization of the project will also be ensured thanks to the multiple and consolidated ongoing collaboration of the proponents with foreign research groups working in extraction and bioactivity assessment of plant-derived compounds.
The expected results for each WP are summarized in Table 1.
The expected impacts of this project are summarized as follows:
- Improved scientific understanding of a complex plant (non-psychotropic Cannabis sativa L.) not fully described in terms of its secondary metabolites, the relationships between agro-technique, genotype, and bioactive natural compounds related traits in hemp;
- Waste handling of hemp by developing an innovative multi-use recycling system that includes the fiber dust, the residual leaves, and the waste from the extraction of inflorescences. This project will rely on the quantity and quality of secondary metabolites present in this residual biomass, thereby generating the know-how needed to fully exploit it;
- Trials and scaling up to ensure that the analytical characterization of hemp waste and by-products to increase commercial applications in terms of high-value chemicals is fully integrated with the economic concept and can be evaluated by end-users; trials and scale-up extractions of High-Value Chemicals will be set up in the second year of the project. This will ensure that pilot-scale amounts of residues can be evaluated by commercial end-users.
- The overall exploitation of hemp's bioactive potential in this project undoubtedly addresses the impact of developing products from waste material and by-products that are more environmentally friendly than existing alternatives.
- The cosmetic sector is eagerly requiring new, safe, and effective natural preservatives. In fact, although “regular” preservatives are carefully included in the new European recast 1223/2009, the market is demanding products that may possess a “preservative-free” claim. Quite obviously, this might be only achieved by natural preservatives and hemp derivatives are promising candidates to fulfill this need. Since the value of the European cosmetic sector is around 50 billion Euros (source: Euromonitor), if only one in a thousand formulations would switch to a natural preservative, this will affect a segment of 50 mil Euros in Europe alone.
- New hit/lead compounds for drug discovery with behavior that goes beyond the strict pharmacological view of cannabis closely related to CB1 and CB2 receptors will be identified. This will set the stage for moving from in vitro to future ex vivo and in vivo experiments to validate their potential to beneficially affect human health.
- Considering the strong social impact of C. sativa often built on misinformation, all the knowledge generated from this project will substantially increase the awareness of the plant and of its potential, which transcends the psychoactive drug. Another important activity will be represented by educational conferences at different levels with the ultimate aim to contribute to fighting the scourge of drug abuse, breaking the vicious circle that associates C. sativa with drug consumption. By highlighting the utility of the plant, it will become clear that one single and occasional trait, namely the presence of Δ9-THC, has a fundamentally polarized interest in this plant, obfuscating all the other merits.

5. Financial aspects: costs of each research unit

nº		**Funds of the Ministry of University and Research (euro)**
1.	SACCHETTI Gianni	98.511

2.	POLLASTRO Federica	67.000
3.	MERLI Daniele	67.488
4.	PELLATI Federica	67.000
		299.999

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7. Time schedule of the research activities (GANTT CHART)

Milestone 1 Development of new green methods for the extraction of hemp waste and by-products

ACTIVITY	ASSIGNED TO	I year						II year					
		BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6
Extraction of the hemp by-products with sustainable strategies for further chemical characterization and bioactivity evaluation	SACCHETTI G PELLATI F	X	X	X	X								
Application of the Design of Experiments (DoE) to optimise the extraction conditions	MERLI D		X	X	X	X							

Milestone 2 Exploring hemp biodiversity to isolate novel high-value bioactive compounds

ACTIVITY	ASSIGNED TO	I year						II year					
		BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6
Fractionation strategies of lipophilic compounds	POLLASTRO F		X	X	X	X	X						
Isolation of secondary metabolites from optimized extracts	POLLASTRO F			X	X	X	X	X	X				
Optimization of the isolation procedures and chemical characterization of the obtained compounds through chromatographic and spectroscopic techniques	MERLI D PELLATI F				X	X	X	X	X	X			
Development of a general synthesis of pre-cannabinoid terpenyl esters and other derivatives	POLLASTRO F			X	X	X	X	X	X	X			

Milestone 3 Chemical analysis of extracts and building a compound data library

ACTIVITY	ASSIGNED TO	I year						II year					
		BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6
Full chemical characterization of the extracts and pure compounds obtained	MERLI D PELLATI F			X	X	X	X	X	X	X	X		
Building a library with all chromatographic and mass spectrometry data of isolated compounds	MERLI D PELLATI F					X	X	X	X	X			
Characterization of the photochemical and thermal stability of the isolated compounds	MERLI D							X	X	X	X		

Milestone 4 Evaluation of the bioactivity of hemp by-products extracts and isolated compounds

ACTIVITY	ASSIGNED TO	I year						II year					
		BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6
Determination of the antioxidant activity of extracts and isolated compounds	SACCHETTI G PELLATI F				X	X	X	X	X	X	X	X	
Determination of the neuroprotective activity of extracts and isolated compounds	PELLATI F					X	X	X	X	X	X	X	
Determination of the antiproliferative activity of extracts and isolated compounds	PELLATI F					X	X	X	X	X	X		
Evaluation of the antimicrobial activity of extracts and isolated compounds against human and plant pathogens	SACCHETTI G					X	X	X	X	X	X	X	
Determination of the safety profile and bioavailability of the isolated compounds	PELLATI F							X	X	X	X	X	

Milestone 5 Project management and coordination

ACTIVITY	ASSIGNED	I year	II year

	TO	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6
Project meetings	SACCHETTI G POLLASTRO F MERLI D PELLATI F	X	X	X	X	X	X	X	X	X	X	X	X
Mid-term report	SACCHETTI G						X						
Final report	SACCHETTI G											X	X

Milestone 6 Dissemination and technological transfer

ACTIVITY	ASSIGNED TO	I year						II year					
		BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6
NOrCa website construction and management, and social media dissemination	SACCHETTI G POLLASTRO F MERLI D PELLATI F		X		X		X		X		X		X
Mid-term stakeholder workshop	SACCHETTI G POLLASTRO F MERLI D PELLATI F						X						
Final event for the dissemination of NOrCa results, free public seminar for the community	SACCHETTI G POLLASTRO F MERLI D PELLATI F											X	X

8. Time schedule of the expenses

nº	Research Units	Expenses	I year						II year					

			BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6	BIM. 1	BIM. 2	BIM. 3	BIM. 4	BIM. 5	BIM. 6
1.	SACCHETTI Gianni	item A1	X	X	X	X	X	X	X	X	X	X	X	X
2.	SACCHETTI Gianni	item A2	X	X	X	X	X	X	X	X	X	X	X	X
3.	SACCHETTI Gianni	item B												
4.	SACCHETTI Gianni	item C												
5.	SACCHETTI Gianni	item D						X					X	X
6.	SACCHETTI Gianni	item E	X			X	X							
7.	SACCHETTI Gianni	item F						X					X	
8.	MERLI Daniele	item A1		X	X	X	X	X	X	X	X	X		
9.	MERLI Daniele	item A2												
10.	MERLI Daniele	item B												
11.	MERLI Daniele	item C												
12.	MERLI Daniele	item D			X			X					X	
13.	MERLI Daniele	item E		X		X			X		X			
14.	MERLI Daniele	item F						X					X	
15.	PELLATI Federica	item A1	X	X	X	X	X	X	X	X	X	X	X	
16.	PELLATI Federica	item A2												
17.	PELLATI Federica	item B												
18.	PELLATI Federica	item C												
19.	PELLATI Federica	item D		X						X				
20.	PELLATI Federica	item E		X						X				
21.	PELLATI Federica	item F						X					X	
22.	POLLASTRO Federica	item A1		X	X	X	X	X	X	X	X			
23.	POLLASTRO Federica	item A2												
24.	POLLASTRO Federica	item B		X										
25.	POLLASTRO Federica	item C												
26.	POLLASTRO Federica	item D		X					X					
27.	POLLASTRO Federica	item E		X					X					

