ATAS DO

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I ENCONTRO DE INVESTIGAÇÃO DA ESS | P. PORTO

Mostra Científica Interna

Organizadores
Cristina Prudêncio
Nuno Rocha
Manuela Vieira da Silva

P.PORTO ESCOLA SUPERIOR DE SAÚDE

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Coleção
I Encontro de Investigação da Escola Superior de Saúde do Politécnico do Porto
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ATAS DO I ENCONTRO DE INVESTIGAÇÃO DA

Escola Superior de Saúde

DO POLITÉCNICO DO PORTO

COMUNICAÇÕES

	Horário	Autores	Tipo
A small couple against the big three (Two4Three)	15h10	Ricardo Ferraz, Cátia Teixeira, Cristina Prudêncio e Mónica Vieira	Projeto
Cianobactérias Marinhas isoladas da costa Portuguesa como fonte de compostos bioativos: citotoxicidade em células tumorais e normais	15h20	Rosário Martins, Margarida Costa, Pedo Leão, João Costa Rodrigues, Maria Helena Fernandes, Mónica Garcia, Piedade Barros, Sara Freitas, Ralph Urbatzka, Valentina Domingues, Fátima Nogueira, Vítor Vasconcelos	Projeto
SMASK - Smart Mask with colorimetric biossensor for SARS-CoV-2 contamination and humidity	15h30	Mónica Vieira, Miguel Costa, Ricardo Ferraz, Elsa Parente, Cristina Prudêncio	Projeto
Imagem corporal durante o período de confinamento devido à pandemia de COVID-19: um estudo transcultural	15h40	Artemisa Rocha Dores	Prémio
Prevenção das infeções respiratórias em crianças até aos 3 anos que frequentam infantário - projeto de intervenção comunitária	15h50	Ana Silva Alexandrino, Rita Santos, Cristina Melo, David Tomé, Natália Oliveira	Linha apoiada por publicações
ForPharmacy - farmácia do futuro como um ecossistema plug-and-play	16h00	Artemisa Rocha Dores, Maria Castro, Equipa ForPharmacy e António Marques	Projeto
Safe Health Elderly Monitoring (SAFHE): biological and environmental signs monitoring to enhance older adults health	16h10	Andreia S.P. Sousa, Rubim Santos, Andreia Noites, Rui Macedo, Juliana Santos Moreira, José Félix e SAFHE team	Projeto
Gestão de prevenção dos riscos profissionais em PMEs	16h20	Matilde Rodrigues e equipa RISKsME	Linha apoiada por publicações
Mad@Work - mental wellbeing management and productivity boosting in the workplace	16h30	Nuno Rocha, Matilde Rodrigues e equipa Mad@Work	Projeto
SmartHealth: artificial intelligence for lifelong personalized health care	17h00	Rubim Santos, Andreia Sousa, José Félix, Juliana Moreira, Ricardo Ferreira e equipa SmartHealth	Projeto
Family Caregiver Support - strategies and tools to promote caregiver mental and emotional health	17h10	Regina A. Silva, Sílvia Fernandes, Paula Portugal e equipa FCS	Projeto
TECH: Technology, Environment, Creativity and Health	17h20	Andreia Sousa, Ruim Santos, José Félix, Juliana Moreira, Ricardo Ferreira e equipa SmartHealth	Projeto
Environmental and food toxicology: the impact of contaminants in our health	17h30	Edgar Pinto	Linha apoiada por publicações
Applied research on environmental and occupational health in hospital context	17h40	Carlos Carvalhais, Ana Xavier, Manuela V. da Silva e Joana Santos	Linha apoiada por publicações
A avaliação multidomínio da eficácia de programas de reabilitação neurocognitiva suportados nas novas tecnologias digitais	18h00	Joana Pinto, Andreia Geraldo, Artemisa Rocha Dores, Bruno Peixoto, Alexandre Castro-Caldas e Fernando Barbosa	Linha apoiada por publicações
Inter-active living for mental health	18h10	António Marques e Raquel Simões de Almeida	Projeto
Effects of microcystin and cylindrospermopsin on the quality and safety of crop plants: their relevance for agriculture and public health	18h20	Marisa Freitas, Alexandre Campos, Joana Machado, Joana Azevedo, Sébastien Planchon, Jenny Renaut, Edgar Pinto, Aldo Barreiro, Dany Gutiérrez-Praena, Maria Llana-Ruiz-Cabello, Angeles Jos, Ana Cameán, Vítor Vasconcelos	Linha apoiada por publicações

POSTERS

	Autores	Tipo
Functional analysis of multiple resistance presented by the yeast debaryomyces hansenii to floconazole, 5-fluorocytosine and amphotericine B	Cristina Prudêncio, Filipe Sansonetty, Maria João Sousa, Manuela Côrte-Real, Cecília Leão	Prémio
Projeto ABC - "Assisting Better Communication": um triénio de atividades ao serviço da terapia da fala	André Araújo, Maria João Gonçalves, Brígida Patrício, Paula Cristina Faria	Projeto
Love.Dist@ance: ensino à distância como forma de equidade no acesso ao ensino superior. resultados preliminares de um projeto em curso	Ângelo Jesus, André Araújo, Maria João Gonçalves	Projeto
Neurodevelopmental correlates of implicit-explicit learning mechanisms in children with specific language impairment: evidence from event-related brain potentials	Ana Paula Soares, Francisco-Javier Gutiérrez-Domínguez, Margarida Vasconcelos, Helena M. Oliveira, David Tomé, Marisa Lousada, Luis Jiménez	Projeto
PEPALHEIRA: revestimentos edíveis ativos baseados nas proteínas do soro do leite e PEPtidos antimicrobianos seus derivados para a indústria da ALHEIRA	Cátia Teixeira, Ricardo Ferraz, Cristina Prudêncio	Projeto
Treino da cognição social de pessoas com doença mental grave	Nuno Rocha e Carlos Campos	Linha apoiada por publicações
Estudos das comunicações celulares que regulam o metabolismo ósseo em contexto fisiológico e neoplástico	João Costa-Rodrigues	Linha apoiada por publicações
Fragilidade multidimensional em pessoas idosas	Tiago Coelho	Linha apoiada por publicações
Projeto NASYTHOR - novos compostos naturais e sintéticos para o tratamento de tumores hormono-resistentes	Filipa Quintela Vieira, Agostinho Cruz, Ana Isabel Oliveira, Cláudia Pinho, Cristina Prudêncio, Mónica Vieira, Piedade Barros, Ricardo Ferraz, Rosário Martins, equipa NASYTHOR e Regina Augusta Silva	Projeto
Projeto SMART PATIENTS - capacitação dos cidadãos para a gestão da sua própria saúde	Sílvia Fernandes, Ângelo Jesus, Brígida Patrício, Cristina Melo, Diana Tavares e equipa Smart Patients e Regina A. Silva	Projeto
Novas abordagens terapêuticas baseadas em líquidos iónicos	Ricardo Ferraz, Cátia Teixeira, Cristina Prudêncio, Dulce Teixeira e Mónica Vieira	Linha apoiada por publicações
Effects of noise frequency on performance and well-being	Jorge Sousa, Raquel Monteiro, David Tomé, Matilde A. Rodrigues	Prémio
IntelWheels - cadeira de rodas inteligente com interface multimodal flexível	Brígida Mónica Faria e Rui Pimenta	Projeto
Biomolecules in the relationship of cancer and obesity	Joana Almeida, Pedro Coelho, Cristina Prudêncio, Mónica Vieira, Rúben Fernandes, Magda Fonseca, Raquel Soares, Liliana Silva, Isabel Faria, Armanda Monteiro, Gabriela Pinto, V. Cea, M. Galesio, J.P. Noronha, M.S. Diniz, C. Sala	Linha apoiada por publicações
Therapy 2.0 - counselling and therapeutic interactions with digital natives	Regina Silva, Artemisa Rocha Dores e equipa Therapy 2.0	Projeto
FATTYMESS: fat diet-induced obesity in melanoma metastasis	CORREIA J., COSTA R., PRUDÊNCIO C., SOARES R., COELHO P.	Projeto
Desenvolvimento, avaliação e quantificação de biomoléculas	Mónica Vieira, Cristina Prudêncio, Ricardo Ferraz, Dulce Teixeira	Linha apoiada por publicações
Resistance to antimicrobial agents by different microorganisms	Cristina Prudêncio, Mónica Vieira, Rúben Fernandes, Ricardo Ferraz e Paula Amador	Linha apoiada por publicações

ÍNDICE

NOTA INTRODUTÓRIA

A Escola Superior de Saúde do Instituto Politécnico do Porto completou 40 anos no dia 23 de setembro de 2020. Ao longo do tempo temos assistido a um crescimento assinalável na produção científica e na captação de financiamento. O momento é oportuno para conhecer a atividade científica da Escola, sobretudo tendo em mente os desafios e oportunidades existentes. Pretendemos criar novas formas de cooperação entre os nossos investigadores e sinergias internas para futuras candidaturas.

No dia 22 de setembro, com a conclusão das celebrações dos 40 anos da Escola, e na transição para os próximos 40 anos, realizou-se uma mostra científica interna, com o objetivo de apresentar a atividade produzida ao longo destes anos. A nossa *faculty* foi convidada a associar-se a este momento, submetendo propostas para apresentações de comunicações orais e posters, com o objetivo de expor e explicar as áreas e/ou linhas de investigação mais relevantes dos investigadores ao longo dos anos, com afiliação obrigatória à ESS/ESTSP. As apresentações foram organizadas numa das seguintes formas:

a. Projeto de investigação com financiamento resultante de concurso competitivo, concluído ou em curso.

b. Tema/linha de investigação sustentada em 5 ou mais artigos publicados em revistas indexadas na Web of Science Core Collection com Fator de Impacto,

desde que o conjunto de artigos apresentasse coerência num tema específico.

c. Investigação que tivesse recebido prémio em congresso europeu ou mundial.

Este livro traduz um pouco da investigação que foi sendo produzida o longo dos anos, sendo apresentados os textos completos de algumas das apresentações orais e pósteres do **I Encontro de Investigação da Escola Superior de Saúde do Politécnico do Porto**, designado de Mostra Científica Interna. Trata-se de uma iniciativa que pretendemos replicar, com diferentes enfases, nos próximos anos.

É notável o nosso progresso e esforço. Os primeiros registos que temos de publicações realizadas pelos nossos professores ocorreram apenas vinte anos depois da fundação da nossa Escola. Antes não há qualquer registo significativo de trabalhos de investigação. Desde então, muito mudou. Fomos capazes de fazer mais investigação com impacto, o que se traduz num número significativamente maior de publicações e num aumento assinalável de captação de financiamento para projetos. Esta evolução é para nós crucial, uma vez que sabemos que a investigação, a inovação e o desenvolvimento são um pilar fundamental da afirmação de uma área de saber e de uma Instituição do Ensino Superior. Ao fim de 40 anos estamos sem dúvida de parabéns. Os próximos anos são de grande responsabilidade. Vamos ao trabalho!

UM PEQUENO

PAR *CONTRA UM* GRANDE TRIO

Autores: Ricardo Ferraz[1,2], Paula Gomes[2], Cátia Teixeira[1,2], Cristina Prudêncio[1,3] e Mónica Vieira[1,3], Paula Gomes[2]

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Resumo

"Um pequeno par contra um grande trio" (Two4Three) é um projeto que se propôs combater Malária, Tuberculose e HIV com Líquidos Iónicos (ILs).

Um dos grandes problemas de saúde do nosso tempo é a resistência dos agentes infeciosos aos fármacos atualmente disponíveis. Este é um problema particularmente dramático no contexto das "3 grandes doenças" - malária, HIV/SIDA e tuberculose, e em que a constante procura pelo próximo fármaco de primeira linha já não parece uma abordagem sustentável. Alternativamente, podemos pensar em olhar para os fármacos "velhos" sob uma perspetiva nova: combinar os fármacos disponíveis de polaridade oposta, no sentido de formar Líquidos Iónicos como uma maneira económica de controlar co-infeções comuns, especialmente em África (HIV/TB, TB/malária, malária/HIV). Estas novas formulações podem exibir não só uma dupla, mas também novas propriedades físico-químicas e biológicas, devido à sua natureza **iónica**, eventualmente contribuindo para melhorar a biodisponibilidade oral, ou até contornar problemas de resistência a cada um dos fármacos individuais.

Com este trabalho demonstramos que a utilização de ILs deve ser incentivada porque pode reciclar muitos dos fármacos que foram colocados na prateleira, não só devido à resistência, mas também devido à sua limitada solubilidade aquosa ou conversão polimórfica.

Abstract

"A small couple for the big-three" (Two4Three) is an innovative and ambitious project where we propose to fight Malaria, Tuberculosis (TB), and HIV-1/AIDS using Ionic Liquids (ILs).

One of the major societal challenges today is the increasing resistance of pathogens against available drugs, a matter of great concern for the Big Three Diseases (BTD). We intend to address this problem from a new perspective: combine known drugs to form IL active against HIV/TB, TB/malaria, malaria/HIV co-infections. Such IL will act as new formulations potentially exhibiting dual action, while possessing physico-chemical properties favoring oral bioavailability, more potent activity, and absence of resistance

This is our working hypothesis which, if proven correct, will open brand new avenues towards cheap and effective dual-action medicines against the BTD. In other words, this is a low-cost innovative approach that may yield a major advance in the control of the most concerning infections of today.

"Two4Three" intends to fight malaria, TB and HIV by using API-derived IL. This project looks at the current group of anti-infective API from a new perspective: recycling ionizable drugs with opposed polarities (basic+acid) to form IL by ion pairing may produce valuable dual-action drug candidates, while returning value to drugs whose clinical use is in decline or put on hold(Cole, Hobden, & Warner, 2015; Prudencio, Vieira, van der Auweraer, & Ferraz, 2020; Teixeira et al., 2014).

The global aim of this project is to bring an innovative concept to the field of co-infections therapy, by taking advantage of both the wide plethora of antimalarial, anti-HIV and anti-mycobacterial drugs available, and the distinct properties of IL.

Assumed that, most drugs are either acidic or basic, their pairing may produce IL with dual anti-infective activity and distinct physic-chemical and biochemical

properties, appropriate for their use as new formulations with enhanced oral bioavailability and limited emergence of resistance. Such innovation will bring safe, effective and affordable medicines against co-infections, given that it will settle on:

a) well-known anti-infectives, previously approved by the relevant agencies (e.g., FDA, EMEA), and whose production pipelines are well-established and optimized to reduce costs;

b) simple ionic combination of two building blocks, one cationic, and one anionic, to form the final IL, hence, no elaborate or expensive chemistry will be required.

There are 5 major experimental goals to attain, which defined the Tasks for this project:

Task 1 - synthesis of novel IL based on acid-base pairing of ionizable anti-malarial, anti-HIV and anti-TB drugs;

Task 2 - biophysical profiling of the API-IL produced;

Tasks 3 and 4 - evaluation in vitro (Task 3) and in vivo (Task 4) of the anti-HIV, anti-TB and anti-malarial properties of the new IL, to both provide proof-of-concept on working hypothesis and propose new co-drug candidates for clinical development against HIV/TB, malaria/TB and HIV/malaria co-infections.;

Task 5 - assessment of structural and functional cellular changes on eukaryote and prokaryote cell models, induced by a subset of IL, chosen according to data from task 3.

Antimalarial activity, as well as toxicity to human host cells, will be evaluated at the Participating Institution "Instituto de Higiene e Medicina Tropical" (IHMT@UNL), in Lisbon, supervised by team member Dr. F. Nogueira. Dr. Nogueira

Anti-TB screenings will be carried out at the Participating Institution "Instituto de Biologia Molecular e Celular" (IBMC@i3S), in Porto, supervised by Prof. M. S. Gomes. Prof. Gomes's team has strong experience in mycobacterial biology and in the screening of anti-mycobacterial compounds. We have been collaborating with this team for some years. Relevantly, some preliminary assays have been recently run that delivered quite promising results regarding the potential of chloroquine-derived IL against TB.

Anti-HIV activity assays will be done on a collaborative basis.

The biological effects of the most promising of the API-IL produced on eukaryote and prokaryote cell models will be evaluated, through assessment of structural and functional changes induced by the IL on those cells. This task will be carried out at "Escola Superior de Saúde do Instituto Politécnico do Porto" (ESS-IPP@I3S), in Porto, supervised by Dr. Cristina Prudêncio.

The first drugs that we used were cationic antimalarials (primaquine (PQ), chloroquine (CQ)). For anionic drugs, we decided to used three types of bioactive compounds: cinnamic acids, fatty acids and fluoroquinolones.

We also produce ionic liquids and covalent compounds from PQ and 7 fatty acids (butyric acid, caprylic acid , lauric acid, myristic acid, palmitic acid, stearic acid and oleic acid) in a total of 10 compounds. We did the same for CQ (A. T. Silva et al., 2020; Ana Teresa Silva et al., 2020).

We synthesized a total of 33 compounds pure and full characterized by NMR and mass spectra with good yields.

About their thermal stability, an important issue for APIs typically employed in the treatment of diseases, such as malaria, that are endemic to tropical and sub-tropical countries, all compounds were analysed by simultaneous thermogravimetric analysis (STA). Herein we demonstrated that the ILs are slightly less thermally stable than the commercial CQ phosphate salt, but still remain unaltered up to about 90 ºC or higher temperatures. As expected, covalent amide analogues displayed higher thermal stability.

Regarding their antimalarial activity, the compounds were submitted to in vitro assays, to assess their activity against a CQ-sensitive (3D7) and a CQ-resistant (Dd2) strain of Plasmodium falciparum. The first remarkable observation was that, while all RTIL displayed adequate solubility in the medium used in the assays, only some amides were sufficiently soluble in these conditions. Besides, RTIL displayed slightly better solubility in aqueous media than covalent analogues. More importantly, all RTIL displayed stronger activity than the parent antimalarial drug, which is classically formulated as a phosphate salt, against both CQ-sensitive and CQ-resistant strains of P. falciparum, the species responsible for the deadliest form of human malaria (A. T. Silva et al., 2020; Ana Teresa Silva et al., 2020).

ILs based on CQ-cinnamic acid conjugates were as effective against M. avium, extracellularly and inside macrophages, as its covalent equivalents. However, they were more soluble and less toxic for the host cells. The conjugation of CQ or primaquine (PQ) with fluoroquinolones, that are sometimes used to treat

mycobacterial infections, resulted in ILs that have the same direct activity as the original antibiotics to M. avium, but are more active against the mycobacteria growing inside macrophages (Bento, Gomes, & Silva, 2020).

The project is in his final months, we now expect to be in shape to deliver novel API-IL as valuable dual-action leads against co-infections arising from host invasion by the most threatening infectious pathogens of today: malaria parasites, TB bacteria, and HIV retro-viruses. This findings will hopefully pave the way towards the next natural step in this context: attracting funds/investors to take forward most promising API-IL into clinical development, towards low-cost and safe medicines, within reach of even the most remote infection sites.

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453

MARINE CYANOBACTERIA

ISOLATED FROM THE PORTUGUESE COAST AS A SOURCE OF BIOACTIVE COMPOUNDS: CYTOTOXICITY AGAINST HUMAN TUMOUR CELLS AND NORMAL CELLS

Autores: Rosário Martins[1,2], Margarida Costa[3], Pedro Leão[2,4], João Costa Rodrigues[5], Maria Helena Fernandes[6], Mónica Garcia[7], Piedade Barros[1], Sara Freitas[2,4], Ralph Urbatzka[2], Valentina Domingues[8], Fátima Nogueira[9], Vitor Vasconcelos[2,4]

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Resumo

As cianobactérias marinhas constituem uma fonte promissora de compostos com potencial antitumoral. Nos últimos anos, um arsenal de compostos tem sido revelado, alargando a gama de novos compostos ou estruturas de base ao desenvolvimento de novas drogas. Neste projeto tivemos como objetivo avaliar o potencial de cianobactérias da coleção LEGE-CC como fonte de compostos antitumorais. Foi também nosso objetivo avaliar os mecanismos que conduzem à inibição do crescimento celular nomeadamente o envolvimento da apoptose. O projeto resultou na seleção de estirpes promissoras com potencial bioativo. Os compostos hierridina B, hierridina C e bartolosidas foram isolados. A hierridina B foi citotóxica para a linha celular de adenocarcinoma do cólon HT-29, reduzindo a atividade mitocondrial e paragem do ciclo celular. A hierridin C não revelou citotoxicidade. No entanto, este composto foi testado quanto à sua atividade antiplasmodial, de onde resultou uma patente.

Abstract

Marine cyanobacteria have proved to be an important source of potential antitumour drugs. In recent years, a plethora of compounds were isolated revealing a great scope for the discovery of novel compounds or lead structures for the development of new drugs. In this project we aimed to evaluate the potential of cyanobacteria strains of the LEGE-CC as a source of anticancer compounds. It was also our objective to evaluate the mechanisms that potentially leads to the inhibition of cell growth namely the involvement of apoptosis. The project led to the selection of promising strains with bioactive potential. The compounds hierridin B, hierridin C and bartolosides were isolated. Hierridin B was cytotoxic to the HT-29 colon adenocarcinoma cell line by reducing the mitochondrial activity and induced a cell cycle arrest. Hierridin C did not reveal any cytotoxicity. However, this compound was tested for its antiplasmodial activity which resulted in a patent.

1. Introduction and aim

Cyanobacteria are prokaryotes with diverse morphological, physiological and biochemical properties. At marine environments they are considered one of the most important components of the microbial communities, both at open ocean and along the shores. Marine cyanobacteria produce structurally diverse products, including terpenes, glycosides polyketides, peptides, and lipopeptides with pharmacological bioactivities ranging from anti-inflammatory, antioxidant, antitumor, antimicrobial and antiparasitic, among others (Demay et al., 2019). The potential of marine cyanobacteria as anticancer agents has however been the most explored and, besides cytotoxicity in tumor cell lines, several compounds have emerged as templates for the development of new anticancer drugs (Costa et al., 2012). The project as a result of the collaboration between the Interdisciplinary Center for Marine and Environmental Research (CIIMAR | UP), the Polytechnic School of Health of Porto (ESS | P. PORTO) and the group of pharmacology of the Faculty of Dental Medicine, University of Porto (FMD | UP). Central to this project is the cyanobacteria culture collection of the Blue Biotechnology and Ecotoxicology – LEGE-CC- https://lege.ciimar.up.pt/ mainly constituted by cyanobacteria isolated from the Portuguese coast. The project included twenty-eight marine cyanobacteria strains that were tested for cytoxicity against tumor and normal cell lines. The main objective

was to evaluate the capability of the cyanobacteria to produce compounds with anticancer activity in order to infer about their potential interest as a source of therapeutic agents.

2. General methodology

Twenty-eight cyanobacteria strains of the picoplanktonic and filamentous marine cyanobacteria genera Nodosilinea, Cyanobium, Synechocystis, Synechococcus, Leptolyngbya, Pseudanabaena and Romeria of the LEGE CC were selected. Strains were extensively cultured under laboratory conditions in order to obtain biomass for the preparation of organic extracts (Costa et al., 2013).

Cyanobacteria extracts were tested for cytotoxicity in the HT-29 human colon adenocarcinoma, SH-SY5Y neuroblastoma, T47D and SK-BR-3breast carcinoma, PC-3 prostate adenocarcinoma, RKO colon carcinoma, HepG2 hepatocellular carcinoma and MG-63 osteosarcoma. Cellular viability was evaluated by the reduction of the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and the LDH Release Assay (Costa et al., 2013). For the most interesting strains a bioassay-guided fractionation was further performed and the fractionation of the fraction that revealed more cytotoxicity was conducted. Fractions were prepared using VLC (Afonso et al., 2016; Leao et al., 2013; Leao et al., 2015).

For strains LEGE 06113 LEGE 06155 we investigate the mechanisms undergoing the cytotoxic effects by a genomic and proteomic approach. From these cyanobacteria strains the mechanisms involved in cytotoxicity on the RKO human colon cancer cell line were evaluated by employing real-time PCR to analyse gene expression of genes involved in cell cycle (CCNB1, CCNE, P21CIP) and apoptosis (BAD, BCL-2) and by two-dimensional gel electrophoresis for protein expression. From strain LEGE06113 the compounds hierridin B and C were isolated.