28.	POLLASTRO Federica	item F						X						X

B.2

1. Scientific Curriculum of the Principal Investigator

- Researcher unique identifier: ORCID Id	0000-0002-6833-1477
- URL for web site:	http://docente.unife.it/gianni.sacchetti
Academic age (years from the beginning of scientific activity, i.e. years from first publication or from the beginning of PhD or Medical Specialisation School)	30
Previous positions	- from 2014 – to today: full professor in Pharmaceutical biology at the University of Ferrara (Italy) - from 2005 to 2014: associate professor in Pharmaceutical biology at the University of Ferrara - from 1999 to 2005: researcher in Pharmaceutical biology at the University of Ferrara - from 1995 to 1998: researcher fellowship (Federchimica-Basell-Polyolefins, now Lyondell-Basell) - Other positions within the University of Ferrara (UNIFE): - From 2005 to present: coordinator of the research unit “Biomass recovery and valorization” of the technopole lab. Terra&Acqua Tech. - From 2021 to present: Coordinator of the degree course in Pharmacy
Prizes and awards	CNR Best Researcher Award 2000 for activities in Sustainable production of biomolecules from agro-food wastes for industrial applications. The award was followed by a grant of CNR for a project entitled “Sustainable production of biomolecules from agro-food wastes for industrial applications. Extraction and characterization of secondary metabolites from plants by-products from agro-food value chain” coordinated as PI.
Visiting academic positions	2006: visiting professors to Universidad Politecnica Salesiana (Quito; Ecuador) (see teaching activities). The activities were both related to research and teaching. The research performed with Ecuadorian colleagues were related to extraction and phytochemical studies of Amazonian medicinal plants belonging to Lauraceae and Celastraceae family. Teaching activities were instead related to Pharmacognostic assays for authentication of crude drugs (2 ECTS).
Teaching activities and PhD supervision	DEGREE COURSE in Pharmacy; University of Bologna - 1999-2000: Pharmaceutical Botany (6 ECTS) DEGREE COURSE in Pharmacy; UNIFE - 1999-2017: Plant Biology (6 ECTS) - 1999-present: Pharmaceutical botany and pharmacognosy (formerly named Pharmacognosy and herbal products; 9 ECTS) DEGREE COURSE in Chemical and Pharmaceutical Technologies; UNIFE - 2000-2009: Plant Biology and Pharmacognosy (10 ECTS) Universidad Politecnica Salesiana, Quito – Ecuador (visiting professor) - 2006: Pharmacognostic assays for authentication of crude drugs (2 ECTS) DEGREE COURSE in Health Products: herbals, nutraceuticals, cosmetics; UNIFE - 2004-2010: Pharmacognosy and herbal products (9 ECTS) DEGREE COURSE in Biotechnology; UNIFE - 2008-present: Biotechnology of medicinal plants (6 ECTS) MASTER COURSE in Cosmetic Science and Technology; UNIFE

	- 2008-present: Properties and characterization of Phytocosmetic extracts (1 ECTS) PhD supervision:6 theses (tutor);more than 20 theses (reviewer)
Other work experience (e.g. consultancy if any)	None
- Administrative role and position responsibility	- Member of of the National Scientific Qualification (ASN) commission for the scientific area 05 / A1 - Botany (2016-2018). - Member of the directive committee of the Italian Botanical Society (2020-present) representing the Pharmaceutical biology sds (BIO/15). - Member of the joint commission of teachers and students for the degree course of Pharmacy of UNIFE (1999-2016) - Coordinator of the joint commissions of teachers and students for the degree courses of Pharmacy, Pharmaceutical Chemistry and Technology, Biology, Biotechnology and Chemistry of the Faculty of Medicine, Pharmacy and Prevention of UNIFE (2016-2021). - Coordinator of the degree course in Pharmacy of UNIFE (2021-present).
- Scientific organisations/Coordination of academic activities	- Scientific and research coordinator of the Pharmaceutical biology lab. (Dept. Life Sciences and Biotechnology, UNIFE); six personnel units (1 associate professor, 1 laboratory technician, 4 young researchers, working in an infrastructure characterized by 5 dedicated labs. - Member for UNIFE Technopole Terra&Acqua Tech of the Clust-ERs “Health” and “Agri-Food” of the Emilia Romagna Region, associations made up of SMEs, laboratories of the High Technology Network, research centers, health facilities and training institutions that share skills, ideas and resources to support the competitiveness of the Health and Agri-Food Industries of the Emilia Romagna Region. - Coordinator of the Research Unit 7 (RU7: “Biomass recovery and valorization”) within the Technopole lab. Terra&Acqua Tech. The activities of the RU7 are focused on the recovery and sustainable valorization of biomass through the application of green extraction strategies, obtaining extracts and biomolecules with industrial applications. - Member for UNIFE Technopole Terra&Acqua Tech of the Operative Group for Innovation (GOI) in agriculture named “Bio-economy-repellants” (applicative areas: plant productions; production area: fruits and vegetable chain, wine and olive production chain) (Emilia Romagna Region). - Member for UNIFE of the national Cluster Spring (Italian Cluster of Green Chemistry) which mainly targets the use of renewable resources as raw materials, the creation of biorefineries integrated with the local areas, and the development of new bio-based products. - Member of the Operative Board of the Cosmetology Center of the University of Ferrara which has the main objective of offering research support to external stakeholders in the cosmetics and cosmeceuticals fields.
Editorial activity	- Member of the Editorial board of Plant Biosystems (subject editor for the Pharmaceutical botany section) - Guest editor of the special issue of the journal “Molecules” entitled “From Ethnobotany to Eco-pharmacognosy: Chemical Characterization and Bioactivity Evaluation of Medicinal and Aromatic Plants”
Membership of scientific societies	- Member of the Italian Botanical Society - Member of the directive board of the Italian Botanical Society - Member of the Italian Phytochemical Society
Funding (current and past)	

Anno	Project title	Person months	Funding organisation

2020	Sistemi innovativi di gestione delle produzioni maidicole da granella finalizzate alla riduzione delle micotossine nella filiera lattiero casearia legata alle produzioni DOP (MIlk_COntrollo) (role: RU Coordinator)	0,5	Emilia Romagna Region (PSR Program; Fondo Europeo Agricolo per lo Sviluppo Rurale)	
2017	Biomolecole dalla valorizzazione integrata di sottoprodotti agroalimentari per applicazioni sostenibili con finalità Fitosanitarie, Alimentari, ed Energetiche (BIOFACE) (role: PI)	0,3	Emilia Romagna Region (PSR Program; Fondo Europeo Agricolo per lo Sviluppo Rurale)	
2016	Valorizzazione sostenibile degli scarti della filiera vitivinicola per l'industria chimica e salutistica (VALSOVIT) (role: RU Coordinator)	6	Emilia Romagna Region (POR-FESR 2014-2020 program)	
2013	Natural compounds for pests control and improving crop production of Ferrara territory (role: PI)	2	Chamber of Commerce project of Ferrara (IT)	
2013	Chemical and bioactivity profile of agro-food wastes to achieve biomolecules for Citrus spp. pests control (role: RU Coordinator)	1	Calabria region (PSR program)	
2010	Management and crop innovations for high-quality pear production (www.ager.innovapero.it). Coordinator of the task: Secondary metabolites extractions and characterization from plants by-products and checking their bioactivity for possible uses as natural agro-pharmaceuticals	n.a.	AGER consortium project: http://www.progettoager.it	
	Chemical characterization (fingerprinting) and bioactivity profile (quality, safety, efficacy) of Ayurvedic crude drugs of the			