3. Results

Results from the cytotoxicity screening revealed that more than 25% of the strains induced a decrease in cell viability between 70-90% (figure 1). 59% of the strains induced a decrease in cell viability below 50% and were considered as no cytotoxic. However, the majority of the tested cyanobacterial strains were capable to induce cytotoxicity in, at least, one of the cell lines (Costa et al., 2013)

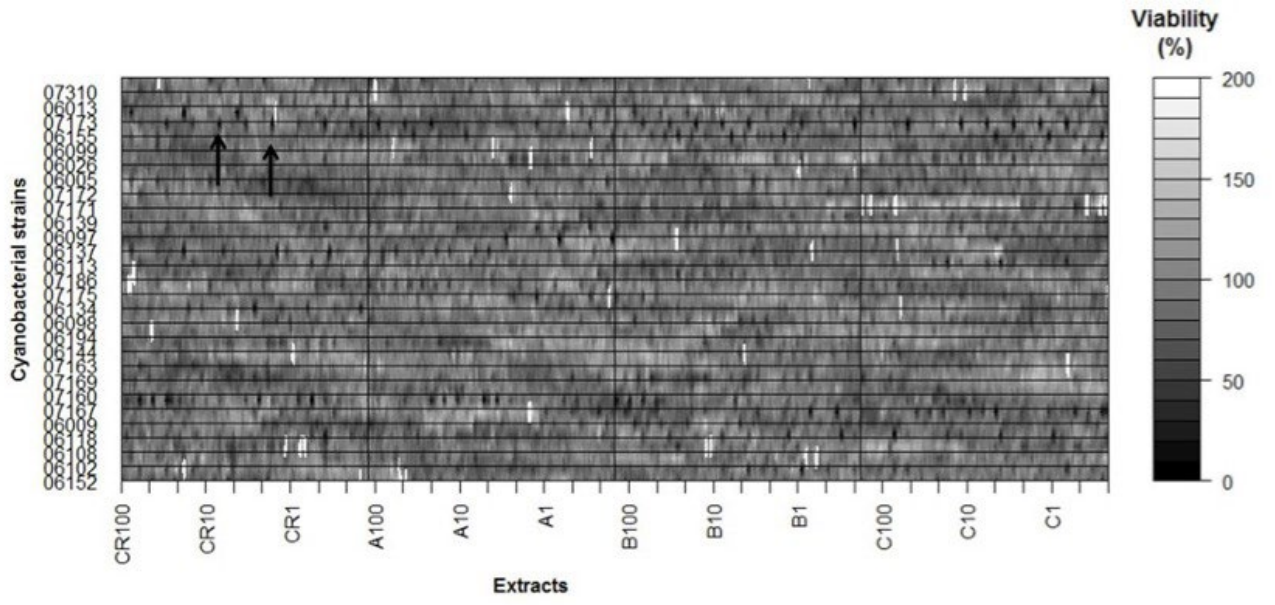

Figure 1. Results of all individual experiments of the MTT assay. The percentage of cell viability was calculated relatively to the control. Dark dots (arrows as example) are indicative of strong and moderate cytotoxicity.

Concerning the mechanisms undergoing the cytotoxic effects on the RKO human colon of the strains LEGE06113 and LEGE06155, RT-PCR results using multiple reference gene normalization showed an increased in the BCL-2 mRNA expression and a decreased the CCNB1 mRNA expression (Fig. 2 and 3). This result supported the hypothesis that there is an interaction with the progression of the cell cycle, since CCNB1 is involved in progression of the cell cycle from G2 to mitosis (M) and the lower expression of this target gene reduce the cells ability to progress in the cell cycle. Progression on cell cycle was also evaluated by flow cytometry and results point also to alterations in the cell cycle. For strain LEGE 06155 an increase in cells in G2/M occurred (Fig.4), which is supported by the decreased the CCNB1 mRNA expression. These results point to a cell cycle arrest at G2/M (Freitas, Martins, Campos, et al., 2016).

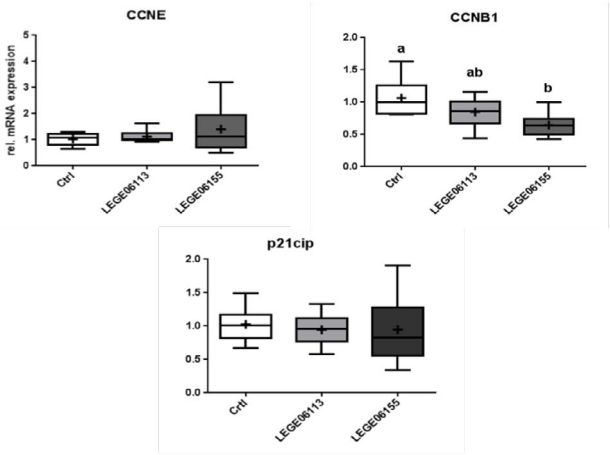

Figure 2. Relative mRNA expression from selected cell cycle genes, CCNE, CCNB1 and P21CIP. CCNB1 showed significant mRNA expression according to the fraction B of the cyanobacterial strain.

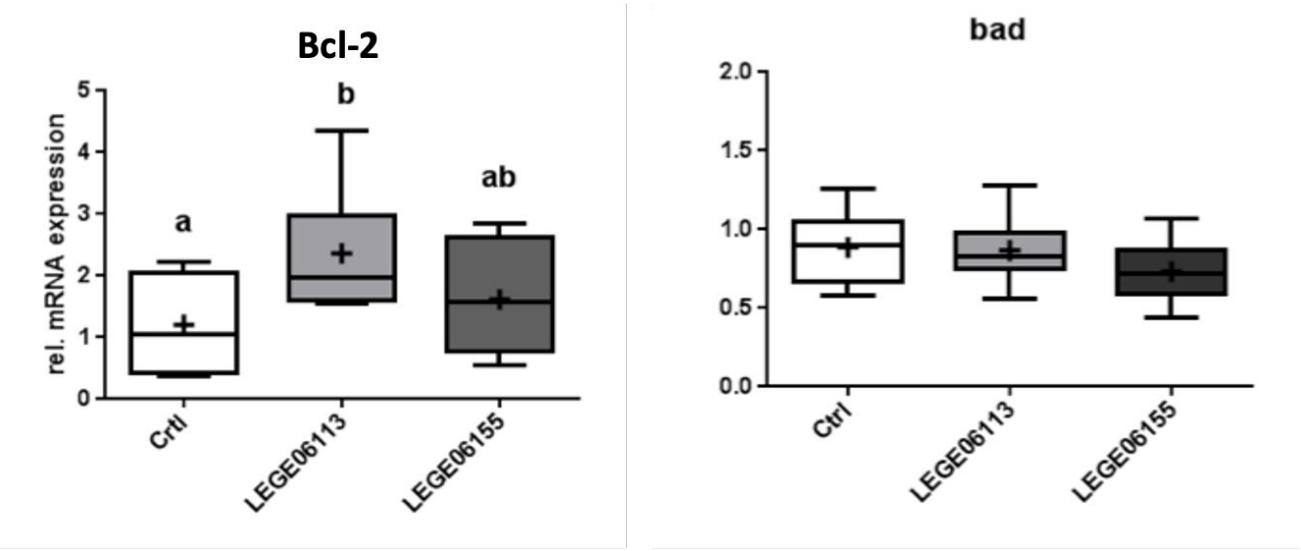

Figure 3. Relative mRNA expression from selected apoptosis genes, BCL-2 (anti-apoptotic) and BAD (pro-apoptotic). BCL-2 showed significant mRNA expression according to the fraction B of the cyanobacteria strains.

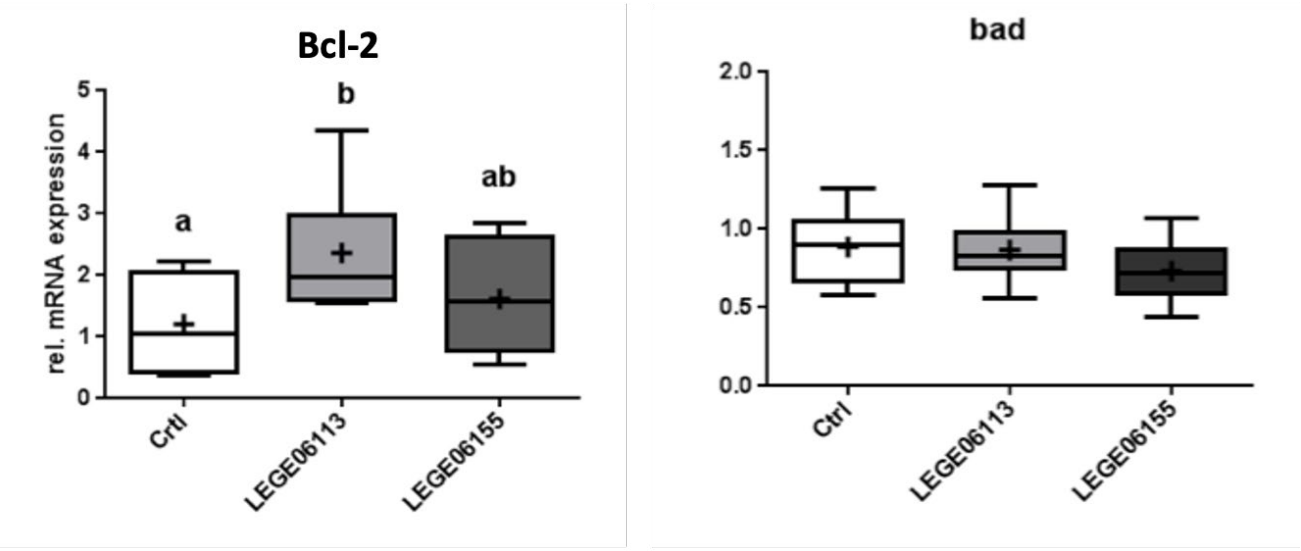

Figure 4. Percentage of RKO cells in S and G2/M phase of the cell cycle. The number of cell in G2/M was significantly higher and in S phase significantly lower in RKO treated with strain LEGE06155 which are indicative of cell cycle arrest.

By applying this bioassay-guided fractionation the crude lipophilic extract from strain LEGE 06113 was fractionated using vacuum-liquid chromatography (VLC). The 1H NMR spectrum (500 MHz, CDCl3) of one of the most non-polar fractions contained two sharp singlets at d3.85 and d3.76, suggestive of aromatic methoxy groups, which led us to further investigate this fraction and ultimately obtain a compound after purification by reversed-phase (RP) HPLC. The identity of the purified metabolite was confirmed as hierridin B, previously isolated from a Phormidium ectocarpi strain (Leao et al., 2013).

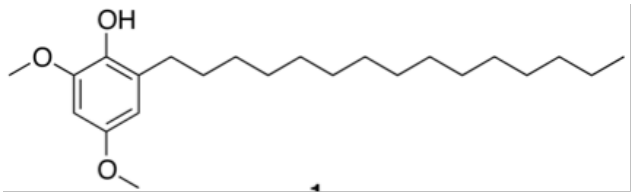

Figure 5. Structure of hierridin B . doi:10.1371/journal.pone.0069562.g001

The cytotoxic activity of hierridin B was exclusively observed on the HT-29 colon adenocarcinoma cell line with an IC50 of 100.2 µM (Leao et al., 2013).

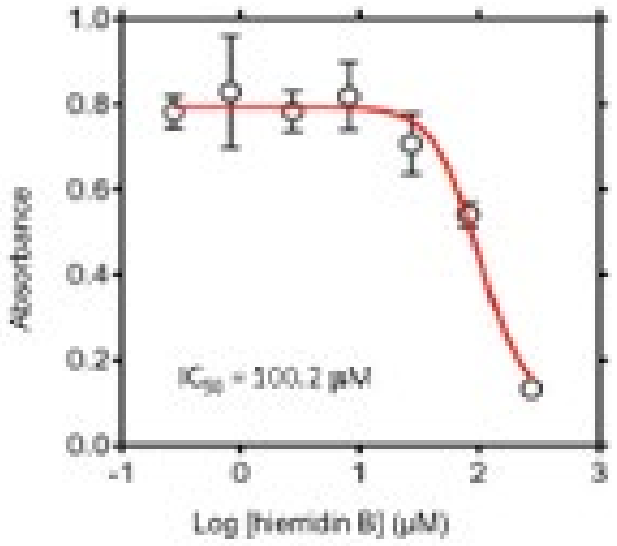

Figure 6. Cytotoxicity of hierridin B isolated from the cyanobacteria strain Cyanobium sp. LEGE06113 in HT-29 human colon adenocarcinoma cells.

The exploration of its mode of action suggested that hierridin B reduced strongly the mitochondrial activity, and induced a cell cycle arrest, which led finally to cell death. Furthermore, an effect was observed on VDAC1 protein expression, which might disturb the formation of mitochondrial channels (Freitas, Martins, Costa, et al., 2016).

Hierridin C was isolated for the first time. Hierridin C did not reveal cytotoxicity against the cells tested however, its antiplasmodial activity was more potent in comparison to its homolog (hierridin C IC50 1.5 ± 0.1µM against 3D7 strain of Plasmodium falciparum and IC50 2.3 ± 0.7µM against Dd2 strain) (Costa et al., 2019). Hierridin C is now in a patent (Leão, P., Rosário, M.M., Costa, M., Vasconcelos, V., Nogueira, F., Domingues, V. (2016) WO2016207869A1.

A group of four bartolosides (A, B C and D), which belong to the chemical class of alkylresorcinols, were isolated from LEGE 06102 and LEGE 06155. Bartoloside A had an IC50 of 21 µM against HT-29. Bartoloside B had an IC50 of

9.5 μM against the PC-3 (Leao et al., 2015). Bartolosides E-K were also isolated, and no cytotoxicity was found (Afonso et al., 2016).

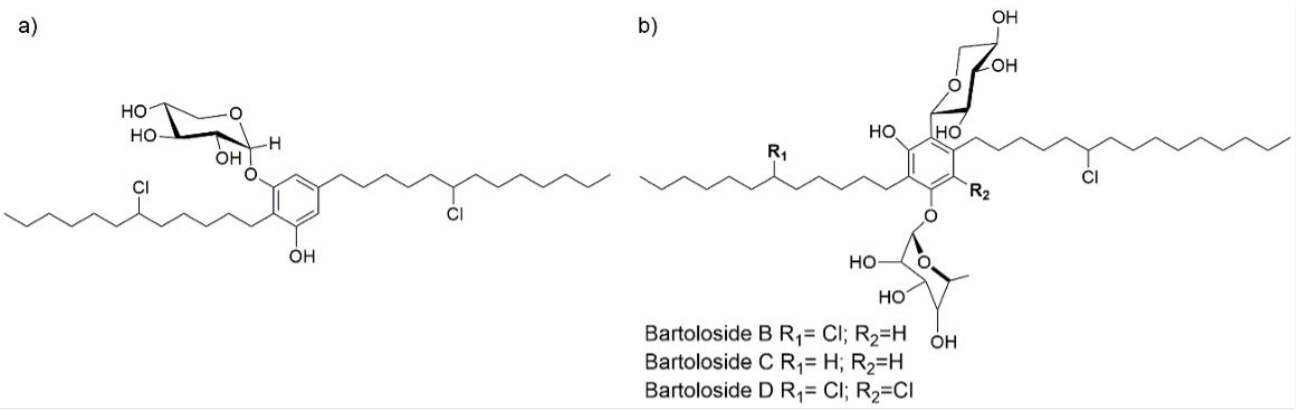

Figure 7. Chemical structures of a) bartoloside A. b) bartoloside B, C and D skeleton.

4. Final remarks

The identification of new sources of natural products is an important step in drug discovery. In this sense, the results from this screening highlight the potential of marine cyanobacteria genera as a source of interesting bioactive compounds.

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SM ASK

Smart Mask with colorimetric biossensor for SARS -CoV-2 contamination and humidity

Smask: Smart Mask with colorimetric biossensor for SARS-CoV-2 contamination and humidity

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Resumo

A atual pandemia, devido ao vírus SARS-CoV-2, exigiu a implementação de medidas de proteção individual, como o uso de máscaras de proteção. A eficácia das máscaras depende do tempo de uso, da quantidade de humidade e do contato com agentes infeciosos. Em atividades que requeiram o uso deste equipamento por longos períodos de tempo e/ou com alto risco de exposição é importante conhecer essa eficácia em tempo real.

O projeto SMASK visa desenvolver um biossensor colorimétrico que permita a deteção da presença do SARS-CoV-2 e da quantidade de humidade que comprometam a eficácia da máscara, e que indique, de forma simples, a necessidade da sua substituição. Esta tecnologia será desenvolvida para máscaras têxteis de nível 2 e 3 e será baseada em nanopartículas funcionalizadas com biomoléculas que reconhecem especificamente o SARS-CoV-2; e em partículas de substâncias higroscópicas, que indiquem a saturação da máscara. Com uma mudança de cor, o biossensor indicará uma perda efetiva da capacidade de proteção.

A transposição desta tecnologia para outras aplicações pode ser uma arma de defesa na prevenção da disseminação do vírus Sars-CoV-2 ou de outros agentes biológicos, uma vez que qualquer utilizador terá informação em tempo real e poderá agir imediatamente, evitando a transmissão.

Abstract

The current pandemic, due to the SARS-CoV-2 virus, has required the implementation of individual protection measures, such as the use of protective masks.

The effectiveness of masks depends on the time of use, the amount of moisture and contact with infectious agents. In activities that require the use of this equipment by long periods of time and/or with a high risk of exposure, it is important to know this effectiveness in real time.

The SMASK project aims to develop a colorimetric biosensor that allows the detection of the presence of the SARS-CoV-2 and the amount of humidity that compromise the effectiveness of the mask, and that indicates, in a simple way, the need for its replacement. This technology will be developed for level 2 and 3 textile masks and will be based on nanoparticles functionalized with biomolecules that specifically recognize the SARS-CoV-2 virus; and in particles of hygroscopic substances, which indicate mask saturation. With a color change, the biosensor will indicate an effective loss of protection capability.

The transposition of this technology to other applications can be a defense weapon in the prevention of spread of the Sars-CoV-2 virus or other biological agents, as any user will have information in real time and can act immediately, preventing transmission.

Após a declaração de Pandemia, devido à disseminação do vírus SARS-CoV2, aumentou significativamente a utilização de máscaras, para proteção dos cidadãos comuns e profissionais, de todas as áreas da economia.

A utilização deste tipo de equipamento requer medidas de manuseamento e cuidados relativamente à sua eficácia de proteção, nomeadamente, a capacidade de filtração e contaminação, sendo necessária a sua substituição sempre que haja comprometimento do fim a que se destinam.

Não existe, à data, nenhuma máscara de proteção que dê indicação específica sobre a sua capacidade de proteção ao longo do período de utilização.

Objetivos e Metodologias

É objetivo do presente projeto, o desenvolvimento de um biossensor colorimétrico, incorporado numa superfície têxtil, com capacidade de indicação direta da capacidade de proteção das máscaras de proteção de nível 2 e de nível 3 – máscaras para uso social de proteção respiratória, que dê ao utilizador informação sobre a capacidade de filtração do equipamento, com um sensor de humidade; e do estado de contaminação, com um sensor de existência de contacto com o vírus SARS-CoV2.

Esta tecnologia será desenvolvida recorrendo à incorporação de nanopartículas de ouro funcionalizadas, para a deteção da presença do vírus SARS-CoV-2 no tecido, de acordo com a tecnologia pré-existente de funcionalização deste tipo de nanoparticulas, com as respetivas adaptações; e de partículas de sílica, para indicação do nível de humidade no tecido, de acordo com o pré-estabelecido para este tipo de aplicação[1,2].

Este tecido inteligente será adicionado às máscaras de proteção na forma de etiqueta e darão, de forma simples, apenas pela mudança de cor, indicação ao utilizador sobre a eficácia e proteção. O utilizador não terá, assim, que ter conhecimentos diferenciadores ou qualquer tipo de formação específica para conseguir "ler" o estado de eficácia da máscara que utiliza, tornando, assim, esta máscara de proteção respiratória mais eficiente, segura e passível de ser utilizado por qualquer indivíduo, no desenvolvimento de qualquer atividade.

Pretende-se desenvolver um biossensor integrado num tecido, que será adicionado às máscaras de proteção respiratória (Níveis 2 e 3) na forma de etiqueta para deteção específica do vírus SARS-CoV-2 e para deteção de nível de humidade que comprometam a segurança de utilização da máscara. À data, desconhece-se a existência de qualquer tecnologia semelhante, após consulta de literatura disponível (bases de dados científicas e tecnológicas), pelo que se considera ser uma mais valia de reconhecido valor proceder ao desenvolvimento do biossensor descrito, de forma a contribuir para a segurança da utilização de máscaras, numa altura em que a sua utilização é obrigatória no dia a dia da sociedade. Este biossensor será desenvolvido de forma a detetar a presença do vírus SARS-CoV-2, por funcionalização de nanopartículas de ouro com biomoléculas de reconhecimento específico do SARS-CoV-2 (SA e ACE2)[1,2]. Para a deteção do nível de humidade, serão desenvolvidas partículas de sílica, com diferentes diâmetros3, e adaptadas à sua utilização em tecido. Os riscos críticos identificados prendem-se com a sensibilidade e especificidade do biossensor, que terá que ser aferida, assim como a eficácia de integração do biossensor no tecido. Com os dados disponíveis para adaptação das metodologias e com a

experiência adquirida dos intervenientes no projeto, cremos que estes pontos críticos serão ultrapassados.

O presente projeto divide-se em 8 atividades, estando, neste momento, as atividades 1 e 2 concluídas. Na atividade 1 fez-se a funcionalização das nanopartículas de ouro, recorrendo a duas biomoléculas propostas (SA e ACE2), para deteção específica de coronavírus, assim como testes de sensibilidade e especificidade. Na atividade 2 construíram-se partículas de sílica e argila para deteção de humidade, de forma a desenvolver partículas para a deteção de presença de moléculas de água. Neste momento, avançamos para as atividades 3 e 4, onde se faz a incorporação das nanopartículas e do detetor de humidade no tecido. Será realizada a incorporação das partículas desenvolvidas nas atividades anteriores em tecidos produzidos e valorizados de acordo com as suas características, com afinidade para a ligação às partículas desenvolvidas. Na atividade 5 será realizada a avaliação do funcionamento do biossensor em contexto de laboratório e avaliar-se-á a funcionalidade do tecido inteligente, em contexto controlado de exposição. Serão calibradas as quantidades necessárias para a deteção dos limites de utilização da máscara em segurança, i.e., a presença da quantidade mínima possível de SARS-CoV-2 e da quantidade de água que comprometa a segurança desta. Na Atividade 6 será desenvolvido o protótipo de máscara de proteção respiratória, após a validação feita na atividade anterior, com valor acrescentado, com a colocação da etiqueta biossensora. Serão avaliados o tamanho da etiqueta e o local de colocação para permitir um funcionamento eficaz e que não comprometam o conforto de utilização. Na atividade 7 será avaliada a funcionalidade do protótipo no formato final, por exposição às biomoléculas detetáveis pelo biossensor e validada a sua resposta em relação à quantidade de exposição. A atividade 8 será dedicada à promoção e divulgação do produto desenvolvido, de forma a impulsionar a sua possível comercialização e desenvolvimento em larga escala.

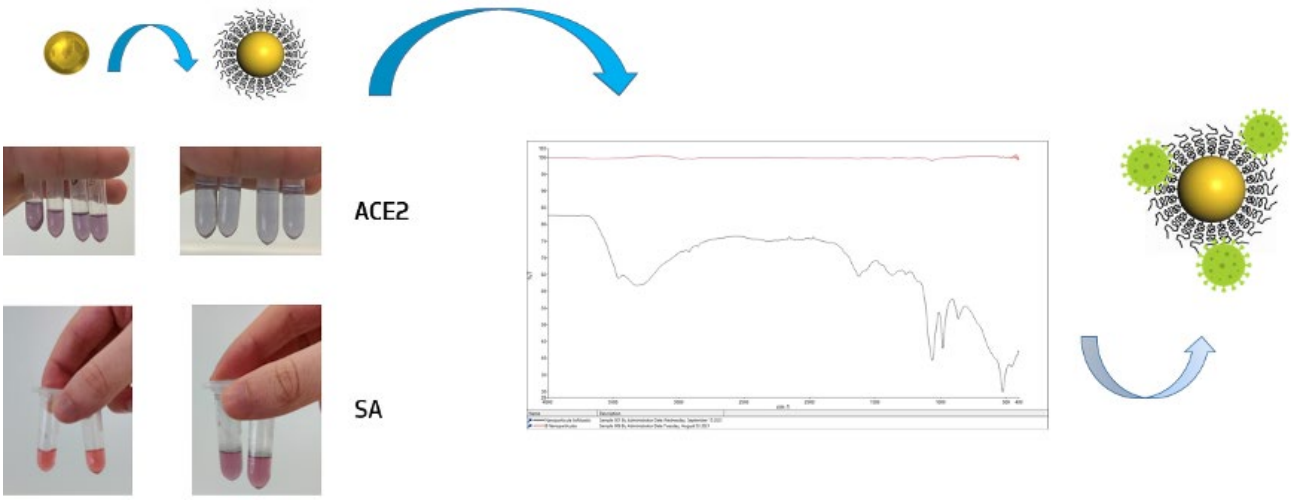

Figura1. Desenvolvimento e avaliação da funcionalização de nanopartículas de outo com SA e ACE2.