2009	herbal market. Definition of innovative formulations (artificial phytocomplexes) and bioactive compounds from chemical synthesis and/or biotransformations of phytocomplexes, fractions and isolated compounds from ayurvedic crude drugs. (role: PI)	3	MUR (PRIN 2009-2009LR9YLF)
2002	Mediterranean medicinal plants. Secondary metabolites profile and biological activities of plant species from Calabria and Sardinia regions (role: RU Coordinator)	n.a.	Calabria and Sardegna Regions (POR-PON programs)
2000	Sustainable production of biomolecules from agro-food wastes for industrial applications. Extraction and characterization of secondary metabolites from plants by-products from agro-food value chain (role: PI)	n.a.	CNR (IT)

Significant career breaks	None
- H-Index (in Scopus):	32
- Total number of publications in peer-reviewed journals	117
- Total IF	445,023
- n. and total IF of publications where the candidate is first author or equivalent (for the disciplines where the position in the list of authors correspond to the role in the work presented)	14 publications as first author (12%); total IF=39,445 (9%)
- N. and total IF of the publications where the candidate is last or corresponding author (for the disciplines where the position in the list of	36 publications as last author or corresponding author (31%); Total IF=144,011 (32%)

authors correspond to the role in the work presented)	

2. Scientific Curriculum of the associated PIs

1. POLLASTRO Federica

- Researcher unique identifier: ORCID Id	orcid.org/0000-0002
- URL for web site:	https://upobook.uniupo.it/federica.pollastro
Academic age (years from the beginning of scientific activity, i.e. years from first publication or from the beginning of PhD or Medical Specialisation School)	16
Previous positions	- from 2022 – to today: Associate Professor of Pharmaceutical Botany, DSF-UNIUPO, Italy - 2019-2022: Senior Researcher RTDB, DSF-UPO, Novara, Italy. - 2014-2019: Fixed term researcher (RTDA) - 2008-2014: Postdoctoral fellow DSF-UNIUPO, Italy - 2008 - PhD in Science of Bioactive Substances, DSF-UNIUPO, Italy
Prizes and awards	- 2005: "Italo Taddei" award from the Società Italiana di Fitoterapia - 2007: "New trends in phytochemistry" award from the Phytochemical Society of europe - 2017: FFABR - Ricercatori 2017
Visiting academic positions	None
Teaching activities and PhD supervision	- 2015- to today Phytochemistry and Laboratory of Herbal Preparations (Fitochimica e laboratorio di preparazioni erboristiche) (8 ECTS) Medicinal Plants (Piante Medicinali) (4 ECTS) - 2022-today Biothecnology of Medicinal Plants (2 ECTS) - 2019-today The Pillar of Drug Discovery and Development (12 h) and Strategies for the Synthesis or Extraction of Novel Compounds and Formulation (30 h) in the international Emotion Master at the DFS-UNIUPO. - 2020-today Natural product in Drug Discovery for the PhD program “Drug Discovery” and “Drug Innovation”, DSF-UNIUPO - 2021-today: Supervisor of the PhD student Dott. Stefano Salamone in the PhD program “Drug Innovation” - 2022-today: member of Collegio Docento for the PhD program “Drug Innovation”, DSF-UNIUPO.
Other work experience (e.g. consultancy if any)	- 2018-2022 C:EO of PlantaChem Srls spin off - 2012.2014: Consultant of the So.Re.Mo. (Ferrero group) in Monaco Montecarlo
- Administrative role and position responsibility	- Member of the “Commissione Orientamento”, DSF-UNIUPO (2021-today) - Member of “Gruppo del Riesame del Corso di Studi in Farmacia”, DSF-UNIUPO (2022-to today).
- Scientific organisations/Coordination of academic activities	- 2022 member of the organizing committee of the international congress RDPA – September 2023. - 2022 member of the organizing committee of the international scientific conference on Plant Biodiversity and Sustainability, October, 13th-14th 2022. - 2022 member of the organizing committee of the international congress of the Italian Society of Phytochemistry jointly with the ICEMAP, June 22th-24th, Bari, Italy - 2021 member of the organizing committee of the congress of the Italian Society of Phytochemistry “Scuola Italo Taddei”, May, 26th-28th, 2021. - 2018-today member of the executive board of the Phytochemistry Italian Society. - 2017- Scientific Responsible of the workshop “Cannabis sativa: il potere medicinale spiegato

	con la moderna drug discovery" during the "Medical Cannabis Mediterranean Conference" – Congressi della Fiera del Levante, September 14th, 2017
Editorial activity	- Member of the Editorial board of Fitoterapia - Guest editor of the special issue of the journal "Plants" 2021-2022 - Guest Author of the peer-reviewed international journal Current Medicinal Chemistry
Membership of scientific societies	- Member of the Phytochemistry Italian Society (SIF).

Funding (current and past)

Anno	Project title	Person months	Funding organisation
2020	PRIME (Processi e prodotti innovativi di chimica verde)	12	P.O.R. FESR 2014/2021 Assse I - Azione I.1b.2.2
2017	COFIN - 2017WN73PL	8	COFIN - 2017WN73PL
2013	TriForC - european project	24	EU-FP7

Significant career breaks	None
- H-Index (in Scopus):	27
- Total number of publications in peer-reviewed journals	82
- Total IF	353
- n. and total IF of publications where the candidate is first author or equivalent (for the disciplines where the position in the list of authors correspond to the role in the work presented)	n. 7, IF: 23
- N. and total IF of the publications where the candidate is last or corresponding author (for the disciplines where the position in the list of authors correspond to the role in the work presented)	n. 6, IF: 21

2. MERLI Daniele

- Researcher unique identifier: ORCID Id	0000-0003-3975-0127
- URL for web site:	http://chimica.unipv.eu/site/home/persone/scheda700003435.html
Academic age (years from the beginning of scientific activity, i.e. years from first publication or from the beginning of PhD or Medical Specialisation School)	17
Previous positions	- from 2018 – to today: Associate Professor of Analytical Chemistry, Department of Chemistry, University of Pavia, Italy - from 2015 to 2018: Senior Researcher (RTDB), Department of Chemistry, University of Pavia, Italy - from 2010 to 2013: Fixed Term Researcher (RTDA) at Department of Chemistry, University of Pavia, Italy - 2007 – 2009 / 2013-2015 Post-doc researcher University of Pavia
Prizes and awards	-
Visiting academic positions	-
Teaching activities and PhD supervision	Degree course in Chemistry; University of Pavia -2020- to today Advanced Analytical Chemistry (Chimica Analitica III) (6 ECTS) -2019 – to today Forensic Chemistry (6 ECTS) -2011– to today Electroanalytical Chemistry (6 ECTS) -2011– to today Food Chemistry and Analysis for the Ph D program “Chemical and Pharmaceutical Sciences and Industrial innovation” at Università di Pavia (6 ECTS) -2019 invited lecture by Collegio Borromeo. Conference title: “Criminalistica: la gaia scienza” -2015 invited lecture by Collegio Ghislieri. Conference title: “From alchemy to chemistry”. Master course in Forensic Science- Manager: Prof Simonetta Lambiase - UNIPV -2019-present: Forensic Chemistry - 2019: member of the commission for the attribution of the Ph D degree in “Chem. Pharm. Sci. and Biotechnology”, at Università di Camerino- Manager Prof . Alessandro Palmieri - 2020 – to today: member of the Collegio Docenti of the Ph.D. in Chem. Pharm. Sci. - UNIPV
Other work experience (e.g. consultancy if any)	- Technical expert and auxiliary of the technical expert in various legal proceeding (as an auxiliary expert with Prof Luca Morini (UNIPV), prof Alberto Brandone (UNIPV) and Prof Silvia Visonà (UNIPV)). - 2020 - 2021 president of the Graduation Examination at IST.TECN.IND. G. CARDANO – PAVIA - Consultancy contract with the company RSE SPA (Milan) - Topic: Recettori sintetici di tipo polimerico a stampo molecolare (MIPs): analisi teorica e sperimentale della risposta del MIP in forma di film sottile e in micro-bulk per la messa a punto di sensori ottici per analisi di sottoprodotti di degradazione del sistema isolante carta-estere naturale di trasformatori"
- Administrative role and position responsibility	- Member of the joint commissions of teachers and students for the degree courses of Chemistry of UNIPV (2020-to today). - Member of the commission of “Biblioteca delle Scienze” of UNIPV (2020-to today).
- Scientific organisations/Coordination of academic activities	- Scientific and research coordinator of the Forensic and Electroanalytical Chemistry lab. (Dept. Chemisty, UNIPV) - Member of INFN (Istituto Nazionale di Fisica Nucleare) section of Milano Bicocca (MILANO, 2020 – to today). - 2013 member of the organizing committee of the annual congress of the Divisione di Elettrochimica of Società Chimica Italiana “GEI 2013- Giornate dell’Elettrochimica Italiana”, Pavia,

	22-26 settembre 2013 - Co-organizer of the International Winter School on Origins of Life - WISOL 23- The future of chemistry and biology towards the origins of life - Pavia, January 16th - 19th, 2023
Editorial activity	- from 2021 Member of the Editorial board of Talanta Open and Chemosensors -2021: Guest editor of the special issue of the journal "Talanta Open" entitled "Chemistry and Crime" – 2022: Guest editor of the special issue of the journal "Chemosensors" entitled "Biomimetic and Chemical Sensors Based on Molecularly Imprinted Polymer (MIP)" – 2022/2023
Membership of scientific societies	- Member of INFN (Istituto Nazionale di Fisica Nucleare) section of Milano Bicocca (MILANO, 2020 – to today).

Funding (current and past)

Anno	Project title	Person months	Funding organisation
2017	PRIN 2017, 2017KKP5ZR, MOSCATo, national coordinator: prof Carlo Lamberti.	2	MIUR
2009	Prin 2009, "Development and characterization of modified electrode surfaces" national coordinator Prof. Renato Seeber	3	MIUR
2009	Fondazione Cariplo: project 2009-2440: Development and safety assessment of nanostructured compounds applicable to boron neutron capture therapy. Principal investigator: Prof Cesare Balduini.	2	Fondazione Cariplo

Significant career breaks	-
- H-Index (in Scopus):	23
- Total number of publications in peer-reviewed journals	91
- Total IF	427
- n. and total IF of publications where the candidate is first author or equivalent (for the	

disciplines where the position in the list of authors correspond to the role in the work presented)	n° 21: IF: 86
- N. and total IF of the publications where the candidate is last or corresponding author (for the disciplines where the position in the list of authors correspond to the role in the work presented)	n°23 : IF: 101

3. PELLATI Federica

- Researcher unique identifier: ORCID Id	0000-0002-9822-6862
- URL for web site:	http://personale.unimore.it/rubrica/dettaglio/fpellati
Academic age (years from the beginning of scientific activity, i.e. years from first publication or from the beginning of PhD or Medical Specialisation School)	20
Previous positions	- 2020-present: Principal Investigator of the research group “Natural Products for Medicinal Chemistry”, Department of Life Sciences, Universiy of Modena and Reggio Emilia (UNIMORE). - 2019-present: Associate Professor in Medicinal Chemistry, Department of Life Sciences, UNIMORE. - 2012-2019: Assistant Professor in Medicinal Chemistry, Department of Life Sciences, UNIMORE. - 2006-2012: Assistant Professor in Medicinal Chemistry, Department of Pharmaceutical Sciences, UNIMORE. - 2006: Post-doctoral fellowship in Medicinal Chemistry, Department of Pharmaceutical Sciences, UNIMORE. - 2004-2005: Post-doctoral fellowship in Medicinal Chemistry, Department of Pharmaceutical Sciences, UNIMORE. - 2004: Doctoral degree (PhD) in Pharmaceutical Sciences, Department of Pharmaceutical Sciences, UNIMORE. - 2000: Graduate degree in Pharmaceutical Chemistry and Technology (cum laude), Faculty of Pharmacy, UNIMORE.
Prizes and awards	- 2022: Winner of the “ElSohly Award”, Cannabis Chemistry Subdivision, American Chemical Society (ACS) for the research “Scientific evidence on the role of Cannabis sativa L. and its non-psychoactive compounds against human chronic diseases”. - 2015: Recognized as a “Chemistry Ambassador” for promoting the value of chemists and chemistry to the community by the American Chemical Society (ACS). - 2014: Awarded by the Rector of the University of Modena and Reggio Emilia with a certificate of merit for having outstanding accomplishments in the ambit of national and international research. - 2013: Best poster communication award, authors Prencipe F.P et al., XIII Day of Chemistry of Emilia-Romagna Region, Bologna, Italy. - 2013: Winner of a participation grant of the Division of Agricultural and Food Chemistry of the American Chemical Society, Young Scientist Award Symposium, 246th ACS National Meeting & Exposition, Indianapolis, USA.
	- 2020: Invited lecturer from the Institute of Pharmacy and Pharmacognosy, University of