Resultados:

Atualmente, estão já funcionalizadas as nanopartículas de ouro, tendo os resultados sido mais promissores com a biomolécula de SA. Foi avaliada a funcionalização das nanopartículas através de análise FTIR, que permite avaliar a presença de ligações químicas entre a biomolécula e a superfície das nanopartículas (figura 1).

No desenvolvimento do biossensor para a humidade, foram avaliadas abordagens recorrendo a argila e ao desenvolvimento de mesoporos de sílica, tendo estes últimos sido mais promissores na avaliação da quantidade de humidade presente (figura 2).

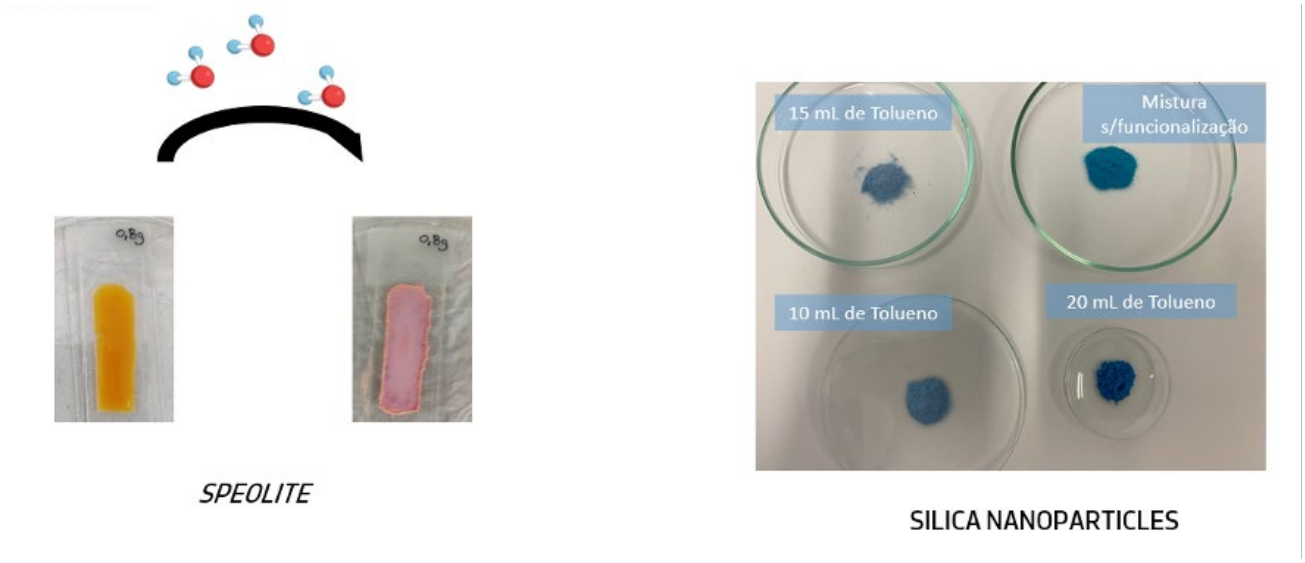

Figura 2. Resultados obtidos para o desenvolvimento de biossensores de humidade, com recurso a argila (esquerda) e mesoporos de sílica (direita).

Produtos resultantes do projeto:

O SMASK prevê o desenvolvimento de um protótipo de máscara que permitirá ao utilizador verificar as condições de segurança em que a máscara se encontra, através de um biossensor colorimétrico, na forma de etiqueta, que servirá para a deteção da presença de SARS-CoV-2 no tecido, através de nanopartículas de ouro funcionalizadas com biomoléculas específicas de reconhecimento; assim como para a deteção da quantidade de água (humidade) que comprometa a eficaz capacidade de filtração da máscara. Os resultados obtidos serão, sempre que justificável, patenteados e/ou divulgados na comunidade através da publicação em revistas científicas internacionais, com revisão por pares, da área de conhecimento adequada e promovidos em feiras e exposições.

Este projeto terá impacto no desenvolvimento regional e da empresa, uma vez que visa a criação de um produto que recorre a tecnologia avançada, de forma a dar resposta a uma necessidade emergente da sociedade. O SMASK valoriza, também, o conhecimento sediado nas Instituições de Ensino Superior, neste caso, a ESS e permite a ligação entre a academia e a indústria, de forma a alavancar a translação do conhecimento para a concretização de soluções comercializáveis. De forma a valorizar o produto desenvolvido, será patenteada a tecnologia desenvolvida e promover-se-á a sua divulgação em feiras e exposições, a nível nacional e internacional, de forma a potenciar a sua comercialização.

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PROJETO

ForPharmacy

Farmácia do futuro com um ecossistema *plug-and-play*

Projeto ForPharmacy: Farmácia do futuro com um ecossistema *plug-and-play*

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Referência do Financiamento: ForPharmacy – Future pharmacy as a plug-and-play ecosystem, POCI-01-0247-FEDER-070053

Resumo

Os serviços prestados nas farmácias comunitárias podem ser otimizados, com a aplicação das tecnologias da informação e comunicação (TICs), dando resposta a necessidades bem documentadas e a outras emergentes, como as associadas à pandemia de COVID-19. O projeto ForPharmacy tem como objetivo desenvolver soluções inovadoras de telefarmácia. Neste trabalho propomos a apresentação do projeto e do consórcio. Como resultado do projeto espera-se que a aplicação das TICs permita a digitalização dos serviços das farmácias, bem como a utilização das telecomunicações com pacientes a distância ou impedidos da presença física. Esta possibilidade pode ser uma grande vantagem para populações vulneráveis, como é o caso dos idosos e pessoas com doenças crónicas, assim como no contexto da pandemia de COVID-19. As soluções digitais geradas permitirão às farmácias oferecer uma vasta gama de cuidados de saúde, contribuindo para expandir o acesso aos serviços prestados e, simultaneamente, melhorar a segurança dos pacientes.

Palavras-chave: Farmácia Comunitária; Telefarmácia; Saúde; TICs

Abstract

The services provided at the community pharmacies can be optimized, with the application of information and communication technologies (ICTs), responding to well-documented needs and other emerging ones, such as those associated with the COVID-19 pandemic. The ForPharmacy project aims to develop innovative telepharmacy solutions. In this work, we propose the presentation of the project and the consortium. As a result of the project, it is expected that the application of ICTs will allow the digitalization of pharmacy services, as well as the use of telecommunications with patients at distance or prevented from physical presence. This possibility can be a great advantage for vulnerable populations, such as the elderly and people with chronic diseases, as well as in the context of the COVID-19 pandemic. The digital solutions generated will allow pharmacies to offer a wide range of healthcare services, contributing to expand access to the services provided.

Keywords: Community Pharmacy; Telepharmacy; Health; ICTs

Introdução

As farmácias são estruturas importantes dos sistemas de saúde e podem oferecer serviços de proximidade devido à ampla diversidade de serviços prestados. Além disso, os profissionais das farmácias são dos profissionais de saúde mais acessíveis à população, providenciando serviços muito além da tradicional venda de medicamentos (Hemberg, Huggins, Michaels, & Moose, 2017). São exemplo, serviços na prestação de cuidados de saúde primários (Martins, van Mil, & Da Costa, 2015), na prevenção da doença e na promoção da saúde.

As farmácias comunitárias distinguem-se na prestação de serviços de proximidade, oferecendo cada vez mais serviços baseados num modelo centrado no doente/utente, por oposição a um modelo tradicional, cujo foco estava centrado no profissional (Hemberg et al., 2017; Kibicho & Owczarzak, 2012; Rasheed, Alqasoumi, & Hasan, 2020). Esta nova abordagem permite providenciar cuidados aos clientes/doentes/utentes na prevenção, mas também na gestão de condições crónicas, como é o caso da diabetes e da hipertensão (Farris et al., 2019), da infeção pelo vírus da imunodeficiência

humana (HIV) (Hirsch et al., 2009), ou mesmo na dependência de substâncias (Murphy, Gardner, & Jacobs, 2019). No entanto, este modelo centrado no cuidado do doente tem sofrido mudanças, resultado dos desafios enfrentados nos últimos anos, de modo a responder às necessidades dos clientes/doentes/utentes e às problemáticas sociais que vão surgindo (Urick & Meggs, 2019). Uma das maiores e recentes crises de saúde pública está associada à pandemia de Covid-19 (Hartley & Perencevich, 2020). Esta exigiu das farmácias comunitárias um papel preponderante no acesso das populações aos medicamentos, no aconselhamento e acompanhamento dos clientes/doentes/utentes (Cadogan & Hughes, 2021). Embora as farmácias tenham sido bem-sucedidas, várias barreiras impediram que as respostas fossem melhores, sobretudo os sucessivos confinamentos que foram sendo impostos pelas autoridades de saúde públicas.

As populações mais vulneráveis, nomeadamente pela idade avançada (Palombi et al., 2020; Chen, 2020), em isolamento (Killgore et al., 2020), e com doenças crónicas (Bambra et al., 2020) vieram a demonstrar várias fragilidades dos Sistemas de Saúde a nível mundial, nomeadamente dos serviços de cuidados primários. Nesse sentido, revelaram-se necessárias medidas de proximidade muito mais capazes do que as existentes. Por conseguinte, algumas farmácias comunitárias começaram a adotar ou a aumentar os serviços que envolviam o usode ferramentas digitais, como uma possível solução para o acompanhamento a distância (e.g., Hoti et al., 2020), designadamente serviços de farmacovigilância, por exemplo, através de serviços de telefarmácia e entregas/apoio ao domicílio (Nadeem, Samanta, & Mustafa, 2021). Estes serviços podem ser uma grande oportunidade a explorar no futuro, tendo em vista os problemas e desafios em termos de acesso aos cuidados de saúde que foram observados durante a pandemia de COVID-19 e que poderão surgir em futuros surtos, caso não se desenvolvam soluções inovadoras para lhes fazer face.

Por outro lado, o aumento da população idosa e da prevalência de doenças crónicas, bem como o aumento dos custos de saúde a um ritmo insustentável é outro fator que exige uma mudança de paradigma e soluções inovadoras. Doenças crónicas comuns como a Doença Pulmonar Obstrutiva Crónica (DPOC), Asma, Diabetes ou Hipertensão, ou doenças agudas com baixo impacto na saúde de um indivíduo, tais como Infeções do Trato Urinário, Rinite Alérgica ou Infeções da Orofaringe, podem ser facilmente rastreadas e monitorizadas localmente pelas farmácias (Strand et al., 2020), desde que seja feito através de uma intervenção devidamente registada e rastreável.

Neste enquadramento, as farmácias poderão assumir um papel crucial na promoção e desenvolvimento dessas soluções. O envolvimento das farmácias na prossecução de objetivos de saúde pública é uma tendência não só na Europa, mas também nos Estados Unidos e na Austrália. Recentemente, o National Institute for Health and Care Excellence (NICE, 2017, 2018; Van Hove et al., 2019) emitiu uma diretriz com o objetivo de integrar as farmácias na rede de cuidados primários. O NICE concluiu que o aconselhamento farmacêutico consegue ganhos efetivos em saúde e bem-estar, tanto com doentes crónicos como com cidadãos interessados em adotar estilos de vida mais saudáveis. A eficácia das farmácias é demonstrada em áreas como a diabetes, hipertensão, cessação do tabagismo, redução do consumo de álcool e controlo do peso corporal. O mesmo pode ser feito em Portugal, como uma forma de aliviar a enorme pressão sobre os serviços de emergência. Estas condições levam a situações de congestionamento, gerando ineficiências e muitas vezes arriscando a propagação de uma epidemia. Isto pode ser facilmente compreendido quando se pensa nos tempos de espera excessivos nos hospitais.

O avanço da segurança dos doentes na Farmácia é também uma prioridade indiscutível nos dias de hoje.Com um Sistema Nacional de Saúde sobrecarregado, as farmácias têm a oportunidade de ser uma alternativa para oferecer serviços de proximidade fiáveis na monitorização da doença em doentes crónicos e também para promover a saúde na população em geral. Duas áreas parecem ser particularmente importantes, designadamente a interação fármaco - suplementos e a DPOC. À medida que a utilização de suplementos aumenta, os clientes/doentes/utentes devem ser sensibilizados para potenciais interações entre suplementos e medicamentos e as farmácias representam um excelente serviço de saúde de proximidade para assegurar esta sensibilização. O desafio aqui é definir a linha de base dos comportamentos dos utilizadores, de modo que o controlo preventivo possa ser utilizado e atenuar o risco de manipulação não autorizada e perigosa dos dados do sistema. A DPOC refere-se a um conjunto de condições pulmonares crónicas que limitam as vias aéreas e causam dificuldade respiratória, envolvendo hospitalizações recorrentes para que seja administrada a terapêutica e suporte de oxigénio (Pauwels & Rabe, 2004). Esta poderia beneficiar de novas intervenções. Por exemplo, uma revisão de literatura concluiu que a monitorização da doença através de comunicação a distância aumentou significativamente a qualidade de vida destes doentes, bem como reduziu o número de hospitalizações (McLean et al., 2011).

Complementarmente ao anteriormente exposto, o esquema legal das farmácias comunitárias sustenta hoje que as farmácias podem fornecer serviços farmacêuticos e outros serviços de saúde que promovam o bem-estar

dos doentes. A Portaria n.º 97/2018 atualizou os serviços farmacêuticos e outros serviços que promovem o bem-estar dos doentes que podem ser prestados pelas farmácias comunitárias. Finalmente, a aplicação das tecnologias da informação e da comunicação (TIC) no setor da saúde abre novas perspetivas na prestação de serviços de saúde.

Uma das oportunidades que pode ser mais explorada são os serviços de telefarmácia. A telefarmácia é definida como a prestação de assistência farmacêutica por farmacêuticos e farmácias registadas através do uso de telecomunicações com doentes localizados à distância (Nadeem, Samanta, & Mustafa, 2021). É um exemplo do fenómeno mais amplo da telemedicina, aplicado no campo da farmácia. Os serviços de telefarmácia incluem monitorização de interações medicamentosas, aconselhamento e acompanhamento de clientes/ doentes/ utentes, autorização para dispensa de medicamentos prescritos e distribuição remota de medicamentos.

Por conseguinte, o projeto ForPharmacy visa responder às circunstâncias e necessidades anteriormente enunciadas, reconhecendo que as farmácias comunitárias já dão uma contribuição dinâmica e sustentável para a saúde dos indivíduos e das comunidades que servem, mas poderão ser ainda desenvolvidas soluções inovadoras. Estas soluções inovadoras envolvem serviços de telefarmácia, com ênfase especial nas questões diretamente relacionadas com a saúde, designadamente a farmacovigilância, adesão terapêutica, interações medicamentosas e serviços de assistência que se esperam radicalmente diferentes dos serviços farmacêuticos convencionais já disponíveis. A partir destas soluções, poder-se-ão ainda identificar novas áreas, nas quais a telefarmácia poderá aumentar a disponibilidade dos serviços de saúde.

O projeto ForPharmacy, que se apresenta neste trabalho, tem um forte enfoque no desenvolvimento de novos serviços que podem ser oferecidos na rede de farmácias, com base nas necessidades dos clientes/doentes/utentes e do sistema de saúde. Uma análise de mercado revela que há áreas que carecem de apoio científico no trabalho do farmacêutico e de outros profissionais da farmácia.

Os principais objetivos deste projeto são expandir o acesso aos cuidados de farmácia e, simultaneamente, melhorar a segurança dos clientes/doentes/ utentes através de um melhor aconselhamento, monitorização da administração de medicamentos e de possíveis reações adversas. Essa expansão será efetuada através da digitalização dos serviços das farmácias comunitárias, em articulação direta com os diferentes profissionais de saúde.

Metodologia

As tarefas do projeto ForPharmacy estão divididas pelo consórcio. O referido consórcio e as tarefas são apresentados na Tabela 1.

Nº Tarefa	Responsável	Tarefa
T.1	Glintt	Gestão do projeto e divulgação dos resultados do projeto
T.2	IPP-ESS	Análise de requisitos de utilizador e especificação funcional
T.3	P.Leiria	Desenvolvimento de serviços de acompanhamento aos utilizadores da farmácia
T.4	Glintt	Dados e interface de serviços do ForPharmacy
T.5	IPP	Serviços de Internet of Things (IoT);
T.6	ISEP	Suporte de decisão inteligente para melhor segurança e a proteção;
T.7	Glintt	Integração do sistema e validação experimental

Este projeto começa o seu desenvolvimento com um estudo exploratório prévio com a utilização de metodologia mista (i.e., quantitativa e qualitativa). Esta fase da metodologia inicial exploratória tem na sua base o Envolvimento do Paciente e do Público [Patient and Public Involvement – PPI] que se refere ao modo como a investigação é realizada "com "ou "por" membros do público e não apenas "para", "acerca" ou "para eles" (Gjoneska et al., 2021). A importância de envolver o público na investigação tem na sua base razões morais, mas também por se tornar mais pragmático, uma vez que a base desta abordagem tem como pressuposto o argumento de que as pessoas, afetadas por uma condição, ou o público em geral, têm o direito de "ter uma palavra a dizer nas decisões sobre investigação e que os possam afetar" (Gjoneska et al., 2021, p. 2). Isto é, a utilização e partilha de recursos é benéfica para o PPI e consequentemente para a investigação. Nesse sentido, esta abordagem compreende a forma como a investigação é concebida e como os resultados dessa investigação são divulgados

e implementados após a conclusão de um estudo. Permite ainda construir e validar soluções que permitam às farmácias fornecer uma vasta gama de serviços e cuidados de saúde, atuando como um centro de saúde personalizado, que responda efetivamente a necessidades reais. O PPI na investigação é, assim, uma abordagem cada vez mais utilizada na conceção de projetos que, consequentemente, se tornam relevantes para os participantes, por se tratar de uma abordagem que aproxima o público da investigação.

No que respeita às tarefas da Escola Superior de Saúde, Instituto Politécnico do Porto (ESS | P. PORTO), a primeira tarefa tem como objetivo precisamente envolver os utilizadores finais, utilizando métodos participativos deste o primeiro momento, para recolher a experiência e perspetiva dos mesmos, através da realização de grupos focais. Os casos de uso, criados pela equipa do projeto, visam refletir as problemáticas em questão, i.e, a interação fármaco – suplemento e a DPOC. Estes servirão primeiro de "gatilho" para a discussão nos grupos focais, numa tentativa de melhor refletir as especificidades de cada problemática ao apresentar cenários. Depois da construção de casos de uso, a etapa seguinte envolve a construção de um guião semiestruturado com o objetivo de recolher a perceção dos participantes acerca das temáticas em estudo. Os grupos focais serão realizado em formato online, com seis elementos. Numa primeira fase da sessão o moderador apresenta os casos de uso e as questões incidirão em cada uma dessas problemáticas, de modo a identificar, através do ponto de vista dos utilizadores, quais os serviços possíveis e necessários para melhorar os serviços prestados pelas farmácias nestas áreas, por exemplo, na comunicação entre os médicos prescritores, os profissionais de saúde das farmácias, outros profissionais de saúde e os clientes/doentes/utentes das farmácia.

Os grupos serão constituídos por Profissionais de Farmácia (Farmacêuticos/ Técnicos de Farmácia). Para conseguir uma participação representativa da realidade portuguesa, o país foi dividido, grosso modo, nas regiões Norte, Centro e Sul, devendo os participantes nos grupos serem destas três regiões e de farmácias de áreas geográficas urbanas, suburbanas e rurais. No total foram realizados quatrogrupos focais, obtendo-se assim um total de 23 participantes.

Para além do envolvimento PPI, os conhecimentos especializados dos parceiros do projeto e a experiência resultante de iniciativas anteriores que envolveram a monitorização da saúde de clientes/doentes/utentes, orientarão a análise das necessidades dos utilizadores finais. Os requisitos dos utilizadores centrar-se-ão também nos aspetos de usabilidade e de aceitação da tecnologia, bem como no impacto socioeconómico, a fim de garantir que os interessados compreendam e aceitem plenamente a(s) solução(ões) geradas,

assegurando a realização dos objetivos do projeto.

Em suma, o projeto ForPharmacy irá propor, pela primeira vez, uma série de serviços de telefarmácia que serão possíveis graças à aprendizagem de máquinas [machine learning]e à aplicação da internet da coisas [Internet of Things (IoT)] desenvolvidas no projeto, partindo de uma abordagem PPI. Alguns exemplos dos serviços que podem ser prestados centram-se na prevenção e ação em doenças no âmbito de protocolos na deteção de sinais e sintomas de doença e na respetiva intervenção terapêutica. É com base nestes casos de utilização que estão a ser desenvolvidas as primeiras tarefas do projeto, análise de requisitos de utilizador e especificação funcional.

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GESTÃO DA

PREVENÇÃO DE RISCOS PROFISSIONAIS *EM PMES*

Gestão da Prevenção de Riscos Profissionais em PMEs

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Resumo

A prevenção de riscos profissionais é um desafio para Pequenas e Médias Empresas (PMEs). Estas são frequentemente associadas a um pior desempenho ao nível da prevenção dos acidentes de trabalho e das doenças profissionais. Ao longo deste trabalho mostramos que o desempenho de Segurança e Saúde no Trabalho (SST) se encontra relacionado com fatores organizacionais e de gestão, bem como com fatores individuais. Durante a investigação, foram também identificados fatores de risco em várias PMEs. A recolha desta informação foi fundamental para o desenvolvimento de métodos de avaliação de risco e definição de estratégias de intervenção eficazes. Desenvolvemos métodos de avaliação de risco semi-quantitativos, cuja a aplicabilidade foi exemplificada com PMEs do setor do mobiliário. Estratégias de intervenção encontram-se a ser testadas em PMEs. Encontra-se a ser desenvolvido um sistema de apoio à gestão da prevenção para estas empresas. A metodologia aplicada em alguns dos estudos tem sido replicada em empresas de grandes dimensões.

Abstract

Occupational risk prevention is a challenge for Small and Medium-sized Enterprises (SMEs). They are often associated with poorer performance in terms of occupational accident and disease prevention. Throughout this work we demonstrated that Occupational Safety and Health (OSH) performance is related to organizational and management factors, as well as to individual factors. During this research, risk factors were also identified in several SMEs. The collection of such information proved to be critical to the development of risk assessment methods and to the definition of effective intervention strategies. We developed semi-quantitative risk assessment methods, whose applicability was exemplified with SMEs from the furniture sector. Intervention strategies are also being tested in SMEs. A prevention management support system is being developed for these enterprises. The methodology applied in some of the studies has been replicated in large sized enterprises.

Introdução

As Pequenas e Médias Empresas (PMEs) são um importante motor da economia e do emprego na Europa, mas também são responsáveis por grande parte dos acidentes de trabalho e das doenças profissionais. Tratam-se de empresas frequentemente caracterizadas pelo seu baixo desempenho ao nível da Segurança e Saúde no Trabalho (SST), o qual tem sido relacionado com fatores como (Barbosa et al., 2019; Rodrigues et al., 2020; Ramos et al., 2020): (1) recursos humanos, económicos e tecnológicos limitados; (2) dificuldades em cumprir requisitos legais ao nível da SST; (3) dificuldades em avaliar e controlar os riscos ocupacionais; (4) tempo limitado do empregador/gestor para lidar com a SST; (5) baixo conhecimento no que se refere ao processo de gestão de risco; (6) deficiências nos processos organizacionais.

Intervenções que contribuam para a redução dos acidentes de trabalho e das doenças profissionais em PMEs são de suma importância. Para serem eficazes, precisam de atuar sobre os principais fatores que prejudicam o desempenho de SST. Assim, é fundamental identificar os fatores com potencial de intervenção.

Adicionalmente, estas empresas carecem de ferramentas e estratégias que apoiem uma eficaz gestão de risco, devendo ser desenvolvidas e testadas novas soluções que contribuam para a melhoria do desempenho de SST. Assim, ao longo das próximas secções serão abordados os estudos desenvolvidos neste âmbito, bem como o trabalho em curso.

Estudos desenvolvidos

Numa primeira fase, foram realizados estudos para a identificação de fatores relacionados com o desempenho de SST em PMEs. Em Barbosa et al. (2019), através de uma revisão sistemática da literatura, foram identificados 14 indicadores de SST relacionados à gestão e organização, bem como 5 indicadores individuais. Estes incluíram tanto leading como lagging indicators, e foram discutidos em relação à sua aplicabilidade para avaliar o desempenho da SST, bem como em relação à sua fiabilidade. Os indicadores que resultam da aplicação de questionários e entrevistas foram considerados mais subjetivos e mais propensos a enviesamento, enquanto que os indicadores que resultam de observações, análises de bases de dados e de outros relatórios foram discutidos como sendo mais confiáveis.