Visiting academic positions	Innsbruck, for a seminar entitled “New strategies for the extraction and analysis of bioactive compounds from Cannabis sativa L.”. - 2013: Invited lecturer from the Ecole de Pharmacie Genève-Lausanne, Université de Genève, for a seminar entitled “Advanced chromatographic techniques for metabolite fingerprinting of natural compounds with antioxidant and antiproliferative activity”. - 2009: Invited lecturer from the Doctoral School of Pharmacy of the CEU San Pablo University of Madrid for a seminar entitled “Recent developments in chromatographic methods for the analysis of phenethylamine alkaloids” (Erasmus Program). - 2009: Teaching activity on “Separation by high performance liquid chromatography” in the Course of “Analytical Techniques” (Prof. Coral Barbas), Bilingual Degree in Pharmacy, Faculty of Pharmacy, CEU San Pablo University of Madrid (Erasmus Program).
Teaching activities and PhD supervision	- 2021-present: Co-Responsible for the Course “Laboratory of Extraction and Synthesis of Drugs” (2 credits), section on Extraction Techniques, Master Degree in Medicinal Chemistry and Technology, UNIMORE. - 2020-present: Responsible for the Course “Medicinal and Toxicological Chemistry II” (11 credits), Master Degree in Pharmacy, UNIMORE. - 2015-2020: Responsible for the lab teaching activity for the Course “Laboratory of Extraction and Synthesis of Drugs” (4 credits) Master Degree in Medicinal Chemistry and Technology, UNIMORE. - 2015-present: Scientific Tutor and Co-Tutor of four PhD students, Doctoral School in Clinical and Experimental Medicine (CEM), UNIMORE. - 2009-2015: Scientific Tutor and Co-Tutor of three PhD students, Doctoral School in Science and Technologies for Health Products, UNIMORE. - 2008-2014: Responsible for the Course “Extraction Principles and Methodologies”, Degrees in Herbal Techniques, UNIMORE.
Other work experience (e.g. consultancy if any)	- 2022: Scientific Responsible for the research contract with Canax s.r.l entitled “Chemical characterization and study of the in vitro antiproliferative properties of Cannabis sativa L. extracts”. - 2014-2018: Co-Founder and member of the board of directors of the University spin-off "Nutrascience s.r.l".
- Administrative role and position responsibility	- 2021-present: Member of the Scientific Committee of the Master on Development, Manufacturing and Authorization of Biopharmaceuticals, UNIMORE. - 2020-present: Member of the Scientific Committee of the Summer School of Pharmaceutical Analysis (SSPA) of the Division of Medicinal Chemistry of the Italian Chemical Society. - 2014-2020: Member of the Executive Committee of the Italian Chemical Society (SCI)-regional section Emilia-Romagna. - 2014-present: International Relationships Delegate at the Department of Life Sciences, UNIMORE. - 2013-2014: Coordinator of International Relations at the Department of Life Sciences, UNIMORE. - 2013-present: Member of the Doctoral School Committee of the Doctoral School in Clinical and Experimental Medicine (CEM), UNIMORE. - 2011-2012: Coordinator of International Relations at the Faculty of Pharmacy of the University of Modena and Reggio Emilia, Italy. - 2007-2013: Member of the Doctoral School Committee of the Doctoral School in Science and Technologies for Health Products, UNIMORE.
- Scientific organisations/Coordination of academic activities	- 2022: Chair of the international symposium "Cannabinoids and their Role in Medicinal Chemistry", Division of Chemical Health and Safety, Spring 2023 ACS National Meeting & Exposition. - 2020-2021: Chair of the international congress on "Recent Developments in Pharmaceutical Analysis" (RDPA 2021), Department of Life Sciences, UNIMORE. - 2020: Member of the organizing committee of the international congress "10th World Congress on Chemistry and Medicinal Chemistry", Rome. - 2019: Member of the scientific committee of the international congress on "Recent Developments in Pharmaceutical Analysis" (RDPA 2019), University of Chieti-Pescara. - 2019: Member of the organizing committee of the international congress "9th World Congress on Chemistry and Medicinal Chemistry", Prague, Czech Republic. - 2017: Member of the scientific committee of the international congress on "Recent Developments in Pharmaceutical Analysis" (RDPA 2017), University of Bologna, Rimini. - 2016: Member of the organizing committee of the international congress "XXV Italo-Latin American Congress of Ethnomedicine" (SILAE 2016), Department of Life Sciences, UNIMORE. - 2014-present: Coordinator of inter-institutional Erasmus+ projects with Universidad San Pablo-

	CEU di Madrid, Univeridad de Salamanca, Universitat de Barcelona, Universidad San Jorge di Zaragoza, Catholic University of Leuven, Justus Liebig University of Giessen, Université de Genève, University of Pardubice, National and Kapodistrian University of Athens. - 2013-2014: Coordinator of the mobility program "Ciência sem Frontieras" at the Department of Life Sciences of UNIMORE, in collaboration with Brazil. - 2013: Member of the scientific and organizing committee of the international symposium "Instrumental Methods for the Analysis of Bioactive Molecules", Division of Agricultural and Food Chemistry, American Chemical Society (ACS), Fall 2013 ACS National Meeting & Exposition, Indianapolis, USA.
Editorial activity	- 2022-present: Member of the editorial board of Pharmaceuticals, ISSN 1424-8247, IF 5.215. - 2022-present: Member of the editorial board of Current Medicinal Chemistry, ISSN 0929-8673, IF 4.740. - 2021-2022: Co-Editor of the special issue “Selected papers from Recent Developments in Pharmaceutical Analysis 2021 (RDPA2021)”, Journal of Pharmaceutical and Biomedical Analysis, Elsevier, ISSN 0731-7085, IF 3.571. - 2021: Co-Editor of the special issue “Analytical issues related to cannabinoids”, Journal of Pharmaceutical and Biomedical Analysis, Elsevier, ISSN 0731-7085, IF 3.571. - 2020-present: Member of the editorial board of Antibiotics, MDPI, ISSN 2079-6382, IF 5.222. - 2019-present: Member of the editorial board of Cannabis and Cannabinoid Research, Mary Ann Liebert Inc., ISSN 2578-5125, IF 4.786. - 2019-present: Member of the editorial board of the International Journal of Molecular Sciences (Bioactives and Nutraceuticals section), MDPI, ISSN 1422-0067, IF 6.208. - 2019-present: Member of the editorial board of Antioxidants, MDPI, ISSN 2076-3921, IF 7.675. - 2019-present: Member of the editorial advisory board of Molecules (Natural Products Chemistry section), MDPI, ISSN 1420-3049, IF 4.927. - 2019-2020: Guest Editor of the special issue “Repositioning Natural Products in Drug Discovery” for Molecules (Medicinal Chemistry section), MDPI, ISSN 1420-3049, IF 4.927. - 2018-present: Member of the editorial board of the Journal of Pharmaceutical and Biomedical Analysis, Elsevier, ISSN 0731-7085, IF 3.571. - 2018-present: Collection Editor of the special issue “Phenolic Compounds from Plants: Chemistry, Analysis and Biological Activity” for Molecules, MDPI, ISSN 1420-3049, IF 4.927. - 2013-2014: Editor of the book “Instrumental Methods for the Analysis and Identification of Bioactive Molecules”, ACS Symposium Series, American Chemical Society, volume 1185, 2014, ISBN: 9780841229761, DOI: 10.1021/bk-2014-1185.
Membership of scientific societies	- 2010-present: Member of the American Chemical Society (ACS), Division of Agricultural and Food Chemistry and Division of Chemical and Safety (Cannabis Chemistry Subdivision). - 2009-present: Member of the Italian Chemical Society (SCI), Division of Medicinal Chemistry.

Anno	Project title	Person months	Funding organisation
2022	Secondary Proposer and WG2 Vice-Leader of the COST Action project “OneHealth drugs against parasitic vector borne diseases in Europe and beyond” (OC-2021-1-25163)	5	European Cooperation in Science and Technology

	2022	Participant to the project “Thymidylate synthase dimer disrupters induce DNA damage, halt cell growth and overcome drug resistance in colorectal cancer” (AIRC 25785)	15	Italian Association for Cancer Research (AIRC)
	2021	Scientific Responsible for the PhD project PON Research and Innovation 2014-2020 “Cannabis sativa L.: a green and sustainable paradigm of medicinal interest”	6	Italian Ministry of Education, University and Research (MIUR)
Funding (current and past)	2019	Co-Principal Investigator of the project “Novel analytical tools for the determination of cannabinoids in Cannabis sativa L. based products and biological fluids” (FAR2019)	12	University of Modena and Reggio Emilia (UNIMORE)
	2018	Participant to the project “Prunus avium L. cherries and other red fruits as new sources of neuroprotective compounds: a multidisciplinary study” (FAR2018)	8	University of Modena and Reggio Emilia (UNIMORE)
	2014	Participant to the project “Design and development of new agents for the treatment of parasitic diseases" (PRIN-2012) (201274BNKN_003)	8	Italian Ministry of Education, University and Research (MIUR)
	2013	Scientific Tutor of the research project “Polichol”	6	Emilia-Romagna Region
	2013	Scientific Tutor of the project “MACAB”- Methodologies for the analysis and characterization of balsamic vinegar	3	Consorzio Spinner of Bologna
		Participant to the project “Advances		