Foram também desenvolvidos estudos empíricos, com o objetivo de identificar indicadores de desempenho relevantes. Foram realizados estudos no setor do mobiliário para analisar a relação do nível de clima de segurança e da aceitação de risco com o nível de desempenho de SST e com o nível de risco das empresas (Rodrigues et al., 2015a; 2015b). Foi também analisada a relação destas variáveis com a perceção de risco, as emoções e a confiança (Rodrigues et al., 2015b). Estes estudos envolveram 14 PMEs do setor. O desempenho de SST foi determinado com um índice criado para o efeito e que teve como base os fatores de risco identificados nos locais de trabalho e o nível de risco foi determinado através das estatísticas fornecidas pelo Gabinete de Estratégia e Planeamento. As restantes variáveis foram avaliadas através de escalas previamente validadas. Em Rodrigues et al. (2015a) mostrou-se que o clima de segurança estava significativamente correlacionado com o desempenho de segurança e também desempenhava um papel importante nos níveis de aceitação de risco. Em Rodrigues et al. (2015b) foi evidenciado que nível de aceitação do risco estava correlacionado com o nível de risco determinado. A perceção de risco, as emoções e a confiança tiveram uma influência importante na aceitação do risco.

Foram também realizados estudos no setor da gestão de resíduos. Em Rodrigues et al. (2020), pretendeu-se caracterizar as práticas de gestão dos riscos profissionais neste setor e analisar a relação entre essas práticas e o nível desempenho de SST. Para isso, foram envolvidas 66 micro e pequenas empresas

de gestão de resíduos. Os resultados mostraram que várias empresas não tinham política ou objetivos de SST definidos, e apresentavam importantes limitações ao nível da avaliação de risco, registo e análise de acidentes de trabalho e formação aos trabalhadores em matéria de SST. O tempo dedicado pelos empregadores às questões de SST e o apoio dos serviços externos de consultoria também foi considerado baixo em algumas das empresas em estudo. Encontrou-se uma relação positiva e estatisticamente significativa entre estas variáveis e o nível de desempenho de SST. Já em Ramos et al. (2020), através de um estudo realizado numa empresa de tratamento de resíduos sólidos de média dimensão, certificada em 2009 com um Sistema Integrado de Gestão da Qualidade, Ambiente e Segurança (SIG-QAS), foi analisado como a implantação deste influenciou a melhoria do processo de gestão dos riscos profissionais. Foi analisada a evolução do índice de frequência e de gravidade dos acidentes de trabalho antes e após a implantação do SIG-QAS e analisada a perceção dos técnicos sobre o processo de gestão de risco. O estudo foi complementado com entrevistas realizadas ao diretor da empresa e ao responsável pela implementação do SIG-QAS. O estudo mostrou uma melhoria no registro de acidentes de trabalho. Adicionalmente, verificou-se a contribuição do SIG-QAS para um maior envolvimento dos trabalhadores para com as atividades de gestão de risco.

Outro fator chave para o desempenho de SST nas PMEs é a realização de avaliações de risco, que auxiliem os empregadores/gestores no processo de decisão sobre a implementação de medidas de controlo. Contudo, a avaliação de risco nas PMEs é muitas vezes considerada um processo subjetivo, devido às características dos métodos de avaliação frequentemente utilizados (Rodrigues et al., 2018). Adicionalmente, a utilização de critérios de aceitação adequados para os acidentes de trabalho é uma questão importante, mas muitas vezes negligenciada na literatura, principalmente quando novos métodos de avaliação de risco são propostos e discutidos. Tendo isto em consideração, em Rodrigues et al. (2015c) propusemos um modelo para a definição de critérios de aceitação de risco em PMEs, exemplificando a sua definição através de um estudo de caso realizado no setor da indústria do mobiliário. Adicionalmente, com base nos critérios definidos, foi proposta uma matriz de risco semi-quantitativa.

As intervenções de SST podem ocorrer em diferentes níveis do sistema de trabalho, nomeadamente ao nível da gestão da SST e em vários subsistemas humanos e técnicos. Apesar da sua importância, a implementação de intervenções nas organizações pode ser complexa, em particular nas PMEs devido a estas disporem de menos recursos para dedicar a estas questões. Em estudos anteriores analisamos e comparamos diferentes métodos de formação/intervenção incluindo, métodos expositivos formais, e métodos ativos

baseados em demonstrações, apresentação e discussão de testemunhos reais e discussões em grupo. Estes estudos foram realizados com estudantes antes da sua integração no mercado de trabalho (Rodrigues et al., 2018) e trabalhadores de PMEs do setor da metalomecânica (Barros et al., 2020). Em geral, métodos ativos estiveram relacionados com melhores resultados.

Estudos em curso

Estudos adicionais encontram-se a ser desenvolvidos. Nestes estudos estão a ser testadas a aplicação de novas teorias ao processo de avaliação dos riscos ocupacionais, aplicações como o Valor do Risco (Leão et al., 2019) ou a teoria do risco atuarial (Brito et al., 2022) à análise de risco de acidentes de trabalho em PMEs, de forma a permitir classificar e ordenar os riscos.

Encontram-se a ser desenvolvidos estudos que testem novas formas de intervenção em PMEs, envolvendo trabalhadores e empregadores (Costa et al., 2020; Lopes et al., 2020), tendo sido algumas estratégias também testadas em empresas de maior dimensão. Encontra-se também a ser desenvolvido e testado um sistema de apoio à gestão dos riscos profissionais.

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MAD@ WORK

MENTAL HEALTH AND PRODUCTIVITY BOOSTING IN THE WORKPLACE

Mad@Work during the year 2021: ESS | P. PORTO contribution

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Referência do Financiamento: ITEA 3 Call 5 international project 18033 e P2020 (Projeto Nº POCI-01-0247-FEDER-046168)

Abstract

Our work life is changing rapidly. Globalization is ramping up competition, and digitalization is transforming all but the simplest manual labor into knowledge work. These changes don't come without a price – and it seems that the price is paid in an increase of stress and burnout. The cost of work-related stress in Europe was estimated to be around 200 billion annually and, in the USA, job stress alone is estimated to cost companies approximately 300 billion dollars a year. To face the high costs, the key to success requires tackling the work stress-related issues, first, in an individual level.

This project aims to develop novel stress detection solutions for workplaces, which will help to manage and reduce stress in the work context and build safe, positive, and productive work environments. Existing technologies for stress detection have been developed in relatively short-term studies and are not practical and/or mature enough for continuous, real-life usage.

To overcome these shortcomings, we will develop novel solutions to detect workplace problems and stress, convenient for long-term real-life use. Pilots in real workplaces will be conducted to achieve project goals and to evaluate developed solutions. Ultimately, our goal is to support and mitigate ongoing transformation, helping individuals flourish and companies thrive, paving the way for healthier workplaces where people throw up their arms, not in frustration or anger but inspiration and excitement.

Introduction

The International Labor Organization (ILO) defines work-related stress as "the harmful physical and emotional response caused by an imbalance between the perceived demands and the perceived resources and abilities of individuals to cope with those demands" (ILO, 2016). Stress is highly destructive, causing several mental health problems (anxiety, insomnia, depression, fatigue, and concentration difficulties), cardiovascular diseases, poor immune function, and presenteeism, as it is costly, making it cost companies hundreds of Billions Worldwide (Hassard et al., 2017).

Studies estimate that about 50% of all lost workdays are related to occupational stress. At a national and pan-European level, the total estimated cost of work-related stress in 2014 was observed to be considerable and ranged substantially from 195.29€ million to 165€ billion. Productivity-related losses were observed to proportionally contribute most of the total cost of work-related stress (between 70 to 90%), with healthcare and medical costs constituting the remaining 10% to 30%.

Solutions to mitigate risk factors related to working settings present an enormous potential and a clear substantial contribution. There is a tremendous need for the development of applications/software that combines multiple sources of data to gather the information that can improve employees' well-being, commitment, and performance. Existing solutions still largely rely on supervised learning methods, requiring extremely large sets of labeled data for each situation enabling work adaptivity. Also, these solutions rarely integrate

recommendations and active lifestyle changes to counterbalance high-stress situations. Research into assessing stress and mental conditions is still mainly conducted in laboratory environments and the results are not directly linked to real-life settings. By proposing an intelligent recommender system that ensures longitudinal data collection, will improve not only the research studies and making the end-users are highly interested in the 'quantified self'. What is the purpose of making stress detection software/systems? If stress has become a significant predictor of disease and illness in modern society, we shall act for change.

Project Evolution

The main goal of the Portuguese consortia is to explore video feed data and turn it into a physiological set using specific software to assess mental health and correlating this dataset with a daily stress report. This will increase accuracy and coverage in comparison to individual data sources. It will also allow detection of long-lasting problems and to assess the evolution of mental states over time, thus providing feedback on effectiveness of interventions.

To evaluate the user acceptance of the software, we conducted a Focus Group to obtain opinions, perceptions, and concerns of end users regarding the system under development to get the necessary information to define the requirements for the system, including monitoring of worker' stress and solutions to support mental health. The goal of these innovations is to get a better understanding of the trigger stressors (poor office environments, work culture, daily routines etc.), as to validate long-term effectiveness of stress-reducing interventions and to identify risk groups.

The needed data to provide this level of individual recommendation can only result from long-term pilots in real workplaces/settings. The developed solutions will be evaluated in multi-month pilots covering varying working periods, e.g., before and after holidays, so that the obtained data will enable (1) deep understanding of stress manifestation in different working situations and (2) thorough evaluation of the developed solutions.

Technological Solutions

The architecture of our solution is divided into three main components that encapsulate a set of features and tasks:

The first component, data acquisition, is on the user-area and provides several features about the employees' behavior. It contains a video-based application that collects, in a non-intrusive way, physiological features of the workers

such as, pupil diameter, eye gaze and blinking, heart rate variability and facial expressions. The employees will also provide several self-reports of stress at the workplace during the working period that will complement data collected through video.

The second component of the architecture is on the server side of the system. It is responsible for the consolidation of the data and its persistence in a database. Moreover, it allows for behavioral models to be trained based on the data and using machine learning algorithms to predict mental health conditions, concretely stress of knowledge workers.

Finally, the third component of the architecture includes a recommendation system that, using the behavioral models and data collected by the video-based application, predicts in real time if the worker will be in stress, informs the worker about his personal state and provides him with personalized stress mediation recommendations such as mindfulness, meditation, coaching, between others.

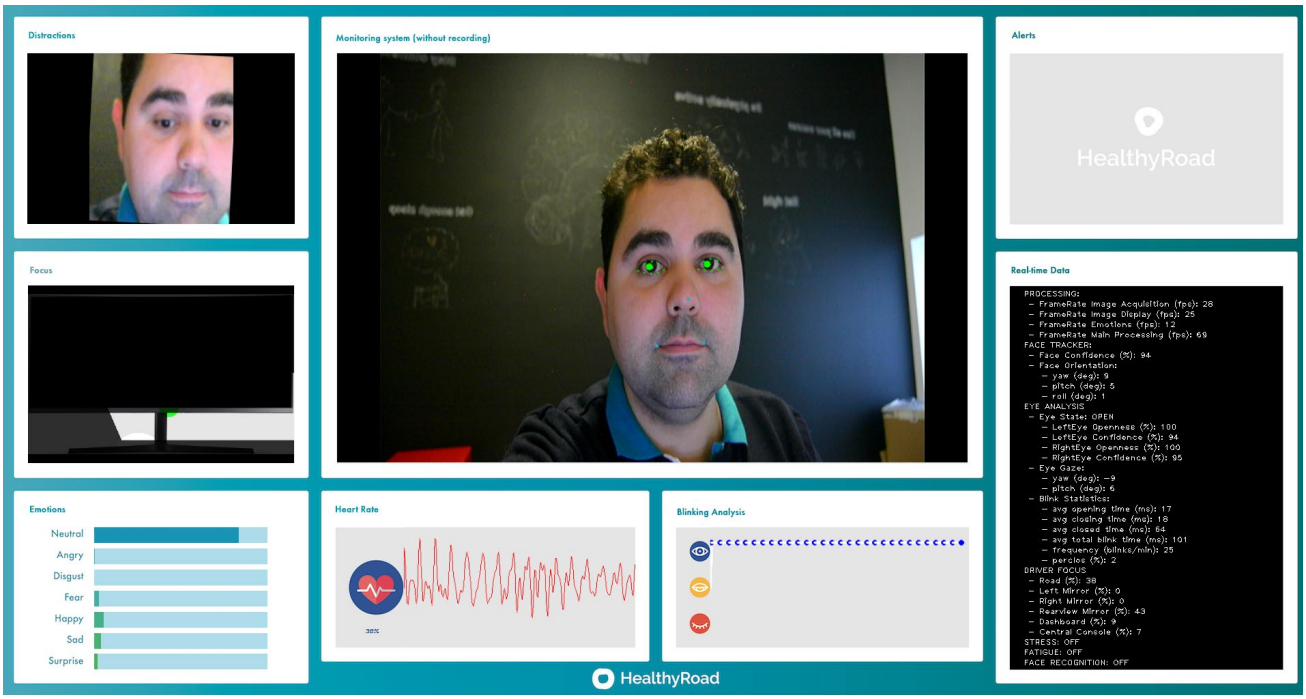

Figure 1: Mad@Work Software Solution for Stress Monitoring

Methods and Recommendations to support mental wellbeing

We are also developing a structured intervention model to mitigate stress that the users feel compelled in using. To do this, user preferences are our top priority, since their adherence and use of the recommended interventions are based on the premise that only preferred recommendations are in each person's model. The next step is to present recommendations for brief stress relief, since the alarm system works with immediate stress peaks, and real-time feedback on experienced stress levels. Experienced stress is analyzed during long periods of time with machine learning algorithms, that will provide the detection of long-term stress.

The digital coach (intervention model) will provide different recommendations and active lifestyle changes such as exercise, task management, weight management, sleep habits, structured pauses, etc. At this stage of the project, we are developing a clear structure that the intelligent software will introduce in the client's routine, preventing, teaching, and providing real-time exercises to mitigate acute stress, long-term stress and aim to change their perception about their own health habits, based on five modules: Be Ready, Be Aware, Be Responsive, Be Rested and Be Minded.

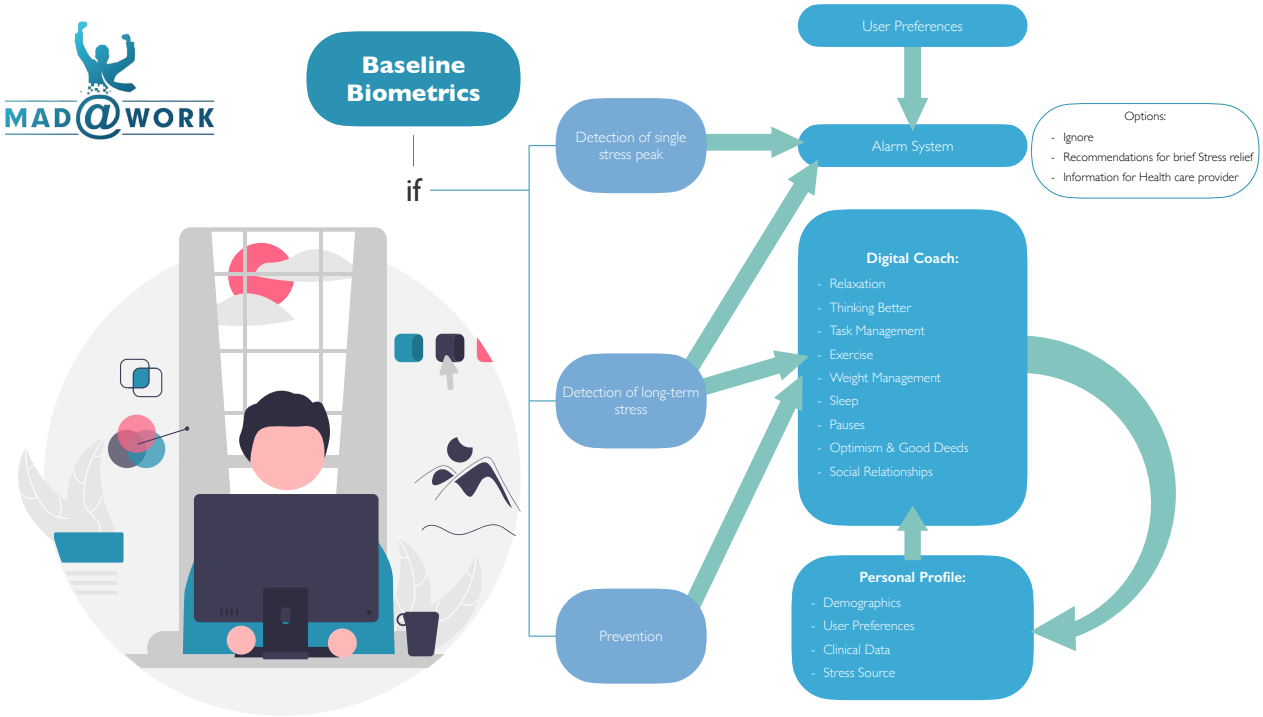

Figure 2: Initial draft of the modules of the Recommendation system for the Portuguese pilot

Be Ready is a module that contains important interventions to prevent stress. Be Aware is where the client can see and analyze his/her own stress data and perceive the needed changes to progress or maintain a healthy lifestyle and a truly improve wellbeing, engagement, and performance. Be Responsive is a module that contains an alarm system and immediate recommendations upon a stress peak during workhours. Be Rested compiles several recommendations of lifestyle changes that will help recovering from stress peaks. Be Minded is a module designed to shape some erroneous beliefs and expectations. The foreseen changes in client's lifestyle and routines will be able to modify his/her perception about certain habits and changes that will improve their performance and engagement, leading to a strong prevention against long-term stress.

For the following project, we collaborated with several Portuguese and international institutions. Specifically, eighteen partners from five different countries, and in Portugal, four principal players: AGEAS/MÉDIS Group, Glintt, ISEP and Healthyroad.

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FAMILY CAREGIVER SUPPORT

Strategies and Tools to Promote Caregiver Mental and Emotional Support

Apoio ao Cuidador Informal - Estratégias e Ferramentas para Promover a Saúde Mental e Emocional dos Cuidadores

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Resumo

Introdução: O cuidado de familiares com doença mental grave acarreta um grande risco para a saúde dos cuidadores, estando associado ao desenvolvimento de problemas emocionais, mentais e de saúde física. O Projeto Family Caregiver Support visa capacitar os cuidadores informais, através do acesso a informações médicas relevantes, que promovam a autoconfiança e as competências, quer no cuidado dos familiares quer relativamente às suas próprias necessidades.

Métodos: Participaram neste projeto parceiros de oito países europeus, incluindo a ESS|P.PORTO, no período compreendido entre 01/11/2018 e 31/10/2020.

Resultados: Este projeto resultou na criação de um Guia e Pacote de Recursos para capacitação dos cuidadores informais, acessíveis através de uma plataforma online gratuita que pode ser acedida por uma aplicação móvel. Todos os materiais foram produzidos em vários idiomas e amplamente divulgados.

Conclusão: Os produtos e conteúdos continuam disponíveis, estimando-se um forte impacto na capacitação dos cuidadores informais, com melhoria da sua qualidade de vida.

Abstract

Introduction: Caring for family members with severe mental illness poses a great risk to the health of caregivers, being associated with the development of emotional, mental and physical health problems. The Family Caregiver Support Project aims to empower informal caregivers, through access to relevant medical information, which promotes self-confidence and skills, both in the care of family members and in relation to their own needs.

Methods: Partners from eight European countries participated in this project, including ESS|P.PORTO, in the period between 01/11/2018 and 31/10/2020.

Results: This project resulted in the creation of a Guide and Resource Pack for training informal caregivers, accessible through a free online platform that can be accessed through a mobile application. All materials were produced in multiple languages and widely disseminated.

Conclusion: The products and contents are still available, with an estimated strong impact on the training of informal caregivers, improving their quality of life.

Introduction

Mental disorders are highly prevalent in Europe and place a heavy burden on individuals, the society and the economy. These types of disorders represent 22% of the disability burden in the EU, measured as Years of Life with Disabilities (YLD). The responsibility for these types of disorders for individuals, society and the economy is associated with the high prevalence of mental health problems, in which the majority of cases start at an early stage of life - in many cases before the beginning of adulthood, and at the fact that about half of people with mental health problems do not receive evidence-based treatments. Furthermore, in 2015 there were an estimated 9.6 million people in EU countries living with dementia, equivalent to almost one in 50 people. Higher life expectancy will undoubtedly lead to an increase in these numbers in the coming years. Family caregivers play a central role in the care of persons with severe mental illness. This is an important fact and the result

is that the majority of caregivers live with the illness of their affected relative 24 hours of the day, each day of the year.

Moreover, we found that in all EU countries the support provided to family caregivers only refers to economic and insurance aspects. In addition to information on monetary or insurance matters, family members are left alone without the possibility of having immediate access to social and psychological support.

Research shows that family members who provide care to individuals with chronic or disabling mental conditions are themselves at risk. Emotional, mental, and physical health problems arise from complex caregiving situations and the strains of caring for frail or disabled relatives. Medical advances, shorter hospital stays, and expansion of home care technology have placed increased care responsibilities on families, who are being asked to shoulder greater care burdens for longer periods of time.

As a response to this situation, this project intends to empower family members as caregivers and to give them access not only to relevant medical information, but also to psychological support for their own needs.

Aims and target-audience

The main objective of this project is empowering citizens to develop self-confidence and skills in caring for family members with mental illness and to give them instant and easy-to- understand access not only to relevant medical information, but also to psychological support for their own needs. To this end, the project aims to develop a Guide and Resource Pack to provide caregivers with helpful tips, tools and information. Two of its main sections will focus on "Caring for YOU" and "Caring for the Individual"; ensure immediate access to these developed products anywhere, anytime and in all languages of project partners. The products will be available not only as interactive web-based content, but also as mobile applications; include refugees, asylum seekers and migrants who do not or have little command of the language of the host country. To this end, we will also produce translations of the materials in Arabic and Pasthun.

The main target groups of the project are adults caring for a family member with a mental illness. The secondary target group are people working in health and social care organizations who can inform family members about the existence of the Guide and Resource Pack or use these materials in their information and counseling activities. Also other stakeholders and counselors, as well as other institutions dealing with migrants and refugee integration, that can disseminate the materials among theirs clients. The project fits into

the partners' common strategy as it is in line with their general research or teaching activities.

Profile of the partners

The partnership comprises partners working in psychiatric, psychological or social research and/or as providers of adult education will enrich the quality of the results, making them immediately applicable to exploitation. Moreover, it includes ICT and multimedia specialists, where only the combined efforts made possible the results of the project. This transnational cooperation develops the best practice approaches and transfer them into localized solutions in the eight European states of the partnership and beyond.

The group of social and medical research organizations specialized in various aspects of health care consists of: 1 - MEDRI - Department for psychiatry and psychological medicine of the Faculty of Medicine, University of Rijeka (Croatia), offering education programs in the field of psychological medicine, psychiatry and communication skills; 2- NUIG - Health Promotion Research Centre at the National University of Ireland, known by producing high quality research that supports the development of best practice and policy in the promotion of health; 3- IUL - Italian University Line, is a non-state public university of telematics; 4- ESS|P.PORTO - School of Health (Portugal) is an applied sciences higher education institution with a strong human, technological and ethical capital dedicated to the development of health technologies; 5- INTEGRA Institute for Development of Human Potentials (Slovenia), with specialized counsellors from the field of special pedagogy, psychology, speech therapy, social work and systemic humanistic psychotherapy; 6 – E-C-C – Association for Interdisciplinary Education and Consulting (Austria), has extensive experience in the design of learning and information materials for ICT communication in virtual environments; 7 - QUALED Qualification and Education (Slovakia) is active in the field of innovative learning technologies for supporting learning processes in different settings for different target groups; 8- CSI (Cyprus), Center for Social Innovation, with expertise in the development and provision of advanced ICT services and applications in teaching and learning.

Activities and Results

- *Needs assessment and strategy*

To reach the objectives there is place for a state of art in Europe and in individual countries of the partnership, analyzing them and find a common starting point for developing the educational materials. The transnational meetings performed

made possible the distribution of activities according to the know-how of the partners, as well as the monitoring and follow up of the project.

- *Guide and Family Caregiver Support Resource*

The Guide aimed to provide safe information, support and resources for family caregivers of adults with chronic mental illness and cognitive conditions to better understand their health and their diagnosed disorders. This Guide gives background information about each disorder, explains which behaviour of the patient can be expected, focuses on concerns which the caregiver may have, and presents strategies what can be done and how to deal with this disorder (**Figure 1**).

The Family Caregiver Support Resource consists of two main sections: caring for YOU and caring for the individual. This resources pack provide learning and information material about mental disorders in an easily understandable way.