	2009	analytical methodologies in the research and development of drugs" (PRIN-2007) (20079SLZMC_004)	18	Italian Ministry of Education, University and Research (MIUR)	

Significant career breaks	2020: Italian Professorship Qualification (ASN 2018) as a Full Professor in Medicinal Chemistry (Area 03/D1-Medicinal, toxicological and nutraceutical-food chemistry and technologies).
- H-Index (in Scopus):	32
- Total number of publications in peer-reviewed journals	103
- Total IF	472,267
- n. and total IF of publications where the candidate is first author or equivalent (for the disciplines where the position in the list of authors correspond to the role in the work presented)	n. 25 and total IF 102,441
- N. and total IF of the publications where the candidate is last or corresponding author (for the disciplines where the position in the list of authors correspond to the role in the work presented)	n. 58 and total IF 257,748

3. Main Principal Investigator's scientific publications (Max. 20)

1. Abdi Bellau, Mohamed Lamin, Chiurato, Matteo Andrea, Maietti, Annalisa, Fantin, Giancarlo, Tedeschi, Paola, Marchetti, Nicola, Tacchini, Massimo, Sacchetti, Gianni, Guerrini, Alessandra (2022). Nutrients and Main Secondary Metabolites Characterizing Extracts and Essential Oil from Fruits of Ammodaucus leucotrichus Coss. & Dur. (Western Sahara). MOLECULES, vol. 27, p. 5013-1-5013-11, ISSN: 1420-3049, doi: 10.3390/molecules27155013 - **Articolo in rivista**
2. Burlini I., Grandini A., Tacchini M., Maresca I., Guerrini A., Sacchetti G. (2020). Different strategies to obtain corn (Zea mays L.) germ extracts with enhanced antioxidant properties. NATURAL PRODUCT COMMUNICATIONS, vol. 15, p. 1-9, ISSN: 1934-578X, doi: 10.1177/1934578X20903562 - **Articolo in rivista**
3. Guerrini, Alessandra, Burlini, Ilaria, Huerta Lorenzo, Belén, Grandini, Alessandro, Vertuani, Silvia, Tacchini, Massimo, Sacchetti, Gianni (2020). Antioxidant and antimicrobial extracts obtained from agricultural by-products: Strategies for a sustainable recovery and future perspectives. FOOD AND BIOPRODUCTS PROCESSING, vol. 124, p. 397-407, ISSN: 0960-3085, doi: 10.1016/j.fbp.2020.10.003 - **Articolo in rivista**
4. Ilaria Burlini, Gianni Sacchetti (2020). Secondary Bioactive Metabolites from Plant-Derived Food Byproducts

through Ecopharmacognostic Approaches: A Bound Phenolic Case Study. PLANTS, vol. 9, p. 1060-1-1060-19, ISSN: 2223-7747, doi: 10.3390/plants9091060 - **Articolo in rivista**

5. José L. Ballesteros, Massimo Tacchini, Antonella Spagnoletti, Alessandro Grandini, Guglielmo Paganetto, Luca Maria Neri, Arianna Marengo, Letizia Angiolella, Alessandra Guerrini, Gianni Sacchetti (2019). Rediscovering Medicinal Amazonian Aromatic Plants: Piper carpunya (Piperaceae) Essential Oil as Paradigmatic Study. EVIDENCE-BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE, vol. 2019, p. 6194640 -1-6194640 -10, ISSN: 1741-427X, doi: 10.1155/2019/6194640 - **Articolo in rivista**

6. Noriega P., Guerrini A., Sacchetti G., Grandini A., Ankuash E., Manfredini S. (2019). Chemical composition and biological activity of five essential oils from the Ecuadorian Amazon rain forest. MOLECULES, vol. 24, p. 1637-1-1637-12, ISSN: 1420-3049, doi: 10.3390/molecules24081637 - **Articolo in rivista**

7. Tacchini, Massimo, Burlini, Ilaria, Bernardi, Tatiana, De Risi, Carmela, Massi, Alessandro, Guerrini, Alessandra, Sacchetti, Gianni (2019). Chemical characterisation, antioxidant and antimicrobial screening for the revaluation of wine supply chain by-products oriented to circular economy. PLANT BIOSYSTEMS, vol. 153, p. 809-816, ISSN: 1126-3504, doi: 10.1080/11263504.2018.1549614 - **Articolo in rivista**

8. Tacchini, Massimo, Burlini, Ilaria, Maresca, Immacolata, Grandini, Alessandro, Bernardi, Tatiana, Guerrini, Alessandra, Lerin, Lindomar, Sacchetti, Gianni (2019). Polyphenols From Vitis vinifera Lambrusco By-Products (Leaves From Pruning): Extraction Parameters Evaluation Through Design of Experiment. NATURAL PRODUCT COMMUNICATIONS, vol. 14, p. 1-7, ISSN: 1934-578X, doi: 10.1177/1934578X19862906 - **Articolo in rivista**

9. Tatiana Bernardi, Olga Bortolini, Alessandro Massi, Gianni Sacchetti, Massimo Tacchini, Carmela De Risi (2019). Exploring the Synergy Between HPTLC and HPLC-DAD for the Investigation of Wine-Making By-Products. MOLECULES, vol. 24, p. 3416-1-3416-16, ISSN: 1420-3049, doi: 10.3390/molecules24193416 - **Articolo in rivista**

10. Tardugno, R., Spagnoletti, A., Grandini, A., Maresca, I., Sacchetti, G., Pellati, F., BENVENUTI, Stefano (2018). Chemical profile and biological activities of Cedrelopsis grevei H. Baillon bark essential oil. PLANT BIOSYSTEMS, vol. 152, p. 120-129, ISSN: 1126-3504, doi: 10.1080/11263504.2016.1255271 - **Articolo in rivista**

11. Tacchini, Massimo, Spagnoletti, Antonella, Brighenti, Virginia, Prencipe, Francesco Pio, Benvenuti, Stefania, Sacchetti, Gianni, Pellati, Federica (2017). A new method based on supercritical fluid extraction for polyacetylenes and polyenes from Echinacea pallida (Nutt.) Nutt. roots. JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, vol. 146, p. 1-6, ISSN: 0731-7085, doi: 10.1016/j.jpba.2017.07.053 - **Articolo in rivista**

12. Tommasi, Elena, Cravotto, Giancarlo, Galletti, Paola, Grillo, Giorgio, Mazzotti, Matilde, Sacchetti, Gianni, Samorì, Chiara, Tabasso, Silvia, Tacchini, Massimo, Tagliavini, Emilio (2017). Enhanced and Selective Lipid Extraction from the Microalga P. tricornutum by Dimethyl Carbonate and Supercritical CO2Using Deep Eutectic Solvents and Microwaves as Pretreatment. ACS SUSTAINABLE CHEMISTRY & ENGINEERING, vol. 5, p. 8316-8322, ISSN: 2168-0485, doi: 10.1021/acssuschemeng.7b02074 - **Articolo in rivista**

13. GUERRINI, Alessandra, SACCHETTI, Gianni, GRANDINI, Alessandro, SPAGNOLETTI, Antonella, Asanza, Mercedes, Scalvenzi, Laura (2016). Cytotoxic Effect and TLC Bioautography-Guided Approach to Detect Health Properties of Amazonian Hedyosmum sprucei Essential Oil. EVIDENCE-BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE, vol. 2016, p. 1638342-1-1638342-8, ISSN: 1741-427X, doi: 10.1155/2016/1638342 - **Articolo in rivista**