This Guide provides the complement to the Resource Pack which is available in the Internet (https://www.family-caregiver-support.eu). On the online platform, interested readers will find modules with information for the following nine mental disorders: ***Dementia, Substance abuse, Schizophrenia, Common mood disorders, Intellectual disability, Attention deficit hyperactivity disorder (ADHD), Autism, Eating disorders and Post-traumatic stress disorder (PTSD).***

For each module/disorder, specific contents were developed covering aspects about understanding the respective disorder, the concerns of the caregiver, the role of nutrition, activities to support and empower the caregiver and activities for the person receiving the care (**Figure 2**).

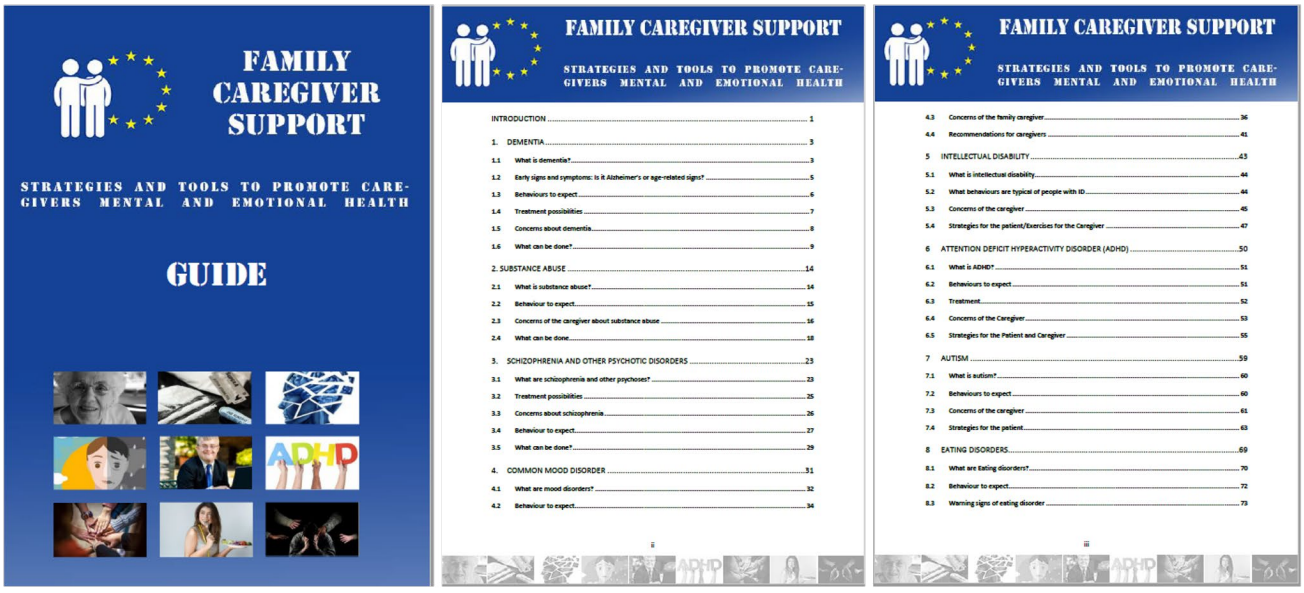

Figure 1. Guide and Family Caregiver Support Resource

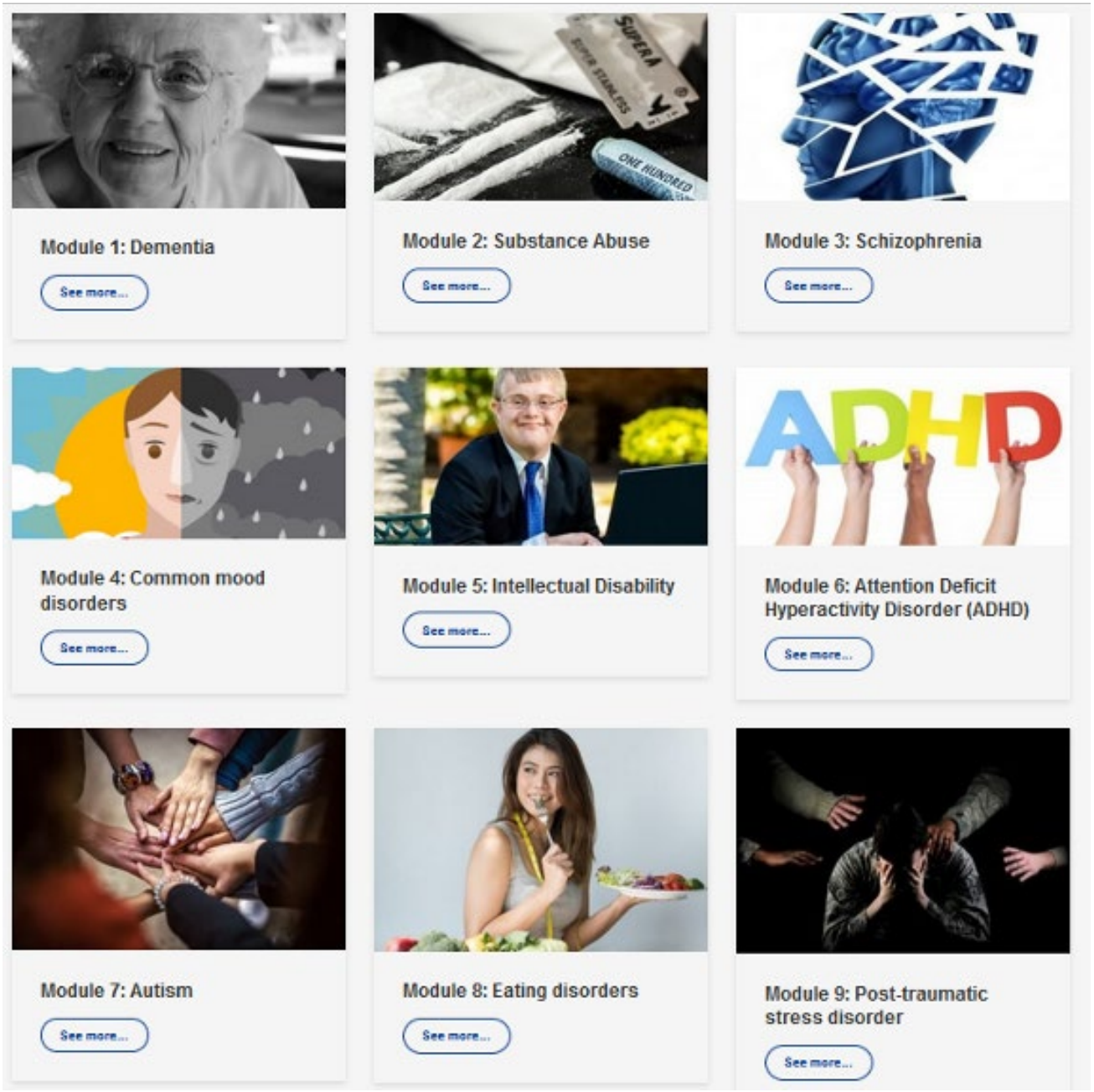

Figure 2. Illustration of contents displayed in the online platform in respect to 9 different mental disorders.

- *The platform and mobile application*

Materials were developed as power point files support that were uploaded after the validation and translation, on an online platform that was created and installed on the project's website. An example of the appearance of the website is showed on **Figure 3**. These developed materials can be consulted anywhere at any time through an App produced for android mobile devices.

Figure 3. Illustration of the website of the Family Caregivers Project, translated in different languages.

- *Validation of the products*

The Resource e-platform needed to be tested thoroughly to ensure that it is stable and fully functional to be used by experts and the targeted end users. Thus, the contents of the Resource Pack were externally evaluated within the platform in order to ensure that they perform as intended and that they are well integrated in the virtual environment. Moreover, the platform was evaluated to ensure that it is fully functional on all the widely used operating systems, browsers and mobile phones. The validation of the materials was carried out in each country within experts and family caregivers focus groups to register the outcomes of the validation and the suggestions and feedback from the participants, in order to reach the most useful approaches.

Online questionnaires were developed by the project team and translated in different languages. Participants of the focus group consisted of family caregivers and citizens interested in caring and Health and Social Services Professionals - Experts. Data were collected and processed anonymously and

confidentially. As an example, **Figure 4** represents the validation results in Portugal concerning the Website and Online Platform (Layout; Registration process; Navigation system, Accessibility to content, Attractive) (**Figure 4A**) and concerning the contents produced (Are the modules useful/informative to support skills and competence development in Family Caregivers?), for both participant groups (**Figure 4B**).

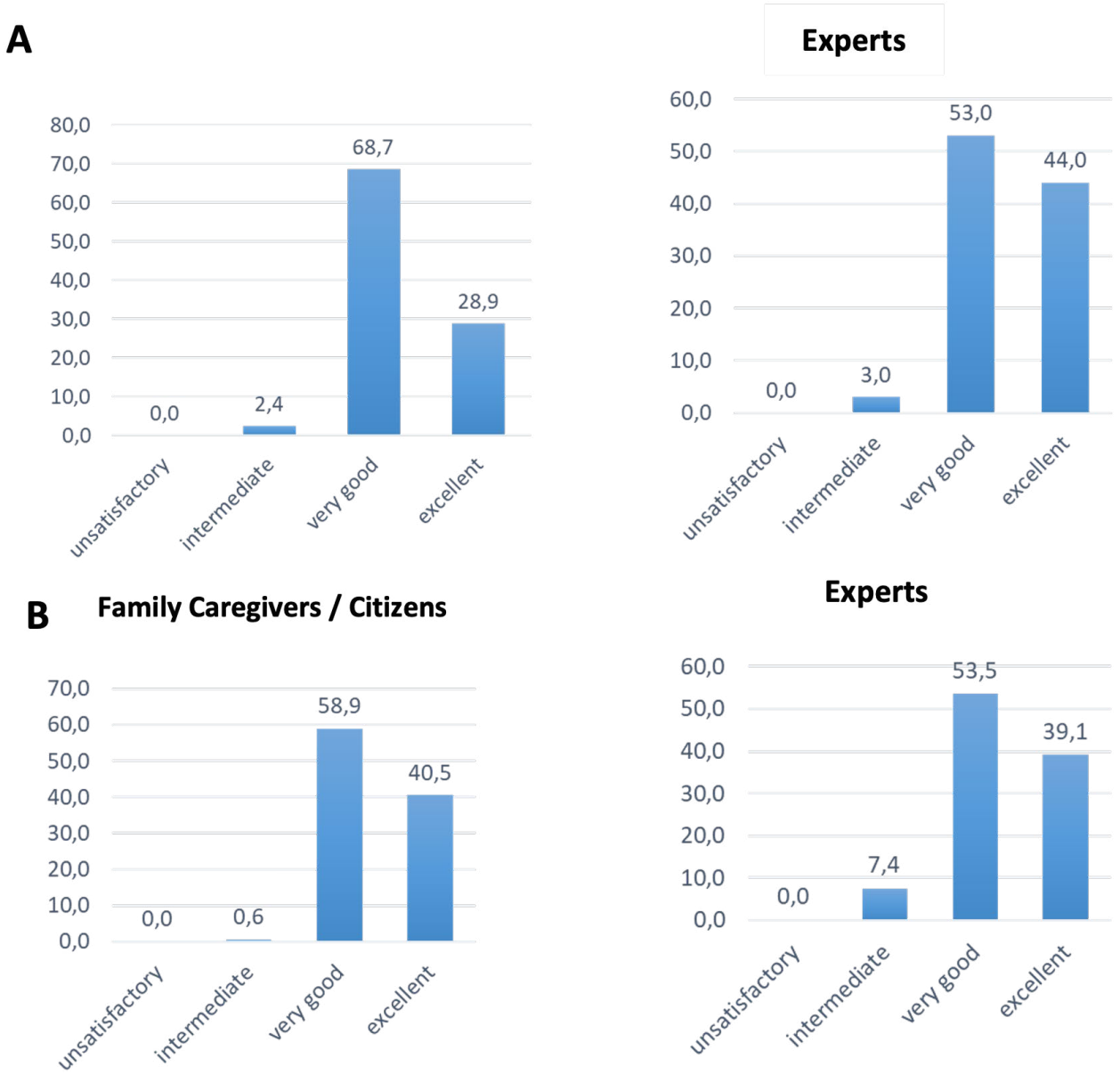

Figure 4. Illustration of the validation results in Portugal concerning the Website and Online Platform (**A**) and the contents produced (**B**), for both Family Caregivers/Citizens and Experts.

In general, the online platform comprising the materials is appealing and very easy to use. The mobile application runs smoothly, and the contents can be accessed anytime and anywhere. However, the necessary changes were performed to the online platform according to the suggestions made by the participants of each country.

Platform contents are generally suitable for their purpose - citizens consider contents well designed and enough for them and consider the platform attractive and easy to use. The platform comprising the materials is appealing and very easy to use and the mobile application runs smoothly, and the contents can be accessed anytime and anywhere.

- *Dissemination of developed materials/contents*

Taking into account the results of the validation results, partners proposed to apply some activities with the aim of dissemination of the results. Thus, some multiplier events of the products were conducted with the objective of publicizing the Family Caregiver's project products. Dissemination activities were made within care providers and social support institutions, through social media, secondary schools, higher education institutions, community and technical-scientific events.

Conclusion

As a conclusion, this project essentially allowed the empowerment of Family Caregivers encouraging them to take care of their physical, mental and emotional health. Family Caregivers and citizens can thus develop their self-confidence and competences in caring of family members with mental illness, including refugees, asylum seekers and migrants who have no or only little command of the host country's language. Moreover, there is a possibility for the immediate access to helpful to the contents and information at any place or any time in all languages of the partnership countries - products of this project are available not only as interactive web-based contents, but also in mobile apps.

The project was concluded and all the objectives were successfully reached. The validation and dissemination phases allowed us to conclude that the materials produced in the context of this project were generally well received and highly appreciated by the inquiries.

It would be interesting to update and improve the materials throughout time, in order to have access to the needs of professionals working in the areas of counselling and therapy. In the upcoming years, it will be important to follow the stakeholders and the experts who are linked to the project in order

to promote online interventions and, consequently, the online materials.

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APPLIED RESEARCH ON

ENVIRONMENTAL AND OCCUPATIONAL HEALTH

IN HOSPITAL CONTEXT

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Resumo

As instalações hospitalares são normalmente muito complexas, que aliadas às exigências dos cuidados de saúde dos pacientes promovem condições para o desenvolvimento potencial de condições de trabalho desconfortáveis. O trabalho em hospitais é assim suscetível de causar danos à saúde resultando em acidentes e doenças ocupacionais. Neste sentido, foi desenvolvido uma linha de investigação com foco em Saúde Ambiental e Ocupacional em Contexto Hospitalar, com o intuito de ser uma contribuição para a compreensão dos fatores de risco aos quais profissionais de saúde e pacientes estão expostos e como essa exposição pode ser reduzida. Esta linha de investigação resultou até à data em 34 publicações e 11 comunicações orais/pósteres: 6 artigos em revistas científicas internacionais, 3 capítulos de livros, 13 artigos/resumos em livros de anais de congressos internacionais, 4 relatórios técnicos, 1 tese de doutoramento e 7 trabalhos de conclusão de curso. O projeto permitiu o estudo de dados sobre exposição ocupacional e acidentes em ambientes hospitalares no Norte de Portugal.

Abstract

Hospital facilities are normally, very complex, which combined with patient requirements promote conditions for potential development of uncomfortable working conditions. The work in hospitals is likely to damage health resulting in occupational accidents and diseases. In this sense, a project focused on Environmental and Occupational Health in Hospital Context was developed to be a contribution to understand the risk factors to which health professionals and patients are exposed in these environments and how this exposure can be reduced. This research line resulted in 34 publications and 11 oral/poster communications: 6 articles in international scientific journals, 3 book chapters, 13 articles/abstracts in books of international congress proceedings, 4 technical reports, 1 doctoral thesis and 7 final course works. The project allowed the study of data about occupational exposure and accidents in hospital environments in the North of Portugal.

Introduction

Workplace-related health impairments, injuries and illnesses cause great human suffering and incur high costs, both for those affected and for society as a whole. Occupational health and safety (OSH) measures and health promotion in workplaces are aimed at preventing this. Hospitals are peculiar workplaces, designed almost exclusively to the needs of users, giving their workers poor working conditions (Carvalhais, Santos, & da Silva, 2016a). The hospital organizations are among the most complex structures, given their diversity of services, facilities, equipment and their hierarchical system of several departments and professions (such as physicians, nurses, health technicians, administrative personnel and general services). The hospital environment has many occupational health risks due to the variety of clinical and non-clinical tasks performed by healthcare workers. The exposures to psychosocial, chemical, physical, mechanical and biological hazards are common in hospital units and predispose healthcare workers to different types of accidents (Nunes et al., 2015). In a paradoxal way, the hospital environment has risks that may pose immediate threats, causing sooner or later health problems to people who maintain direct contact and/or daily life with this kind of environment. There

is also the risk of work accidents with serious consequences for healthcare workers and sometimes for patients. In hospitals, patient exposure has been studied more frequently over the years, than occupational exposure, but in general, vulnerable groups are underrepresented in study populations. This research line pretends to be a contribution to understand the risk factors to which health professionals and vulnerable patients are exposed in these environments and how this exposure can be reduced.units and predispose healthcare workers to different types of accidents (Nunes et al., 2015). In a paradoxal way, the hospital environment has risks that may pose immediate threats, causing sooner or later health problems to people who maintain direct contact and/or daily life with this kind of environment. There is also the risk of work accidents with serious consequences for healthcare workers and sometimes for patients. In hospitals, patient exposure has been studied more frequently over the years, than occupational exposure, but in general, vulnerable groups are underrepresented in study populations. This research line pretends to be a contribution to understand the risk factors to which health professionals and vulnerable patients are exposed in these environments and how this exposure can be reduced.

Occupational accidents in Hospitals: A case study

A study aiming to compare different methods for work accidents (WA) investigation and to verify their suitability in hospital environment (Nunes et al., 2015). For this purpose, three types of accidents that were related with needle stick, worker fall and inadequate effort/movement during the mobilization of patients, were selected. The types of WA analysed were selected according to the national prevalence of WA in Portuguese hospitals. A total of thirty accidents were analysed with six different work accidents investigation methods. The results showed that organizational factors were the group of causes which had the greatest impact in the three types of work accidents. Accident investigations are an integral part of any good safety and health initiative. This study showed that “organizational influences” are the most relevant cause of WA in hospitals, independently of the method applied. The methods used are not mutually exclusive. They can complement each other and be adaptable to the hospital environment. However, the Registration, Research and Analysis of Work Accidents method (RIAAT) showed to be an optimal technique to use in this context. This study was a contribution to OHS practice, for the selection of methods for the analysis of occupational accidents in hospitals and a helpful contribute to improve the investigation system of work accidents in these institutions and in similar sectors.

Thermal comfort among hospital workers: Assessment in two sterilization services through analytical and subjective approaches

The hospital facilities are normally, very complex, which combined with patients requirements, promote conditions for the development of uncomfortable working conditions (Carvalhais, Santos, & da Silva, 2016a). Thermal discomfort is one example of many. This study aimed to determine levels of thermal comfort, sensations and preferences, from a field study carried out in two sterilization services (SS), of two Hospitals from Porto and Aveiro, Portugal. The analytical determination and interpretation of thermal comfort was based on the assumptions of ISO 7726:1998 and ISO 7730:2005. The predicted mean vote (PMV) and predicted percentage of dissatisfaction (PPD) indices were obtained analytically by measurement and estimation of environmental and personal variables, respectively, and calculated according to ISO 7730 equations. The subjective variables were obtained from thermal sensation (subjective PMV) and affective assessment (subjective PPD), reported by questionnaire based on ISO 10551:1995. Both approaches confirmed thermal discomfort in both sterilization services (codified as SS1 and SS2). For all areas, PMV and PPD exceeded in all periods of the day the recommended range of -0.5 to +0.5 and <10%, respectively. No significant differences were found between day periods. The questionnaire results showed that SS2 workers reported a higher level of thermal discomfort. Although, there are no significant differences between PMV and thermal sensations and between PPD and affective assessment. The PMV/PPD model has been found suitable to predict the thermal sensations of the occupants in hospital sterilization services located in a mild climate.

NeoNoise Project: Integrated Approach to Minimize Sound Pressure Levels in Neonatal Intensive Care Units

Exposure to sound pressure levels in neonatal intensive care units has been recognized as a factor which influences the quality and well-being of the occupants (workers and others), as well as the recovery of premature infants who are hospitalized (Carvalhais et al., 2017). Prematurity and low birth weight of newborns lead to the need of a special care in neonatal units, and their permanence in these places can be extended for a long period. Evidence indicates that exposure to high levels of noise adversely affects human health, and these effects are dependent upon various factors (Carvalhais et al., 2015). In hospitals, there are many sources of noise, and high levels exert an impact on patients and staff, increasing both recovery time and stress, respectively.

This study aimed to make an integration of all relevant factors, with the intention to contribute to change the working practices and occupant's

behaviors (Carvalhais, Santos, Xavier, et al., 2016b). This project provided data on sound pressure levels by objective and subjective approaches, as well as information about the exposure factors and sensitivity of the occupants to noise. With this in mind several studies were performed, such a systematic review to examine the studies related to noise in NICUs to understand the sources and effects of noise, as well as some strategies to reduce noise exposure (Carvalhais et al., 2018). Since the Portuguese reality regarding noise levels in NICU wasn't very explored yet, a study aiming to evaluate and characterize the sound pressure levels in three Portuguese NICUs and the noise perceptions of staff, was performed (Santos et al., 2018). Additionally, a study with the purpose to assess the newborns exposure to noise during several health care activities of two NICU, was conducted (Carvalhais et al., 2017). After those studies concerning the characterization of environmental conditions of NICU, more two studies were carried out to test two noise reduction strategies. One of them a study aiming to develop, implement, and evaluate the effectiveness of a training program on noise reduction in NICU, was performed (Carvalhais et al., 2015). The other one, pretended to evaluate the sound pressure levels and to assess noise perception of professionals in a NICU before and after structural modifications and layout redesign (Carvalhais et al., 2021). Finally, some good practices guidelines were summarized in order to promote a healthier environment and to prevent noise production (Carvalhais et al., 2019). All the mentioned studies involved walkthrough inspections, noise measurements and questionnaire surveys. It was found that the noise levels to which the newborns and staff are exposed in NICU, often exceeds the recommended levels for these spaces. But it should be recognized that is very difficult accomplish the proposed levels. However, slightly improvements were found in terms of noise reduction, but unfortunately, the pattern was similar to other studies. Evidence also shows several adverse health effects for newborns and health care staff perceptions of noise. Staff working in NICU environments need more education to understand the effects of noise on the preterm infant's physiological stability. With this education, they will be more aware of the need to change their actions and behavior to reduce noise, which can benefit their patients, and parents, as well as themselves. Even recognizing that a training program is important to change behaviors, this need to be considered in a broader context to effectively control noise in the NICU. Some initial resistance to the implementation of some recommendations is expected, but evidence shows that in general, with training, health care staff recognize the need of changes. Also, the enrolment of hospital top management is fundamental.

Achievements

This research line resulted in 34 publications and 13 oral/poster communications: 6 articles in international scientific journals, 3 book chapters, 13 articles/summaries in books of international congress proceedings, 4 technical reports, 1 doctoral thesis and 7 final course works. Also, it was recognized with two distinctions by PAPRE program from Polytechnic Institute of Porto. The project allowed the study of data about occupational exposure and accidents in hospital environments in the North of Portugal.

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A AVALIAÇÃO MULTIDOMÍNIO DA EFICÁCIA DE PROGRAMAS DE

REABILITAÇÃO NEUROCOGNITIVA

SUPORTADOS NAS NOVAS TECNOLOGIAS DIGITAIS

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Resumo

O envolvimento das novas tecnologias digitais nos processos de estimulação e reabilitação neurocognitiva (RNC) tem potenciado a eficácia e eficiência dos serviços de RNC, nomeadamente através de uma maior personalização aos perfis funcionais de cada indivíduo. Apesar disso, os protocolos de avaliação da eficácia destes processos baseiam-se maioritariamente em resultados de instrumentos tradicionais que não fornecem informação específica sobre as alterações que produzem quer no funcionamento cerebral *per se*, quer no seu funcionamento multissensorial.

Desta forma, o projeto de investigação em curso foca-se na avaliação da eficácia de programas de RNC suportados nas novas tecnologias digitais, em diferentes patologias neurológicas utilizando protocolos de avaliação constituídos por medidas de resultado multidomínio. Os protocolos incluem medidas de: avaliação neuropsicológica tradicional, do estado emocional, qualidade de vida, funcionalidade, neurofisiologia (i.e., conectividade funcional), e das funções sensoriopercetivas.

Abstract

The involvement of new digital technologies in neuropsychological stimulation and rehabilitation programs (NRP) have been potentiated the efficacy and efficiency of NRP services, namely through a larger customization of these services to the functional profiles of each person. Nonetheless, the protocols that are being used for assessing the efficacy of these processes are mostly based in the results of traditional assessment instruments, that do not provide specific information regarding the changes produced neither in the brain functioning itself, either in the multisensory functioning.

Therefore, this research project focus on the assessment of the efficacy of NRP supported on new digital technologies, in different neurological pathologies using assessment protocols composed by multidomain outcome measures. The protocols included different types of outcome measures, among which: traditional neuropsychological assessment, emotional state, quality of life, functionality, neurophysiology (i.e., functional connectivity), and of sensory-perceptive functions.

A reabilitação neurocognitiva (RNC) tem como objetivo o alcance de um estado ótimo de funcionalidade, com base num primeiro momento de avaliação compreensiva dos défices individuais através da análise das relações cérebro-comportamento (Cicerone et al., 2000). Os rápidos avanços tecnológicos característicos das últimas décadas contribuíram significativamente para o desenvolvimento de novas ferramentas de estimulação e RNC suportados na utilização das novas tecnologias digitais, traduzindo-se numa redução dos custos dos cuidados de saúde e num aumento da eficácia e eficiência da reabilitação (Caltagirone & Zannino, 2008; Dores et al., 2020; Entwistle & Newby, 2013; Musiat & Tarrier, 2014). Estas ferramentas têm como principais características a adequação e personalização do curso da RNC ao desempenho individual, através do ajuste automático da dificuldade das tarefas, e a preocupação com a diversificação e carácter motivador e ecológico das mesmas, potenciando o processo de aquisição e generalização de competências (Cruz et al., 2013; Dores et al., 2016).

A necessidade de sustentar a prática clínica em evidência científica tem evidenciado a importância de avaliações compreensivas da eficácia das práticas

de estimulação e RNC. Não obstante, os protocolos de avaliação utilizados baseiam-se maioritariamente em instrumentos de avaliação neuropsicológica tradicional que, apesar de serem extremamente relevantes para o desenho das intervenções, não fornecem informação específica acerca do funcionamento cerebral e multissensorial *per se*.

Uma revisão sistemática da literatura focada na avaliação da eficácia dos programas de RNC para pessoas com Lesão Encefálica Adquirida (LEA) suportados nas novas tecnologias digitais demonstrou que a mesma tem sido feita através de um desenho experimental maioritariamente pré- e pós-intervenção, com um número reduzido de estudos a incluir medidas de avaliação follow-up ou durante a intervenção. Adicionalmente, os protocolos de avaliação tendem a focar-se na avaliação da memória, atenção e funcionamento executivo, apesar de se verificar uma tendência crescente para a inclusão de medidas relacionadas com o funcionamento diário, revelando uma preocupação crescente com a validade ecológica destes protocolos. No que diz respeito às medidas de resultado utilizadas, verificou-se uma preponderância da utilização de instrumentos de avaliação neuropsicológica tradicionais, com uma grande heterogeneidade, e uma utilização escassa de métodos de avaliação complementar, como por exemplo métodos de avaliação do funcionamento cerebral (Geraldo et al., 2018a). De facto, a conjugação de tarefas de avaliação neuropsicológica tradicional com técnicas de neurofisiologia parece ser relevante por auxiliar o diagnóstico precoce de algumas condições clínicas; por permitir ultrapassar algumas limitações dos instrumentos de avaliação neuropsicológica tradicional, nomeadamente em pessoas com perturbações ao nível da comunicação; e por dar informação relevante para o planeamento e sobre a eficácia de programas de RNC (Geraldo et al., 2018b).

Considerando o impacto das alterações sensoriais associadas ao envelhecimento nas atividades da vida diária e a interação entre funcionamento sensorial e cognitivo, foi conduzida uma revisão narrativa com o objetivo de compreender a utilidade das tarefas de integração multissensorial na avaliação cognitiva e funcional de idosos. Atendendo ao caráter multissensorial da maioria das atividades da vida diária concluiu-se que a inclusão de medidas de integração multissensorial nos protocolos de avaliação neuropsicológica de idosos com e sem comprometimento cognitivo tem potencial para aumentar a validade ecológica da avaliação, possibilita a obtenção de uma medida pura do processamento sensoriopercetivo e é consistente com o modelo neurocognitivo de Luria, que propõe uma abordagem dinâmica na avaliação neuropsicológica (Pinto et al., 2021).

Esta linha de investigação foca-se, por isso, na avaliação da eficácia de

programas de RNC suportados nas novas tecnologias digitais, em diferentes patologias neurológicas (Geraldo et al., 2018a; Pinto et al., 2020a; Pinto et al., 2020b; Pinto et al., 2021) e através de protocolos de avaliação constituídos por medidas de resultado multidomínio. Tem como principal objetivo contribuir para o estabelecimento de práticas baseadas na evidência ao nível da RNC, com especial enfoque nas novas tecnologias digitais.

Os protocolos de avaliação utilizados nos estudos em curso integram medidas de resultado multidomínio, de entre as quais constam instrumentos de avaliação neuropsicológica tradicional, avaliação do estado emocional, qualidade de vida e funcionalidade, medidas e conectividade funcional (neurofisiologia), e/ou medidas de avaliação das funções sensoriopercetivas.

Como produtos finais da linha de investigação, que teve origem num projeto de doutoramento concluído, estão previstas duas teses conducentes ao grau de Doutor em Psicologia, pela Faculdade de Psicologia e de Ciências da Educação da Universidade do Porto, já em curso, na área das neurociências cognitivas e afetivas.

A tese intitulada "Estudo randomizado controlado da eficácia da estimulação e reabilitação neurocognitiva de base tecnológica na Lesão Encefálica Adquirida, com medidas de resultado multidomínio", financiada pela Fundação para a Ciência e a Tecnologia com a referência SFRH/BD/138723/2018, pretende contribuir para o desenvolvimento de um programa de estimulação e RNC baseado nas novas tecnologias digitais, em língua portuguesa e tomando como referência características-chave reportadas na literatura, e para a implementação de medidas de resultado multidomínio nos protocolos de avaliação da eficácia das intervenções. Será constituída por dois estudos experimentais, que têm o objetivo transversal de verificar a relevância de um protocolo de avaliação constituído por medidas de resultado multidomínio na avaliação neuropsicológica, dos quais constam medidas comportamentais e neurofisiológicas. Os dois estudos encontram-se atualmente em desenvolvimento, sendo que o primeiro estudo pretende pilotar um programa de base tecnológica, enquanto ferramenta de estimulação neurocognitiva em amostras da população idosa saudável/com défice cognitivo ligeiro, avaliando os seus efeitos; e que o segundo estudo pretende implementar e avaliar a eficácia de um programa de RNC de base tecnológica em amostras da população portuguesa com LEA, em comparação com programas de RNC tradicionais. No âmbito deste projeto de doutoramento foi conduzida a tradução e adaptação cultural da plataforma de estimulação e RNC NeuronUP para o português europeu, que já se encontra atualmente em comercialização em Portugal. A tese intitulada "Eficácia de um Programa de Estimulação Cognitiva (EC) e Multissensorial na Demência: Estudo Randomizado Controlado"

pretende contribuir para a melhoria dos serviços de saúde mental na demência, fornecendo ferramentas de eficácia comprovada, de maior validade ecológica e baseadas em evidência científica. Os principais objetivos desta investigação consistem em explorar se: (a) programas manipulativos (papel e lápis) produzem resultados equiparáveis ou melhores do que programas de estimulação cognitiva em suporte informático na demência leve a moderada; (b) a EC com base em programas manipulativos combinada com Integração Multissensorial tem melhores resultados nesta população específica do que a EC aplicada de forma isolada. A investigação encontra-se em curso e no âmbito deste projeto foi desenvolvido um modelo teórico para o planeamento individualizado das sessões de treino neurocognitivo, partindo dos resultados da avaliação neuropsicológica (Pinto et al., 2020c). Além disso, desenvolvemos um programa de Integração Multissensorial suportado por uma revisão crítica que propõe um enquadramento teórico para a intervenção combinada (treino neurocognitivo e sensorial (Pinto et al., in press). Atendendo à relevância de garantir a validade ecológica da avaliação neuropsicológica, desenvolvemos uma revisão sistematizada combinada com análise de conteúdo com o objetivo de identificar as dimensões da validade ecológica e compreender como este conceito é operacionalizado na avaliação neuropsicológica (Pinto et al., in press). Por último, partindo os resultados desta revisão desenvolvemos uma checklist para avaliação da validade ecológica dos testes de avaliação neuropsicológica (Pinto et al., in press).

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LOVE. DIST@ANCE

ENSINO À DISTÂNCIA COMO FORMA DE EQUIDADE NO ACESSO AO ENSINO SUPERIOR

Resultados preliminares de um projeto em curso

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Resumo

O Ensino Superior tem assistido a um crescimento em todo o mundo nas últimas décadas. Contudo, verificam-se grandes assimetrias no que respeita ao acesso, com países/regiões específicos a apresentar acentuadas desigualdades de oportunidades, especialmente em grupos populacionais sub-representados devido ao status socioeconómico, raça, etnia, religião, idade, sexo, deficiência ou origem geográfica. Paralelamente, o acesso à internet tem vindo a massificar-se e provar o seu potencial como forma de democratização no acesso à informação.

O projeto Love.Dist@nce foi criado para responder às necessidades da Geórgia e de Israel, com o contributo de parceiros Europeus, com o objetivo de promover a educação inclusiva através de ensino à distância. Após 18 meses de atividade o projeto segue o seu curso e foram já criados vários relatórios e materiais de apoio que servirão de base à implementação de unidades curriculares piloto atualmente em curso, envolvendo docentes, estudantes e não-docentes.

Abstract

Higher Education has seen growth across the world in recent decades. However, there are large asymmetries in terms of access, with specific countries/regions showing marked inequalities of opportunities, especially in population groups that are underrepresented due to socioeconomic status, race, ethnicity, religion, age, sex, disability or origin geographic location. At the same time, access to the internet has become widespread and has proven its potential as a way of democratizing access to information.

The Love.Dist@nce project was created to respond to the needs of Georgia and Israel, with input from European partners, with the aim of promoting inclusive education through distance learning. After 18 months of activity, the project is continuing its course and several reports and support materials have already been created that will serve as a basis for the implementation of pilot curricular units currently in progress, involving teachers, students and non-teaching staff.

O Ensino Superior (ES) tem assistido a um crescimento surpreendente em todo o mundo nas últimas décadas. Contudo, verificam-se grandes assimetrias no que respeita ao acesso, com uma taxa bruta de matrícula de 68% na Europa, 23% no Sul da Ásia e 9% na África Subsaariana (dados do Instituto de Estatística da UNESCO). Além disso, verifica-se que países/regiões específicos apresentam acentuadas desigualdades de oportunidades, pelo que muitos definiram metas para aumentar a parcela da população com ES e/ou ampliar o acesso ao ES para indivíduos que estão sub-representados devido ao status socioeconómico, raça, etnia, religião, idade, sexo, deficiência ou origem geográfica.

Paralelamente, o acesso à internet tem vindo a massificar-se e provar o seu potencial como forma de democratização no acesso à informação. O Ensino a Distância (EaD) tem vindo a ser explorado como uma solução, na medida em que o processo de ensino-aprendizagem à distância se desenvolve através da utilização meios eletrónicos, nomeadamente recorrendo às Tecnologias

Digitais da Informação e da Comunicação, acionadas em rede, através da internet. Contudo, não basta uma transição no canal de comunicação para que o ensino ocorra de forma eficiente. Diversas metodologias de ensino têm vindo a ser desenvolvidas e validadas incluindo combinação de estratégias e meios de comunicação síncrona/simultânea ou assíncrona/diferida, de modo unilateral, bilateral ou multilateral (Singh & Thurman, 2019). O uso de EaD tem vindo também a ser demonstrado como forma de democratização do acesso à educação para grupos desfavorecidos (Barger, 2020; Drolia et al., 2020; Shearer et al., 2020). Neste sentido o projeto Love.Dist@nce foi criado para responder às necessidades da Geórgia e de Israel, com o contributo de parceiros Europeus (Portugal, Espanha e Roménia).

Na Geórgia identificaram-se como principais grupos-alvo os trabalhadores-estudantes, estudantes com acessibilidade reduzida ou deslocados em regiões remotas, minorias étnicas (Azerbaijão e Arménia) e populações de território ocupado (zona de conflito). Em Israel os grupos-alvo integram grupos étnicos ou religiosos minoritários como, Árabes, Beduínos, mulheres Druze, Etíopes e ultra-ortodoxos, mas também estudantes com necessidades especiais.

Assim, o principal objetivo é promover a educação inclusiva através de EaD, ampliando o acesso ao ES para alunos de grupos vulneráveis. Assim, são objetivos operacionais do projeto:

- Desenvolver oferta curricular em EaD;
- Formar professores e funcionários em processos e tecnologias EaD;
- Criar recursos na Geórgia e Israel que permitam suportar estes programas;
- Sensibilizar a população para o acesso à equidade e democratização do ES;
- Captar e formar estudantes de grupos vulneráveis identificados;
- Adaptar metodologias de ensino-aprendizagem aos grupos vulneráveis identificados (Araújo et al., 2020).

Caracterização do Projeto

Tendo sido realizado o levantamento de necessidades em Instituições de Ensino Superior (IES) de Israel e Geórgia, as quais eram já parceiras da Escola Superior de Saúde do Instituto Politécnico do Porto (ESS-P.Porto) num projeto internacional anterior (Projeto ABC – Assisting Better Communication), a ESS-P.Porto foi convidada e liderar um consórcio integrando 10 instituições de

Portugal, Espanha e Roménia, países da União Europeia (UE) e Geórgia e Israel, países parceiros (Quadro 1).

País	Instituição	
Program Countries	Portugal	P. PORTO - Instituto Politécnico do Porto
	Espanha	FUNIBER - Fundação Universitária Iberoamericana
		UVIGO - Universidade de Vigo
	Roménia	TUCN - Technical University of Cluj Napoca
Partner Countries	Geórgia	ISU - Ilia State University
		TeSaU - Iakob Gogebashvili Telavi State University
		BSU - Shota Rustaveli Batumi State University
	Israel	OAC - Ono Academic College
		LCE - Levinski College of Education
		MEITAL - Interuniversity Computation Center

Quadro 1. Países e instituições integrantes no consórcio Love.Dist@nce

O projeto foi desenhado para decorrer num período de 3 anos, tendo iniciado em Janeiro de 2020 e prevendo-se a sua conclusão em Janeiro de 2023. Foi aprovado pela European Education and Culture Executive Agency (EACEA) com um financiamento de 800.368€, dos quais 27.559€ atribuídos ao P.Porto. Está dividido em workpackages incluindo: preparação, desenvolvimento, qualidade, disseminação e gestão.

O plano de trabalho inclui, resumidamente:

1. realização prévia de relatórios de caracterização institucional e nacional (tanto para os países da EU como para os beneficiários);
2. desenvolvimento de um campus virtual e de materiais de apoio (textos, infografias, modelos, etc.)
3. uma formação intensiva (Training of Trainers) para docentes e pessoal não-docente;
4. duas fases de estudos piloto, incluindo unidades curriculares de todas as IES de países parceiros, intercaladas com reuniões de análise e supervisão conjunta;
5. formação interna em cada IES de países parceiros, promovendo a transmissão de competências dos docentes e não-docentes envolvidos para a restante comunidade institucional;
6. aquisição de recursos tecnológicos para as IES dos países parceiros;
7. reuniões de gestão (presenciais ou à distância) em cada trimestre, incluindo auditorias externas;
8. definição de processos de avaliação da qualidade, incluindo formação, reuniões periódicas e auditorias internas e externas;
9. plano de disseminação, incluindo criação de um site, presença em redes sociais, participação em eventos dentro e fora de cada IES envolvida e publicação dos outputs do projeto e organização de uma conferência internacional no final do projeto.

Resultados Preliminares

Após 18 meses de atividade o Love.Dist@nce cumpre o cronograma previsto tendo submetido o relatório intermédio à EACEA em setembro de 2021. Contudo, a pandemia Covid-19 teve várias implicações no desenrolar do projeto,

nomeadamente a necessidade de supressão ou adiamento das atividades presenciais, como reuniões ou formações. Por outro lado, a relevância do projeto foi destacada pela própria pandemia, já que o acesso ao ES foi comprometido durante este período, não apenas para grupos desfavorecidos, mas para toda a população. Durante a primeira metade do projeto desenvolveram-se recursos e conteúdos que começam a dar os seus primeiros frutos. Destacam-se diversos materiais disponíveis para uso livre no site do projeto (*www.lovedistance.eu*), muitos deles em Inglês, Georgiano e Hebraico, maioritariamente produto das fases de preparação (já concluída) e desenvolvimento (em curso). Foram formados até ao momento 37 docentes e 12 não-docentes. Atualmente está e curso a primeira fase de pilotos, da qual se destacam as unidades curriculares apresentadas no Quadro 2.

Instituição	Unidade Curricular	Grupo-alvo
ISU	Georgian as Second Language	Trabalhadores-estudantes; Estudantes de regiões remotas; Minorias étnicas (Azerbaijão e Arménia).
	Marketing	
	Food Toxicology	
TeSaU	General English	Estudantes de regiões remotas; Minorias étnicas (Azerbaijão e Kisti).
	Information and Technology	
BSU	English A1.2.	Trabalhadores-estudantes.
	Basics of Tourism and Hospitality	
OAC	Math for pre-academic studies	Necessidades especiais; Minorias étnicas (Árabes); periferias; Ultra-religiosos.
	Academic Literacy	
LCE	Academic English Proficiency	Necessidades especiais; Minorias étnicas (Árabes); periferias; Ultra-religiosos.
	Racism in the Israeli Society	
	English for Academic Purposes	
	Basic Mathematics	

Quadro 2. Unidades curriculares desenvolvidas na fase 1 dos estudos piloto

Até ao momento foram ainda realizadas a maioria das aquisições de equipamentos e recursos necessários à adequada capacitação de cada IES para o EaD, num total de 50.000€. O consórcio tem vindo a estabelecer uma excelente comunicação interna e uma eficiente disseminação, como pode ser comprovado pela atividade regularmente divulgada nas redes sociais: *https://www.facebook.com/CBHELoveDistance*.

Impacto e Trabalhos Futuros

Durante a segunda metade do projeto, o Love.Dist@nce pretende encontrar as melhores estratégias, não apenas para promover o acesso ao ES, mas especialmente o sucesso das populações mais desfavorecidas. Assim, está definido um plano de trabalho ambicioso, que inclui avaliação de resultados dos pilotos da fase 1, formação interna para transmissão de competências entre pares, realização da fase 2 de pilotos e diversas atividades de disseminação. Caso haja possibilidade de retomar atividade presenciais, será ainda promovida a visita a IES europeias de referência, permitindo identificar e transferir modelos de trabalho e de organização. O projeto culminará com uma conferência internacional sobre a temática. Assim, até 2023 prevê-se um impacto exponencial dentro e fora das suas instituições envolvidas, resultando na adoção de práticas de EaD devidamente adaptadas e testadas de acordo com as necessidades das populações com mais dificuldade no acesso ao ES em cada país.

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NEURODEVELOPMENTAL CORRELATES *OF IMPLICIT-EXPLICIT LEARNING MECHANISMS IN CHILDREN WITH SPECIFIC LANGUAGE IMPAIRMENT*

Evidence from event-related brain potentials

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Abstract

This project has the grant POCI-01-0145-FEDER-028212, started in June of 2019 ending in May of 2022, with researchers from ESS | P. PORTO, University of Minho and University of Aveiro. Aims to analyze the neurocognitive correlates of implicit-explicit learning mechanisms in preschool specific-learning impairment (SLI) children and to track their developmental trajectories until they enter primary school. Studies aiming to explore the nature and dynamics of procedural memory-declarative memory functioning in SLI using brain techniques and following the same children on time are inexistent. This project aims to address these issues by combining an artificial grammar paradigm with ERPs in a longitudinal design, which will contribute not only to clarify the role of procedural memory deficits-declarative memory compensation on SLI, but also to the development of effective intervention programs for children who are at risk of dyslexia.

Introdução

The environment in which we live is characterized by a series of sounds, objects, and events that do not occur randomly. The ability to pick up these regularities in time and space is a fundamental skill of our cognitive system to structure the world in a regular and predictable way, and to constantly develop adaptive responses to it The mechanism by which we are capable of extracting those regularities, even without intention and/or awareness of doing it, is called statistical learning (SL). The SL can be implicit and explicit and studies lack in correlating the neural mechanisms with event-related potentials (ERPs) in children with specific learning impairment (SLI).

Due time: 1st of June 2019 to 31st of May 2022 | Funding: 226 245,62 €

Goals

This project aims to analyze the neurocognitive correlates of implicit-explicit learning mechanisms in preschool SLI children and to track their developmental trajectories until they enter primary school. A key question in psycholinguistic research is whether the language impairments observed in SLI are due to deficits in implicit learning mechanisms, and at what extent declarative system can compensate for these deficits, helping SLI children to overcome their difficulties and to prevent severe difficulties in reading-writing. Moreover, this project aims to address these issues by combining an artificial grammar paradigm with ERPs in a longitudinal design, which will contribute not only to clarify the role of procedural memory deficits-declarative memory compensation on SLI, but also to the development of effective intervention programs for children who are at risk of Dyslexia.

Methods

The neural mechanisms underlying SL under other learning conditions remain largely unknown. Here, we investigated the neurofunctional correlates of SL using triplets (i.e., three-syllable nonsense words) with a mean TP of 1.00 (easy "words") and 0.50 (hard "words") in an SL task performed under incidental (implicit) and intentional (explicit) conditions. ERPs (N100, N250 and N400) were recorded while participants listened first to a continuous auditory stream made of the concatenation of four easy and four hard "words" under implicit instructions, and subsequently to another auditory stream made of the concatenation of four easy and four hard "words" drawn from another artificial language under explicit instructions.

In the N400 ERP component, we found an effect of type of "word" showing that easy "words" elicited larger amplitudes as compared to hard "words" (see figure), which might suggest facilitated access to these specific words' representations in memory and/or more successful integration of those representations in higher-order language structures. Also, significant differences in the N100 were found as a result of the interaction between transitional probability instructions, and the amount of exposure to the auditory stream. Taken together, our findings suggest that triplets' predictability impacts the emergence of "words" representations in the brain both for statistical regularities extracted under incidental and intentional instructions, although the prior knowledge of the "words" seems to favor the recruitment of different SL mechanisms.

With project´s tasks 8-10 approaching, we can correlate results with literacy skills assessment that will clarify the role of procedural memory deficits-declarative memory compensation on children with SLI.