14. Rolli, Enrico, Marieschi, Matteo, MAIETTI, Silvia, GUERRINI, Alessandra, GRANDINI, Alessandro, SACCHETTI, Gianni, Bruni, Renato (2016). Phytotoxic Effects and Phytochemical Fingerprinting of Hydrodistilled Oil, Enriched Fractions, and Isolated Compounds Obtained from Cryptocarya massoy (Oken) Kosterm. Bark. CHEMISTRY & BIODIVERSITY, vol. 13, p. 66-76, ISSN: 1612-1872, doi: 10.1002/cbdv.201500010 - **Articolo in rivista**

15. GUERRINI, Alessandra, ROSSI, Damiano, GRANDINI, Alessandro, L. Scalvenzi, P. F. Noriega Rivera, E. Andreotti, TACCHINI, Massimo, SPAGNOLETTI, Antonella, POPPI, Irene, MAIETTI, Silvia, SACCHETTI, Gianni (2014). Biological and chemo-diverse characterization of Amazonian (Ecuador) Citrus petitgrains. JOURNAL

OF APPLIED BOTANY AND FOOD QUALITY, vol. 87, p. 108-116, ISSN: 1613-9216, doi: 10.5073/JABFQ.2014.087.017 - **Articolo in rivista**

16. MAIETTI, Silvia, ROSSI, Damiano, GUERRINI, Alessandra, USELI, Chiara, C. Romagnoli, F. Poli, R. Bruni, SACCHETTI, Gianni (2013). A multivariate analysis approach to the study of chemical and functional properties of chemodiverse plant derivatives: lavender essential oils. FLAVOUR AND FRAGRANCE JOURNAL, vol. 28, p. 144-154, ISSN: 1099-1026, doi: 10.1002/ffj.3145 - **Articolo in rivista**

17. ROSSI, Damiano, GUERRINI, Alessandra, PAGANETTO, Guglielmo, BERNACCHIA, Giovanni, F. Conforti, G. Statti, MAIETTI, Silvia, POPPI, Irene, TACCHINI, Massimo, SACCHETTI, Gianni (2013). Croton lechleri Müll. Arg. (Euphorbiaceae) stem bark essential oil as possible mutagen-protective food ingredient against heterocyclic amines from cooked food. FOOD CHEMISTRY, vol. 139, p. 439-447, ISSN: 0308-8146, doi: 10.1016/j.foodchem.2013.01.076 - **Articolo in rivista**

18. BORGATTI, Monica, MANCINI, Irene, BIANCHI, Nicoletta, GUERRINI, Alessandra, LAMPRONTI, Ilaria, ROSSI, Damiano, SACCHETTI, Gianni, GAMBARI, Roberto (2011). Bergamot (Citrus bergamia Risso) fruit extracts and identified components alter expression of interleukin 8 gene in cystic fibrosis bronchial epithelial cell lines. BMC BIOCHEMISTRY, vol. 12, p. 15-1-15-12, ISSN: 1471-2091, doi: 10.1186/1471-2091-12-15 - **Articolo in rivista**

19. GUERRINI, Alessandra, ROSSI, Damiano, PAGANETTO, Guglielmo, M. TOGNOLINI, MUZZOLI, Mariavittoria, C. ROMAGNOLI, F. ANTOGNONI, VERTUANI, Silvia, MEDICI, Alessandro, BRUNI, Alessandro, USELI, Chiara, TAMBURINI...(2011). Chemical characterization (GC-MS and NMR fingerprinting) and bioactivities of South-African Pelargonium capitatum (L.) L'Herit. (Geraniaceae) essential oil. CHEMISTRY & BIODIVERSITY, vol. 8, p. 624-642, ISSN: 1612-1872, doi: 10.1002/cbdv.201000045 - **Articolo in rivista**

20. ROSSI, Damiano, GUERRINI, Alessandra, MAIETTI, Silvia, R. Bruni, PAGANETTO, Guglielmo, POLI, Ferruccio, SCALVENZI, Laura, RADICE, Matteo, SARO, Katia, SACCHETTI, Gianni (2011). Chemical fingerprinting and bioactivity of Amazonian Ecuador Croton lechleri Müll. Arg. (Euphorbiaceae) stem bark essential oil: a new functional food ingredient?. FOOD CHEMISTRY, vol. 126, p. 837-848, ISSN: 0308-8146, doi: 10.1016/j.foodchem.2010.11.042 - **Articolo in rivista**

4. Main scientific publications of the associated PIs (Max. 20, for each associated PI)

1. **POLLASTRO Federica**

1. Durante, Caterina, Anceschi, Lisa, Brighenti, Virginia, Caroli, Clarissa, Afezolli, Cindy, Marchetti, Andrea, Cocchi, Marina, Salamone, Stefano, Pollastro, Federica, Pellati, Federica (2022). Application of experimental design in HPLC method optimisation for the simultaneous determination of multiple bioactive cannabinoids. JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, vol. 221, ISSN: 0731-7085, doi: 10.1016/j.jpba.2022.115037 - **Articolo in rivista**
2. Salamone, Stefano, Waltl, Lorenz, Pompignan, Anna, Grassi, Gianpaolo, Chianese, Giuseppina, Koeberle, Andreas, Pollastro, Federica (2022). Phytochemical Characterization of Cannabis sativa L. Chemotype V Reveals Three New Dihydrophenanthrenoids That Favorably Reprogram Lipid Mediator Biosynthesis in Macrophages. PLANTS, vol. 11, ISSN: 2223-7747, doi: 10.3390/plants11162130 - **Articolo in rivista**
3. Pollastro F., Minassi A. (2021). Exploring the universe of natural products: Recent advances in synthesis, isolation and structural elucidation. PLANTS, vol. 10, 2368, ISSN: 2223-7747, doi: 10.3390/plants10112368 - **Articolo in rivista**
4. Salamone, Stefano, Appendino, Giovanni, Khalili, Adil, Pollastro, Federica, Munoz, Eduardo, Unciti-Broceta, Juan D (2021). Agathadiol, a labdane diterpenoid from juniper berries, is a positive allosteric modulator of CB1R. FITOTERAPIA, vol. 155, ISSN: 1873-6971, doi: 10.1016/j.fitote.2021.105059 - **Articolo in rivista**
5. Talmon M., Bosso L., Quaregna M., Lopatriello A., Rossi S., Gavioli D., Marotta P., Caprioglio D., Boldorini R., Miggiano R., Fresu L. G., Pollastro F. (2020). Anti-inflammatory Activity of Absinthin and Derivatives in Human Bronchoepithelial Cells. JOURNAL OF NATURAL PRODUCTS, vol. 83, p. 1740-1750-1750, ISSN: 0163-3864, doi: 10.1021/acs.jnatprod.9b00685 - **Articolo in rivista**
6. Talmon, Maria, Rossi, Silvia, Lim, Dmitry, Pollastro, Federica, Palattella, Gioele, Ruffinatti, Federico A, Marotta, Patrizia, Boldorini, Renzo, Genazzani, Armando A, Fresu, Luigia G (2019). Absinthin, an agonist of the bitter taste

receptor hTAS2R46, uncovers an ER-to-mitochondria Ca2+-shuttling event. THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 294, p. 12472-12482, ISSN: 0021-9258, doi: 10.1074/jbc.RA119.007763 - **Articolo in rivista**