Task	Task Denomination
1	Recruitment and selection of participants (SLI and TD controls). (2019)
2	Stimuli selection. (2019)
3	Setup of the experimental tasks and paradigms. (2019)
4	Preschool data collection 1 (SLI and TD controls, experimental session 1). (2020)
5	Preschool data collection 2 (SLI and TD controls, experimental session 2). (2021)
6	Preschool data analysis (SLI and TD controls, experimental sessions 1 and 2) and research dissemination. (2021)
7	Primary school data collection 1 (SLI and TD controls, experimental session 3). (2021)
8	Primary school data collection 2 (SLI and TD controls, experimental session 4). (2022)
9	Primary school data collection 3 (SLI and TD controls, literacy skills assessment). (2022)
10	Primary school data analysis (SLI and TD controls, experimental sessions 3 and 4, and literacy skills assessment) and research dissemination. (2022)

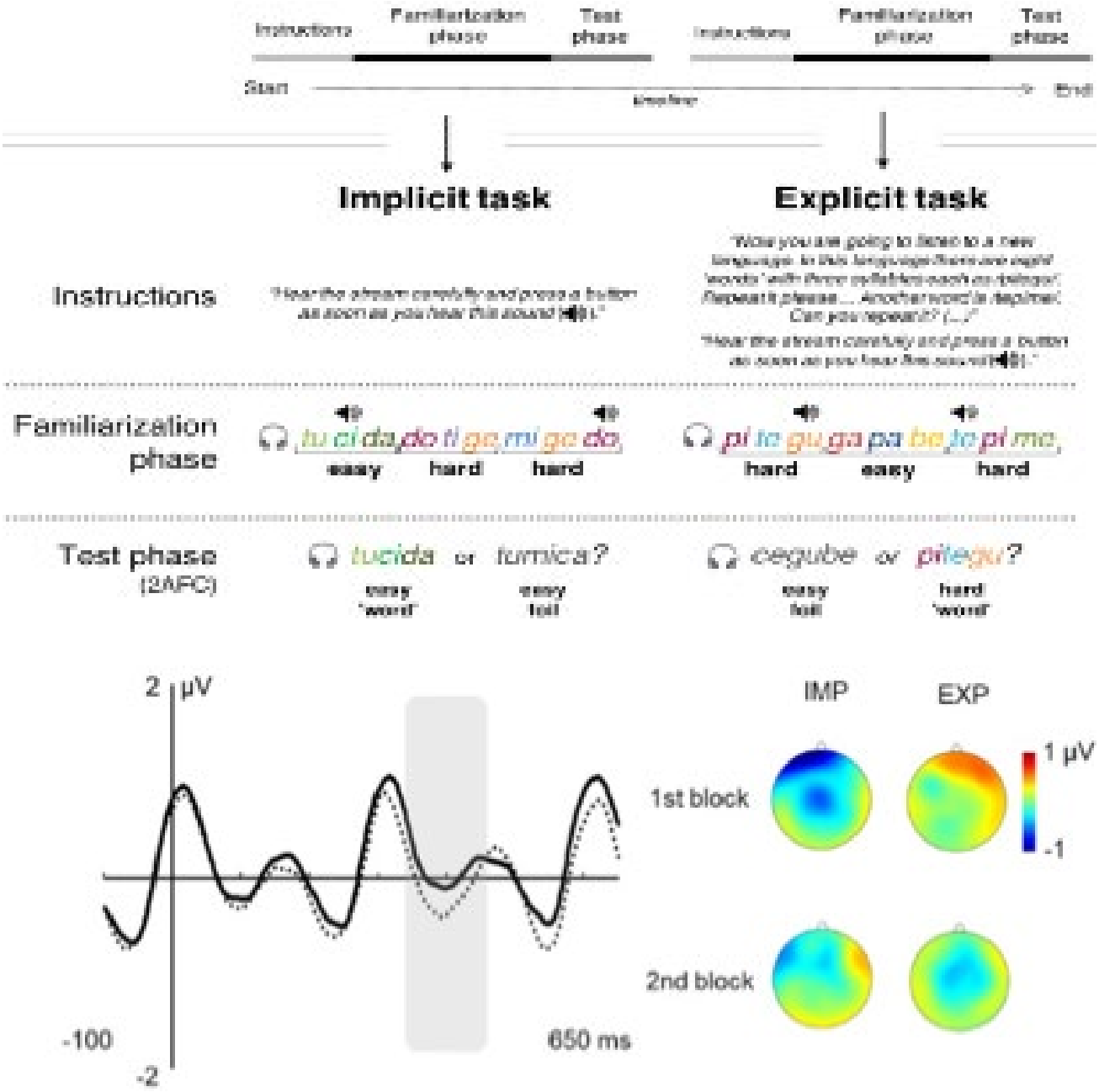

Figure. Effect of type of "word" in the N400 time window (solid line: hard; dotted line: easy) and voltage map of the difference between easy and hard "words".

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PEP ALHEIRA

Revestimentos edíveis ativos baseados nas proteínas do soro do leite e peptidos antimicrobianos seus derivados para a indústria da alheira

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Resumo

Alheira é uma carne fumada da região Norte de Portugal (Trás-os-Montes) que foi nomeada como uma das 7 maravilhas da gastronomia portuguesa, sendo um verdadeiro "cartão de visita" de Trás-os-Montes e muito apreciado em Portugal e internacionalmente.

Devido à importância económica que a Alheira representa para a região de Trás-os-Montes, onde são produzidas anualmente mais de 500 toneladas, há um interesse crescente desta indústria em estender a vida útil da Alheira para evitar perdas económicas e expandir o produto para novos mercados internacionais, incluindo no exterior. Neste contexto, este projeto visa desenvolver um revestimento comestível ativo baseado em proteínas de soro de leite, um subproduto da indústria do queijo, e incorporar peptídos derivados de proteínas do leite que funcionarão como agentes antimicrobianos.

Ao todo, este projeto apresenta um elevado potencial com benefícios financeiros diretos no desenvolvimento de um novo produto e na sua consequente valorização e competitividade em novos mercados.

Abstract

Alheira is a smoked meat from the North of Portugal("Trás-os-Montes") that has been named as one of the 7 wonders of Portuguese gastronomy, being a true "business card" of Trás-os-Montes and very appreciated in Portugal and internationally.

Due to the economic importance that Alheira represents for the region of Trás-os-Montes, where more than 500 tons are produced annually, there is a growing interest in this industry in extending the shelt-life of Alheira to avoid economic losses and expand the product to new international markets. In this context, this project aims to develop an active edible coating based on whey proteins, a by-product of the cheese industry, and to incorporate peptides derived from milk proteins that will act as antimicrobial agents.

Altogether, this project has a high potential with direct financial benefits in the development of a new product and its consequent appreciation and competitiveness in new markets.

Introduction

Food is normally susceptible to physical, chemical and microbiological deterioration throughout storage and distribution, (Cha & Chinnan, 2004) leading to a constant search for new strategies to increase food's shelf-life. (Cha & Chinnan, 2004; Livney, 2015). Consequently, packaging became one of the most relevant areas in food industry (FI), where a great investment from the Science,Technology and Industrial sectors has been applied. (Cha & Chinnan, 2004; Livney, 2015). Furthermore, the current increase in consumer demand for natural 'organic' foods has forced companies and researchers to explore different ways to improve their market penetration by offering products with improvements in freshness, quality and food safety. (Peelman et al., 2013) One of the most fashionable trends consists of the development of innovative biopolymers based on natural polysaccharides, proteins or lipids obtained from by-products of the FI. (Valdes, Mellinas, Ramos, Garrigos, & Jimenez, 2014)

Therefore, the use of such biopolymers in food packaging applications has emerged as an alternative with regard to their film-forming properties to produce edible films and coatings (EFC) and as an environmentally friendly technology.(Cha & Chinnan, 2004; Livney, 2015; Peelman et al., 2013; Umaraw & Verma, 2017; Valdes et al., 2014) These biopolymers offer extra advantages such as barrier properties to gases and/or moisture, biocompatibility, nontoxicity, and low cost. (Silva-Weiss, Ihl, Sobral, Gomez-Guillen, & Bifani, 2013) Additionally, they can act as carriers for antimicrobial additives to extend food's shelf-life and safety of packaged foods, by reducing and/or preventing growth of pathogenic and spoilage microorganisms and, thus, leading to active edible films and coatings (AEFC). (Cagri, Ustunol, & Ryser, 2004) Noteworthy, the introduction of natural active additives to packaging materials provides advantages compared to the direct addition to food, such as the lower amount of active substances required, controlled release to food, and elimination of additional steps on processing. (Ramos, Jimenez, Peltzer, & Garrigos, 2014) whey proteins (WP) have been successfully employed as raw material for AEFC because they come from a renewable source and are a by-product of the cheese-manufacturing industry. Hence, they are widely available, relatively easy to handle and essentially inexpensive. Noteworthy, WP have shown promising mechanical features, as well as moisture and gas barrier properties comparable to those exhibited by the best synthetic polymer-based films. (Khwaldia, Perez, Banon, Desobry, & Hardy, 2004) Besides, WP-based films proved excellent biomaterials for use as carriers of food additives, as antimicrobials, improving the functionality of the packaging by bringing about novel features. (Ciesla, Salmieri, & Lacroix, 2006)

In current FI approaches to AEFC, additives are usually added as free components to the EFC mixture, such as natural preservatives (e.g. bacteriocins), or synthetic antibiotics (e.g. enilconazole). (Cagri et al., 2004) Recent trends point out antimicrobial peptides (AMP) as promising alternatives to current food preservatives. (Espitia et al., 2012) AMP are well-known components of the innate immune system that are rapidly gaining relevance, as opposed to conventional antibiotics whose effectiveness is declining. (Theolier, Fliss, Jean, & Hammami, 2014) This is explained by a group of special features, including wide activity spectrum, high efficacy at low concentrations, and low propensity for eliciting resistant microbial strains. (Costa, Carvalho, Montelaro, Gomes, & Martins, 2011). Strictly, AMP are not as new as food preservatives since bacteriocins, as pediocin, a 62-residue naturally occurring AMP, are of wide use in the FI. (Cagri et al., 2004) However, smaller AMP have not been yet explored as food preservatives, although they might represent cheaper alternatives to bacteriocins in use. Moreover, small peptides are usually non-immunogenic, so

they do not usually trigger allergic reactions as proteins or longer peptides may do. (Costa et al., 2011) In this context, AMP that might be of particular interest for the FI are the ones derived from bovine lactoferrin (bLf),(Theolier et al., 2014) a protein that occurs naturally in cow's milk, and whose use as nutraceutical has been recently considered as safe by the European Food Safety Authority. (Albano, Henriques, Correia, Hogg, & Teixeira, 2008).

The potential of bLf-derived AMP as key components in AEFC, through its addition to the coating solution, has never been reported and seems to be worth exploring. Alheira, 'the King of Portuguese sausage', is a typical smoked sausage of the Northern region in Portugal (Trás-os-Montes) that was nominated as one of the 7 wonders of Portuguese gastronomy, being a true 'calling card' of Trás-os-Montes and greatly appreciated in Portugal and internationally. (Albano et al., 2008) Alheira is produced from pork and poultry meat, and pork fat, wheat bread and olive oil. Ingredients are mixed with salt, garlic and spices until they form a paste,which is then stuffed into natural or artificial casings and submitted to a smoking process for no longer than 8 days. (Albano et al., 2008) Alheira shelf-life is about 1 month if stored at 4 ºC in air or longer if the sausages are packed under modified atmosphere (ca. 60 days) or vacuum (ca. 90 days). Due to the economic importance that Alheira represents for Trás-os-Montes region, where more than 500 tons are produced annually, there is an increasing interest from this industry to extend Alheira shelf-life to avoid economic losses and to expand the product into new international markets, including overseas.

The development of AEFC on meat food products have been subject of a great number of scientific publications and patents during the last decade. (Korhonen & Pihlanto, 2003) However, there is a wide diversity of meat products with different characteristics making it difficult to standardize a single AEFC application procedure. Thus, there is the need to develop the appropriate AEFC for a specific meat product. Altogether, the above shows that increasing Alheira shelf-life by developing an active edible coating produced from WP, a by-product of the cheese-manufacturing industry, incorporating bLf-derived AMP as antimicrobial agents, is a truly innovative approach that may become a breakthrough for the FI.

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FRAGILIDADE MULTIDIMENSIONAL

EM PESSOAS IDOSAS

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Resumo

A fragilidade é um estado de vulnerabilidade aumentada, presente em populações mais envelhecidas, que resulta num elevado risco de incapacidade e morte. Conceptualizações recentes da fragilidade caracterizam-na como de natureza multidimensional, afastando de definições mais tradicionais da condição como uma síndrome exclusivamente física. No presente capítulo apresenta-se um conjunto de estudos focados na compreensão da manifestação de fragilidade multidimensional, especialmente em contexto português. Estes estudos incluem a adaptação e a análise das propriedades psicométricas de um instrumento de avaliação de fragilidade, a análise dos preditores e resultados associados a fragilidade, assim como uma revisão sistemática sobre os componentes de fragilidade social.

Abstract

Frailty is a state of increased vulnerability, present in older populations, which results in a high risk of disability and death. Recent conceptualizations of frailty characterize it as having a multidimensional nature, moving away from more traditional definitions of the condition as an exclusively physical syndrome. In this chapter, a set of studies focused on understanding the manifestation of multidimensional frailty, especially in the Portuguese context, will be presented. These studies include the adaptation and analysis of the psychometric properties of a frailty assessment instrument, the analysis of predictors and outcomes associated with frailty, as well as a systematic review of the components of social frailty.

Introdução

A fragilidade trata-se de um estado de elevada vulnerabilidade em que o mínimo fator de stresse pode levar a resultados adversos clinicamente significativos, tais como incapacidade, institucionalização, hospitalização e morte (Morley et al., 2013; Rockwood & Mitnitski, 2007). Apesar de ser uma condição específica da população mais envelhecida, não faz parte do envelhecimento normal, podendo ser prevenida, atenuada ou revertida (Dent et al., 2019; Marcucci et al., 2019).

Fragilidade é tradicionalmente definida como uma síndrome clínica com manifestações exclusivamente físicas, nomeadamente as que constituem o fenótipo de fragilidade: perda de peso, fraqueza muscular, exaustão, lentidão e baixa atividade física (Dent et al., 2019; Fried et al., 2001). Contudo, conceptualizações recentes caracterizam-na como de natureza multidimensional, destacando a importância de aspetos não apenas físicos, mas também psicológicos e sociais para a manutenção da saúde e qualidade de vida (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Hoogendijk et al., 2019). Nesta linha de pensamento, foi proposto o modelo integral de fragilidade (Gobbens, Luijkx, Wijnen-Sponselee, & Schols, 2010), em que fragilidade é definida como um estado de pré-incapacidade resultante de perdas em um ou mais domínios do funcionamento humano (físico, psicológico e social), resultante da interação de uma vasta gama de variáveis (idade, sexo, estilo de vida, acumulação de doenças, declínio da reserva fisiológica, etc.).

Considerando a escassez de estudos focados na manifestação de fragilidade multidimensional em idosos portugueses, desenvolveu-se, em 2013, uma linha de investigação com o objetivo geral de analisar a aplicabilidade e pertinência do modelo integral de fragilidade no contexto português. O presente capítulo visa descrever os estudos que, até ao momento, integram essa linha.

Descrição dos estudos que integram a linha de investigação

O estudo inicial (Coelho, Santos, Paúl, Gobbens, & Fernandes, 2015) teve como objetivo traduzir e adaptar culturalmente o instrumento estandardizado que operacionaliza o modelo integral de fragilidade – o Tilburg Frailty Indicator (TFI) (Gobbens, van Assen, Luijkx, Wijnen-Sponselee, & Schols, 2010) – e analisar as propriedades psicométricas da versão portuguesa. O TFI é um questionário de aplicação rápida que inclui 10 questões sobre preditores/ determinantes de fragilidade (idade, sexo, estado civil, naturalidade, escolaridade, rendimento mensal, estilo de vida, comorbilidade, eventos significativos no último ano, satisfação com ambiente habitacional) e 15 questões sobre componentes de fragilidade, divididas por três domínios: físico (declínio da saúde física geral, perda de peso involuntária, dificuldades na marcha, problemas de equilíbrio, dificuldades de audição, dificuldades de visão, fraqueza muscular e exaustão), psicológico (problemas de memória, problemas de humor, problemas de ansiedade e dificuldade para lidar com problemas) e social (viver sozinho, falta de apoio de outros e solidão). Cada item da segunda parte do instrumento é cotado dicotomicamente, produzindo uma pontuação máxima de 15, que representa o valor mais elevado de fragilidade.

O processo de tradução e adaptação cultural do TFI decorreu de acordo com normas previstas na literatura (Wild et al., 2005), envolvendo passos como tradução, retroversão, harmonização e teste piloto. Após a execução destes procedimentos, procedeu-se à análise das propriedades psicométricas da versão portuguesa, tendo para tal sido recrutada uma amostra não-probabilística de 252 pessoas com 65 anos de idade ou mais, residentes na comunidade e sem défices cognitivos severos (média de idades de 79 anos; 76% mulheres). Através da análise foi possível constatar que a versão portuguesa do instrumento apresentou boa consistência interna (KR-20 de 0.78) e boa fiabilidade teste-reteste, com concordância substancial para a maioria dos itens, destacando-se a semelhança dos resultados com os verificados noutros estudos de validação do TFI (Gobbens, van Assen, et al., 2010; Santiago, Luz, Mattos, Gobbens, & van Assen, 2013; Uchmanowicz et al., 2014). Paralelamente, verificaram-se indicadores favoráveis de validade de construto e de validade de critério, sendo que a análise da sensibilidade e da especificidade do instrumento

permitiu selecionar a pontuação de seis como ponto de corte para a presença de fragilidade. Consequentemente, classificou-se uma elevada proporção de participantes como frágeis (cerca de 55%), o que, por sua vez, destacou a importância de se implementarem programas de deteção destas situações de elevada vulnerabilidade na comunidade, assim como programas de apoio terapêutico para prevenir fragilidade e os seus resultados adversos.

Após preparação da versão portuguesa do TFI e análise da sua fiabilidade e validade, procedeu-se ao estudo da associação entre nível de fragilidade multidimensional (total, física, psicológica e social) e os preditores previstos no modelo integral de Gobbens, Luijkx, et al. (2010). Paralelamente, neste estudo (Coelho, Paúl, Gobbens, & Fernandes, 2015a), procurou-se compreender se o número de medicamentos consumidos diariamente poderia ser considerado como preditor do nível de fragilidade, essencialmente tendo em conta a evidência prévia dos efeitos nefastos da polimedicação (Gnjidic et al., 2012).

Neste âmbito, recorreu-se à base de dados elaborada para o estudo das propriedades do TFI, tendo sido realizada uma análise estatística através de regressões múltiplas, com o objetivo de se analisar o contributo de cada variável para a explicação da variância de fragilidade, independentemente dos restantes preditores. Foi então possível verificar que níveis superiores de fragilidade total foram explicados por ser mulher, possuir rendimentos mais baixos, ter experienciado a morte de uma pessoa querida no último ano, ter um estilo de vida não saudável, estar insatisfeito com o ambiente habitacional, ter duas ou mais doenças e tomar mais medicamentos por dia. Constatou-se, também, que o conjunto de variáveis associado a cada domínio de fragilidade era distinto. Todavia, verificou-se que os estilos de vida não saudáveis e a insatisfação com ambiente habitacional se associaram a fragilidade total e a todos os seus domínios. Neste sentido, tratando-se de fatores potencialmente modificáveis, salientam-se aspetos sobre os quais se podem atuar com o objetivo de prevenir fragilidade. Para além disso, este estudo contribuiu para a evidência sobre quais os grupos populacionais em maior risco de se tornarem frágeis.

Por sua vez, com o objetivo de identificar variáveis adicionais que pudessem estar associadas a maior fragilidade multidimensional, realizou-se um terceiro estudo (Coelho, Paul, Gobbens, & Fernandes, 2017), especificamente focado na relação entre fragilidade e a presença de dor durante o desempenho de atividades diárias. Este estudo, realizado com base na amostra já identificada e a métodos estatísticos similares, teve como motivação a elevada prevalência de dor nas populações mais envelhecidas, assim como os seus efeitos incapacitantes (Bruckenthal, Reid, & Reisner, 2009).

Como resultado da investigação, foi possível verificar que uma maior intensidade de dor se associou a maior fragilidade total, física e psicológica, mesmo ajustando para o efeito dos determinantes de fragilidade previstos no modelo integral de Gobbens, Luijkx, et al. (2010). Consequentemente, gerou-se evidência que sugere que a redução da dor sentida durante o desempenho de atividades quotidianas poderá ser importante para prevenir situações de elevada vulnerabilidade, particularmente a nível físico e psicológico.

Concomitantemente, com o objetivo de reforçar a conceptualização de fragilidade como uma condição de elevada vulnerabilidade e risco para a saúde, funcionalidade e qualidade de vida, realizou-se um quarto estudo (Coelho, Paúl, Gobbens, & Fernandes, 2015b), de natureza longitudinal, tendo, para tal, reavaliado parte dos participantes nos estudos anteriores, 10 meses após o primeiro contacto. Consequentemente, foi possível verificar que a fragilidade medida pelo TFI (mês 0/ baseline) se associou a maior dependência em atividades de vida diária e pior qualidade de vida na reavaliação (mês 10/ follow-up), assim como a um maior número de contactos com médico de família durante esse período.

Paralelamente, constatou-se que o TFI foi melhor fator preditor de resultados adversos do que uma medida exclusivamente física (avaliação do fenótipo de fragilidade), destacando a importância de uma operacionalização multidimensional de fragilidade. Contudo, uma análise do contributo de cada domínio de fragilidade para a predição de resultados adversos permitiu constatar que, enquanto os domínios físico e psicológico apresentaram contributos significativos, o domínio social não se associou a qualquer resultado.

Por fim, considerando o reduzido contributo do domínio social do TFI para a predição de resultados adversos, evidenciado desde logo na literatura (Gobbens & van Assen, 2014; Santiago et al., 2018), procurou-se gerar uma maior compreensão sobre esta dimensão de fragilidade. Assim, realizou-se uma revisão sistemática (Bessa, Ribeiro, & Coelho, 2018) para identificar os instrumentos de avaliação de fragilidade que incluíam componentes sociais, assim como quais os indicadores mais referidos.

Como resultado da análise da evidência científica publicada entre 2001 e 2018, foram identificados 27 instrumentos de avaliação de fragilidade distintos, verificando-se uma elevada variabilidade sobre quais os componentes sociais incluídos. Contudo, foi possível identificar cinco fatores sociais com maior expressividade: viver sozinho, solidão, reduzido apoio social, isolamento social e baixa participação social. Assim, constatou-se a importância de estudos subsequentes explorarem com maior detalhe a dimensão social de fragilidade, particularmente no que se refere aos componentes que mais

contribuem para a predição de resultados adversos para a saúde e qualidade de vida.

Conclusão

Em suma, esta linha de investigação resultou, em primeiro lugar, no desenvolvimento da versão portuguesa de um instrumento de avaliação de fragilidade, resultante de perspetivas contemporâneas e multidimensionais sobre o conceito. Este instrumento, disponível para a comunidade científica e clínica, é de rápida e fácil aplicação, apresentando bons indicadores de fiabilidade e validade.

Em segundo lugar, gerou-se evidência da aplicabilidade do modelo integral de fragilidade em contexto português, na medida em que se evidenciaram relações significativas entre determinantes, domínios de fragilidade e resultados adversos previstos no modelo. Neste processo, destacou-se a identificação de determinados indicadores que podem estar associados a uma situação de fragilidade, fornecendo informações úteis para o planeamento de programas terapêuticos neste âmbito. Paralelamente, salientou-se a importância da prevenção de fragilidade, tendo em conta que pode resultar numa pior situação de saúde e bem-estar.

Por fim, destacou-se a pertinência de uma abordagem multidimensional de fragilidade, na sequência do seu maior contributo para a predição de resultados negativos para a vida da pessoa idosa, comparativamente a uma medição unidimensional (apenas física). Contudo, verificou-se que são necessários mais estudos para melhor compreender a dimensão social de fragilidade e, consequentemente, justificar a sua inclusão em operacionalizações da síndrome.

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PROJETO

NASY THOR

Novos compostos naturais e sintéticos para o tratamento de tumores hormono-resistentes

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Resumo

Introdução: Uma equipa multidisciplinar do CISA-ESS | P. PORTO em colaboração com o CI|IPOP dedicou-se ao estudo do potencial anti-tumoral de novos compostos em tumores de grande incidência em Portugal: cancro da mama e da próstata.

Metodologia: O potencial anti-tumoral de extratos de plantas e compostos sintéticos foi avaliado em linhas celulares de cancro da próstata e da mama, sendo a resposta terapêutica prevista através de amostras biológicas.

Resultados: Um líquido iónico provou estar associado à atenuação do fenótipo maligno das linhas celulares testadas, mostrando-se um promissor agente terapêutico anti-tumoral. A expressão de genes que se mostrou alterada após tratamento foi validada em amostras de pacientes com cancro da próstata e da mama.

Conclusão: Os resultados foram divulgados sob a forma de artigo científico e de várias comunicações orais e posters em congressos nacionais e internacionais.

Abstract

Introduction: A multidisciplinary team from CISA-ESS|P.PORTO in collaboration with CI|IPOP was dedicated to the study of the antitumor potential of new compounds in tumors of high incidence in Portugal: breast and prostate cancer.

Methodology: The antitumor potential of plant extracts and synthetic compounds was evaluated in prostate and breast cancer cell lines, and the therapeutic response was predicted through biological samples.

Results: An ionic liquid proved to be associated with the attenuation of the malignant phenotype of the cell lines tested, proving to be a promising antitumor therapeutic agent. The expression of genes that were shown to be altered after treatment was validated in samples from patients with prostate and breast cancer.

Conclusion: The results were published in the form of a scientific article and several oral communications and posters at national and international conferences.

Introdução

O cancro é uma das principais causas de mortalidade no mundo, apesar dos avanços na pesquisa médica. Últimos dados de incidência de cancro revelam o cancro da próstata e da mama como dos mais incidentes quer mundialmente quer em Portugal (Bray et al., 2018). Apesar dos avanços na deteção precoce e tratamento, as taxas de mortalidade elevadas e os efeitos colaterais adversos ou tóxicos da quimioterapia e radioterapia, torna-se imperativa a descoberta de novos agentes anti-tumorais, especialmente útil em casos de tumores de próstata resistentes à castração e tumores de mama independentes de estrogénio.