7. Federica Pollastro, Diego Caprioglio, Danilo Del Prete, Federica Rogati, Alberto Minassi, Orazio Taglialatela-Scafati, Eduardo Munoz, Giovanni Appendino (2018). Cannabichromene. NATURAL PRODUCT COMMUNICATIONS, vol. 13, p. 1189-1194, ISSN: 1934-578X - **Articolo in rivista**
8. Federica Pollastro, Maria Talmon, Simone Gaeta, ROSSI, Silvia, Annalisa Lopatriello, Luigia Grazia Fresu (2018). An Artemisia-derived natural product-based fluorescent probe for the bitter taste receptor hTAS2R38. FITOTERAPIA, ISSN: 1971-551X, doi: 10.1016/j.fitote.2018.02.030 - **Articolo in rivista**
9. POLLASTRO, Federica, MINASSI, Alberto, FRESU, Luigia Grazia (2018). Cannabis phenolics and their bioactivities. CURRENT MEDICINAL CHEMISTRY, vol. 24, ISSN: 0929-8673, doi: 10.2174/0929867324666170810164636 - **Articolo in rivista**
10. Pollastro, Federica, Caprioglio, Diego, MAROTTA, Patrizia, Moriello, Aniello Schiano, De Petrocellis, Luciano, Taglialatela-Scafati, Orazio, Appendino, Giovanni (2018). Iodine-Promoted Aromatization of p-Menthane-Type Phytocannabinoids. JOURNAL OF NATURAL PRODUCTS, ISSN: 0163-3864, doi: 10.1021/acs.jnatprod.7b00946 - **Articolo in rivista**
11. MINASSI, Alberto, POLLASTRO, Federica, Chianese, G., CAPRIOGLIO, DIEGO, Taglialatela Scafati, O., APPENDINO, Giovanni Battista (2017). Carbonyl Activation in Electrophilic Polyene Cyclizations: A Toolboxfor the Design of Isoprenoid Libraries. ANGEWANDTE CHEMIE, vol. 56, p. 7935-7938, ISSN: 1521-3773, doi: 10.1002/anie.201703455 - **Articolo in rivista**
12. Pollastro, Federica, De Petrocellis, Luciano, Schiano-Moriello, Aniello, Chianese, Giuseppina, Heyman, Heino, Appendino, Giovanni, Taglialatela-Scafati, Orazio (2017). Amorfrutin-type phytocannabinoids from Helichrysum umbraculigerum. FITOTERAPIA, vol. 123, p. 13-17, ISSN: 1971-551X, doi: 10.1016/j.fitote.2017.09.010 - **Articolo in rivista**
13. DEL PRETE, DANILO, Millán, E, POLLASTRO, Federica, Chianese, G, Luciano, P, Collado, Ja, Munoz, E, APPENDINO, Giovanni Battista, Taglialatela Scafati, O. (2016). Turmeric Sesquiterpenoids: Expeditious Resolution, Comparative Bioactivity, and a New Bicyclic Turmeronoid. JOURNAL OF NATURAL PRODUCTS, vol. 79, p. 267-273, ISSN: 1520-6025, doi: 10.1021/acs.jnatprod.5b00637. - **Articolo in rivista**
14. POLLASTRO, Federica, Golin, S, Chianese, G, Putra, My, Moriello, As, De Petrocellis, L, Garcia, V, Munoz, E, Taglialatela Scafati, O, APPENDINO, Giovanni Battista (2016). Neuroactive and Anti-inflammatory Frankincense Cembranes: A
Structure−Activity Study. JOURNAL OF NATURAL PRODUCTS, vol. 79, p. 1762-1768, ISSN: 1520-6025, doi: 10.1021/acs.jnatprod.6b00141 - **Articolo in rivista**
15. APPENDINO, Giovanni Battista, MINASSI, Alberto, Collado, Juan A., POLLASTRO, Federica, Chianese, Giuseppina, Taglialatela Scafati, Orazio, Ayyari, Mehdi, Garcia, Victor, Munoz, Eduardo (2015). The Thia-Michael Reactivity of Zerumbone and Related Cross-Conjugated Dienones: Disentangling Stoichiometry, Regiochemistry, and Addition Mode with an NMR-Spectroscopy-Based Cysteamine Assay. EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, p. 3721-3726, ISSN: 1099-0690 - **Articolo in rivista**
16. Taglialatela Scafati, O., POLLASTRO, Federica, Chianese, G, MINASSI, Alberto, Gibbons, S., Arunotayanun, W., Mabebie, B., Ballero, M., APPENDINO, Giovanni Battista (2013). Antimicrobial phenolics and unusual glycerides from Helichrysum italicum subsp. microphyllum. JOURNAL OF NATURAL PRODUCTS, vol. 76, p. 346-353, ISSN: 0163-3864 - **Articolo in rivista**
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5. Main staff involved (max 10 professors/researchers for each research unit, in addition to the PI or associated PIs), highlighting the expected time commitment

List of the Research Units

Unit 1 - SACCHETTI Gianni

Personnel of the research unit

nº	Surname Name	Qualification	University/ Research Institution	e-mail address	Months/person expected
1.	SACCHETTI Gianni	Professore Ordinario (L. 240/10)	Università degli Studi di FERRARA	scg@unife.it	2,4
2.	TACCHINI Massimo	Ricercatore a t.d. - t.pieno (art. 24 c.3-b L. 240/10)	Università degli Studi di FERRARA	tccmsm@unife.it	2,5

Unit 2 - POLLASTRO Federica

Personnel of the research unit

nº	Surname Name	Qualification	University/ Research Institution	e-mail address	Months/person expected
1.	POLLASTRO Federica	Professore Associato (L. 240/10)	Università degli Studi del PIEMONTE ORIENTALE "Amedeo Avogadro"-Vercelli	federica.pollastro@uniupo.it	6,0

Unit 3 - MERLI Daniele

Personnel of the research unit

nº	Surname Name	Qualification	University/ Research Institution	e-mail address	Months/person expected
1.	MERLI Daniele	Professore Associato (L. 240/10)	Università degli Studi di PAVIA	daniele.merli@unipv.it	2,5
2.	BONANNI Alessandra	Professore Associato confermato	Università degli Studi di PAVIA	alessandra.bonanni@gmail.com	2,5
3.	PROFUMO Antonella	Professore Ordinario	Università degli Studi di PAVIA	antonella.profumo@unipv.it	2,0

Unit 4 - PELLATI Federica

Personnel of the research unit

nº	Surname Name	Qualification	University/ Research Institution	e-mail address	Months/person expected
1.	PELLATI Federica	Professore Associato (L. 240/10)	Università degli Studi di MODENA e REGGIO EMILIA	federica.pellati@unimore.it	3,0
2.	TAGLIAZUCCHI Davide	Professore Associato (L. 240/10)	Università degli Studi di MODENA e REGGIO EMILIA	davide.tagliazucchi@unimore.it	2,0
3.	BIAGINI Giuseppe	Professore Ordinario (L. 240/10)	Università degli Studi di MODENA e REGGIO EMILIA	gbiagini@unimore.it	1,0
4.	CORSI Lorenzo	Ricercatore confermato	Università degli Studi di MODENA e REGGIO EMILIA	corsi.lorenzo@unimore.it	1,0

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6. Information on the new contracts for personnel to be specifically recruited

nº	Associated or principal investigator	Number of expected research contracts	Number of expected PhD scholarships	Overall expected time commitment (months)
1.	SACCHETTI Gianni	0	1	24
2.	POLLASTRO Federica	0	0	0
3.	MERLI Daniele	0	0	0
4.	PELLATI Federica	0	0	0
	Total	**0**	**1**	**24**

7. PI "Do No Significant Harm (DNSH)" declaration, in compliance with article n. 17, EU Regulation 852/2020. (upload PDF)

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