Nos últimos anos, membros da presente equipa de investigação têm desenvolvido estudos sobre o potencial bioativo de compostos naturais e sintéticos no Centro de Investigação em Saúde e Ambiente (CISA) da Escola Superior de Saúde, do Politécnico do Porto (ESS | P. PORTO). Este projeto contou ainda com a colaboração com o Instituto Português de Oncologia (IPO-Porto), dada a sua vasta experiência em cancro, nomeadamente no cancro de próstata e mama.

De trabalhos anteriores, extratos isolados de plantas do género *Taraxacum* assim como compostos sintéticos como líquidos iónicos e quinoxalinas, revelaram um potencial bioativo com interesse anti-tumoral (Ferraz et al., 2011; Ferraz et al., 2015; M. Vieira et al., 2014). No seguimento destes resultados, e considerando a experiência de membros da equipa de investigação, na área do cancro, foi objetivo principal deste projeto inferir sobre o potencial destes compostos como drogas anti-tumorais, em tumores hormono-resistentes comuns nomeadamente os tumores de próstata resistentes à castração e tumores de mama independentes de estrogénio.

Metodologia

O projeto envolveu as seguintes atividades: a) produção e caracterização de compostos naturais e sintéticos (Silva, et. Al., 2019; Oliveira, et al., 2019); b) avaliação *in vitro* em linhas celulares de próstata e mama do potencial anti-tumoral dos compostos, a fim de selecionar os mais promissores (Silva, et. Al., 2019; Marques-Magalhães, et al., 2019); c) avaliação *in vivo* do potencial anti-tumoral dos compostos selecionados anteriormente, utilizando como modelo o peixe-zebra (Silva, et. Al., 2019; Barros, et al., 2019); d) identificação da expressão génica por tratamento com os compostos selecionados de forma a inferir sobre o mecanismo de ação molecular subjacente aos efeitos citotóxicos em células tumorais; e) avaliação da utilidade clínica da expressão génica de forma a prever a resposta terapêutica (Silva, et. Al., 2019; F. Q. Vieira, et al., 2019).

Resultados

Foram produzidas quinoxalinas (1,4-dióxido de quinoxalina e 1,4-dióxido de 2-metilquinoxalina) e líquidos iônicos baseados em ampicilina ([C2OHMIM][Amp] e [C16Pyr][Amp]). Adicionalmente, as partes aéreas de Taraxacum hispanicum foram recolhidas e a biomassa seca das plantas (folhas e flores) extraída, tendo-se produzido um extrato etanólico e um aquoso (Pinho, et al., 2018). Os compostos foram testados em 10 linhas celulares: 5 linhas celulares de mama e 5 de próstata. De cada modelo tumoral foi utilizada uma linha celular normal, 2 linhas tumorais hormono-sensíveis e 2 hormono-resistentes. De entre os compostos testados, apenas o composto [C16Pyr][Amp] e o extrato alcoólico do Taraxacum hispanicum (EAL) levaram a uma diminuição da viabilidade celular, tendo-se observado um elevado índice de seletividade no que diz respeito à comparação dos resultados obtidos nas linhas celulares tumorais quando comparados com a respetiva linha normal (F. Q. Vieira, et al., 2020). Adicionalmente, ambos os compostos mostraram, na maioria das linhas testadas, índices de seletividade superiores aos observados com o tratamento com cisplatina, droga amplamente usada em quimioterapia. Os resultados mais

promissores foram observados aquando do tratamento com o [C16Pyr] [Amp], uma vez que este mostrou ter capacidade de redução da viabilidade em todas as linhas celulares, tornar as células mais sensíveis aos mecanismos de apoptose e diminuição da capacidade de formação de colónias pelas células tumorais (Marques-Magalhães, et al., 2018a, 2018b, 2018c, 2018d; F. Q. Vieira, et al., 2020).

Posteriormente, foram selecionadas 2 linhas celulares de cancro da próstata e 2 de cancro da mama, sendo para cada modelo tumoral uma linha celular hormono-resistente e outra linha celular hormono-independente. As linhas foram tratadas com [C16Pyr][Amp] e a análise do transcriptoma revelou que o referido tratamento levava à diminuição da expressão de genes como LDHA, CPT2, MCM2 e SKP2 (F. Q. Vieira, et al., 2020).

Foi determinada a utilidade clínica da expressão utilizando tecidos humanos extraídos de pacientes com cancro da próstata e da mama. A intensidade de imunocoloração, padrão de imunoexpressão e/ou percentagem de células positivas para CPT2, LDHA, MCM2 e SKP2 foram associados ao tipo histológico e/ou resistência à terapia de privação de androgênio nas amostras de próstata. Por sua vez, a expressão de LDHA foi associada ao subtipo molecular de cancro da mama (F. Q. Vieira, et al., 2021a, 2021b, 2021c).

Conclusão

Como principal conclusão deste estudo, o líquido iônico [C16Pyr][Amp] mostrou-se associado à atenuação do fenótipo maligno das linhagens testadas, revelando-se um promissor agente terapêutico antitumoral (F. Q. Vieira, et al., 2020). A expressão génica alterada após o tratamento foi validada em amostras de pacientes com cancro da próstata e da mama, revelando que estes biomarcadores poderão ser úteis para a gestão clínica e orientação terapêutica.

PROJECT

SMART PATIENTS

Holistic Emporwerment of Citizens to Become Experts in Their Own Health

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Resumo

Introdução: Alinhado com o Quadro Estratégico da UE para a Saúde, o projeto Smart Patients tem como principal objetivo capacitar os cidadãos, colocando-os no centro do sistema e envolvendo-os na gestão da sua própria saúde. Assim, o projeto visa aumentar o grau de literacia em saúde dos cidadãos, desenvolvendo as suas competências e autoconfiança na gestão das suas necessidades de saúde.

Métodos: O projeto foi coordenado localmente pela ESS | P. PORTO, com a participação de 5 Áreas Técnico-Científicas, em colaboração com o consórcio de sete países europeus, e decorreu no período entre 01/09/2016 e 31/10/2018.

Resultados: Como resultado deste projeto, foram criados materiais de sensibilização, orientação e informação para os cidadãos; uma plataforma online para partilha de materiais e ferramentas; uma página web e folhetos informativos; e um aplicativo móvel. Todos os materiais foram traduzidos em vários idiomas e amplamente divulgados.

Conclusão: É expectável que os produtos e conteúdos desenvolvidos tenham um forte impacto na capacitação da saúde dos cidadãos europeus.

Abstract

Introduction: In line with the EU Strategic Framework for Health, the main objective of the Smart Patients project is to empower citizens, placing them at the center of the system and involving them in the management of their own health. Thus, the project aims to empower citizens with better health literacy, developing their skills and self-confidence in managing their health needs.

Methods: Project was coordinated locally by ESS | P. PORTO, with the participation of 5 Technical-Scientific Areas, in collaboration with the consortium of seven European countries, in the period between 09/01/2016 and 10/31/2018.

Results: As a result of this project, materials were created to raise awareness, guidance and information for citizens; an online platform for sharing available materials and tools; webpage and information leaflets; and a mobile app. All materials were translated in multiple languages and widely circulated.

Conclusion: Appropriate products and contents are expected to have a strong impact on the health empowerment of European citizens.

Introduction

The Smart Patients project addresses an important topic of Health literacy by the means of non-formal education, i.e. it empowers citizens to acquire health literacy, and to understand that health cannot be maintained only by medical intervention, but depends also on lifestyle as well as on social and environmental factors.

The design of the learning materials takes into consideration not only the educational level of disadvantaged learners, but it also responds to the current refugees' crisis in Europe, by providing selected materials in the two most widely used languages of refugees, i.e. Arabic and Pashtun.

A concrete theme identified in the EU Health Strategy includes empowering citizens – putting patients at the heart of the system and encouraging them to be involved in managing their own healthcare needs. Preventive care should

therefore not be left alone to doctors and hospitals, also the individual must be empowered and become a "smart patient".

The objectives of this project were:

- To empower citizens to become expert patients and to develop self-confidence and patients competence in interaction with medical experts;
- To develop support that empowers them preventing disease and detecting health issues at an early stage that are essential to living a healthy life;
- To develop internet and mobile application based tools with recommendations, advices and guidelines for preventive care, healthy nutrition and food, wellbeing, lifestyle;
- To provide a glossary that explains medical terms for readers with lower educational levels
- To reach refugees, asylum seekers and migrants who have no or only little command of the host country's language and would not understand the information given to them by doctors, through translations of the materials also into Arabic and Pashtun.

Profile of the partners

The partnership comprises of a multi-disciplinary team of health organizations, education and pedagogic expert partners as well as ICT and multimedia specialists, where only the combined efforts made possible the results of the project. In a world of globalization, the project will therefore develop transnational best practice approaches and transfer them into localized solutions in the eight European states of the partnership and beyond.

The group of social and medical research organizations specialized in various aspects of health care consists of: 1 - MEDRI - Department for psychiatry and psychological medicine of the Faculty of Medicine, University of Rijeka (Croatia), offering education programs in the field of psychological medicine, psychiatry and communication skills; 2- NUIG - Health Promotion Research Centre at the National University of Ireland, known by producing high quality research that supports the development of best practice and policy in the promotion of health; 3- „Was hab ich?" (a German non-profit organisation) provides, with their online portal, free of charge translations of medical reports and hospital discharge summaries; 4- ESTSP - School of Allied Health Technologies (Portugal) is an applied sciences higher education institution with a strong human, technological and ethical capital dedicated to the development of health technologies; 5-

INTEGRA Institute for Development of Human Potentials (Slovenia), with specialized counsellors from the field of special pedagogy, psychology, speech therapy, social work and systemic humanistic psychotherapy; 6 - WIN – Science Initiative Lower Austria has extensive experience in the design of learning and information materials for ICT communication in virtual environments; 7 - QUALED Qualification and Education (Slovakia) is active in the field of innovative learning technologies for supporting learning processes in different settings for different target groups; 8- GUNET (Greece), with expertise in the development and provision of advanced ICT services and applications in teaching and learning.

Activities and Results

Needs assessment

The first step to reach these objectives was mapping the state of art in Europe and in individual countries of the partnership, analyzing them and find a common starting point for developing the educational materials. Thus, a Needs Assessment Report was made through desk-based research, which included the analyses and discussions on the current state of art, best practices, pedagogical approaches and the needs of the target groups in the countries of the partnership: Croatia, Austria, Germany, Greece, Ireland, Portugal, Slovakia and Slovenia. This report was of utmost importance for the beginning of the project, as it guided the work all over the project, including production, testing and implementation of educational materials.

Development of information and training materials/content

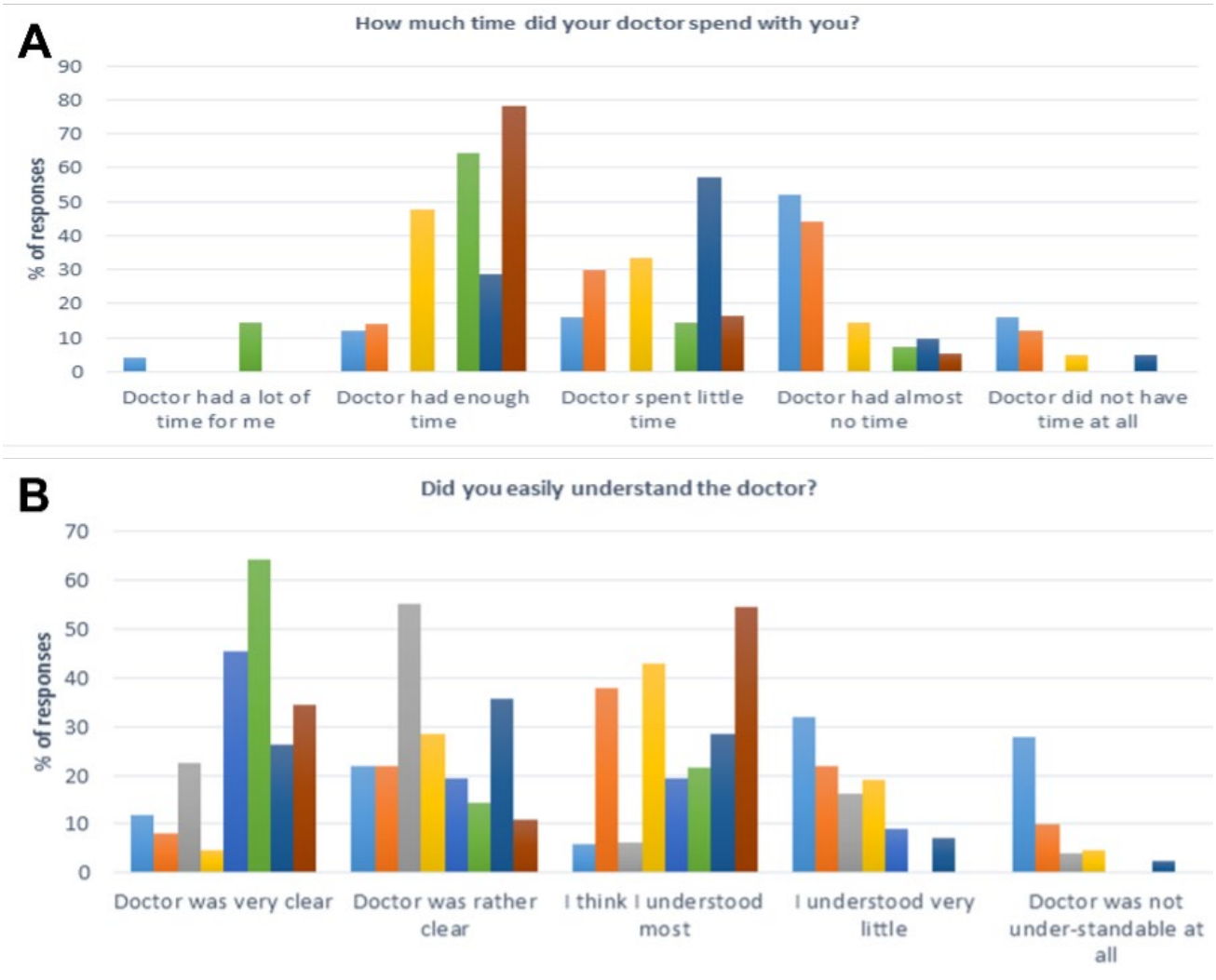
The field research focused on the identification of the needs of both individuals and stakeholders with respect to the desired educational materials for smart patients, considering also the adjustment of the technological development concerning the target groups in such tools.

The first step of the field research were the discussions with focus groups. In each country, there were established focus groups comprising of experts from healthcare organizations, science education institutions, adult education providers and citizens, who took part in the focus groups discussions during the framework analysis phase.

The second step was the production distributing, and analysing questionnaires, which targeted two groups: experts in the healthcare field and individuals. The questionnaires aimed to investigate the health status of the patients and knowledge of the existing online tools. The results of the questionnaires were

analysed on national level in the national reports and on the European level in this final report. The focus groups included 6-10 participants representing all the target groups and stakeholders. There was a discussion followed by interviews with selected members of the target groups and stakeholders.

The needs assessment analysis showed that the results provided by the experts are extremely clear about the need of online health information platforms (20% of the experts don't know they even exist) and that patients should have a better basic medical knowledge. For those reasons, the implementation of an online health information platform could be extremely useful. Moreover, we can highlight that in each country, members of the public had a more positive view than professionals, both of their physical and mental/emotional health. Some of the results of questionnaires administered to target groups are shown on **Figure 1** - results of the patients (**A** and **B**) and experts/stakeholders (**C** and **D**).



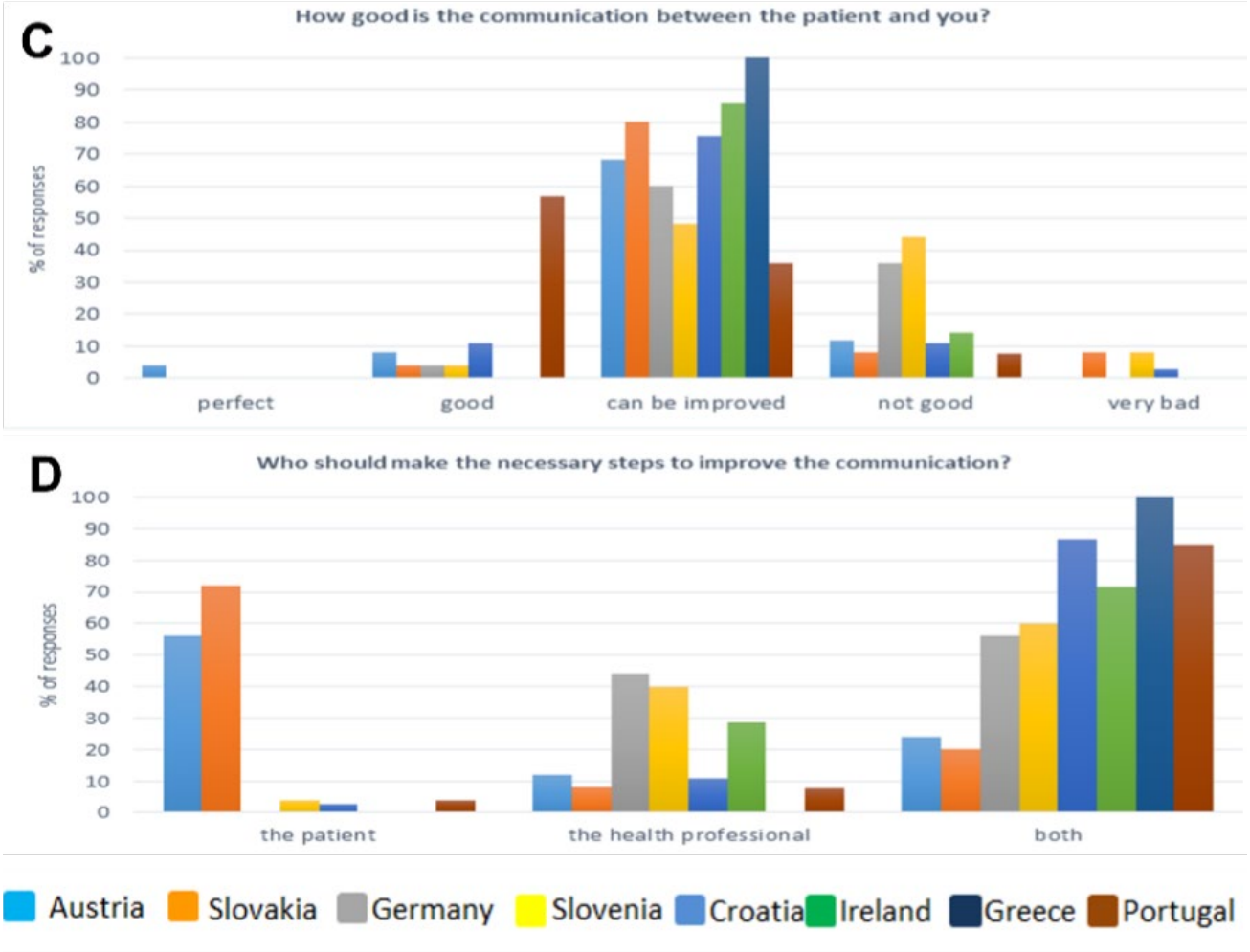


Figure 1. Illustration of some of the results extracted from the questionnaires administered to patients (**A** and **B**) and experts/ stakeholders (**C** and **D**).

After discussion among the partnership, the contents development was organized in three different modules, which one with different submodules, considering the skills/competences for the target population. **Table 1** shows the themes of the medical and informative contents produced.

Table 1. Contents developed in the project

Module 1: Prevent	Module 2: Empower	Module 3: Participate
Submodule 1 Work life balance	Submodule 1 Understand your role	Submodule1 Building relationship
Submodule 2 Nutrition	Submodule 2 Patient Skills	Submodule 2 Compliance
Submodule 3 Physical Activity	Submodule 3 Know your rights	Submodule 3 Reactions to illness
Submodule 4 Sexual life	Submodule 4 Cultural awareness	Submodule 4 Recovery - healing
Submodule 5 Mental health	Submodule 5 Patient Knowledge	Submodule 5 New perspective

Creation of the online platform and mobile application and its evaluation

Materials were developed as power point files support that were uploaded after the validation and translation, on an online platform that was created and installed on the project's website (https://smart-patients.eu). An example of the appearance of the online platform is showed on Figure 2. These developed materials can be consulted anywhere at any time through an App produced for android mobile devices.

Evaluation and dissemination of developed materials/contents

The main conclusion one can take from the study performed in the validation and dissemination phases is that the materials produced in the context of this project were generally well received and highly appreciated by the citizens and the experts/stakeholders. Platform contents are generally suitable for their purpose - citizens consider contents well designed and enough for them and consider the platform attractive and easy to use. The platform comprising the materials is appealing and very easy to use and the mobile application runs smoothly, and the contents can be accessed anytime and anywhere.

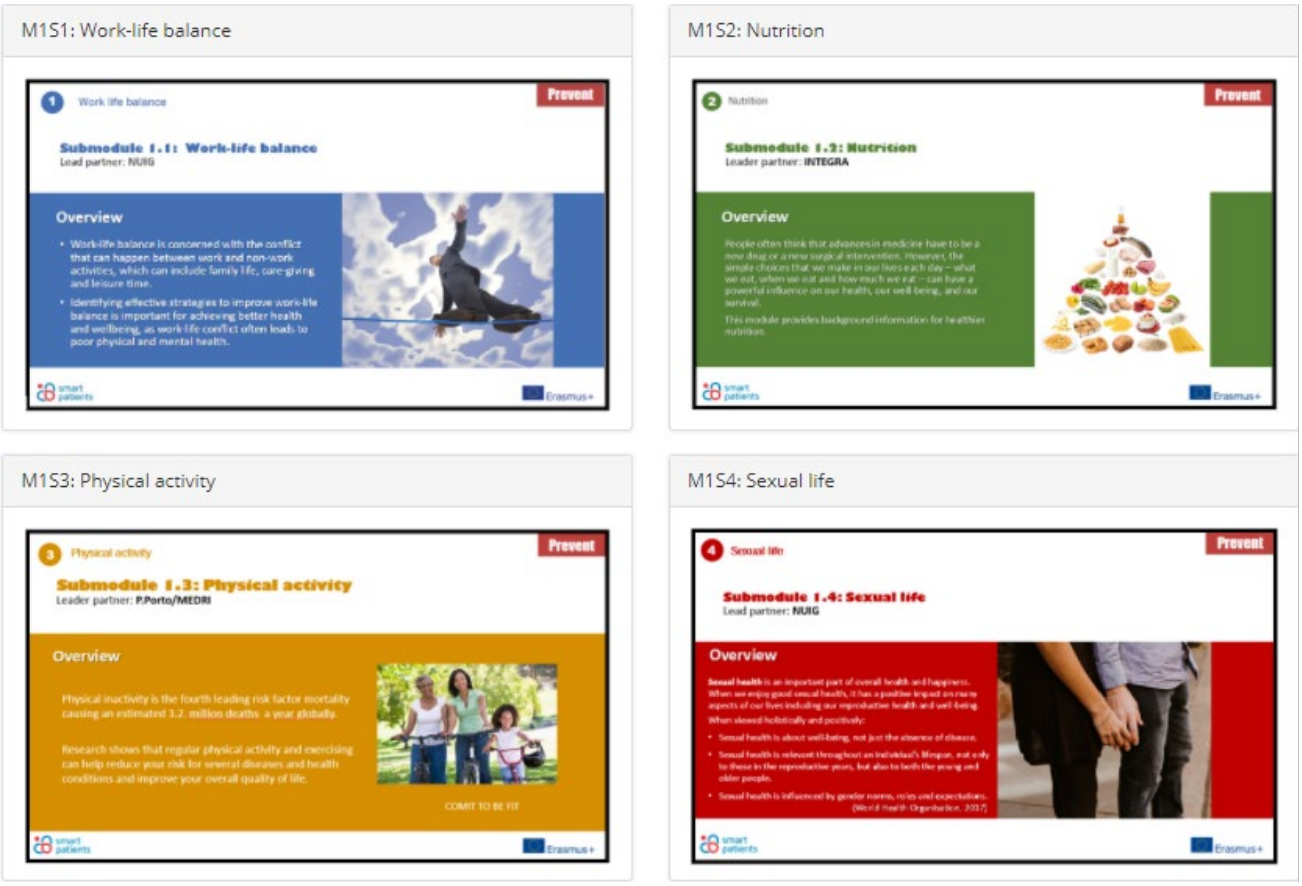


Figure 2. Illustration of contents displayed in the online platform in a colored and attractive way.

Taking into account the results of the pilot test surveys, as well as the conversations with some external evaluators and other health professionals, partners proposed to apply some other activities with the aim of dissemination, improvement and updating of the materials of the project, intending to reach a large number of people who wants to become a smart patient, including the presentation of online training platform to the student community (secondary schools and undergraduate finalists on health degrees - nursing, occupational therapy, physiotherapy, speech therapy, audiology, pharmacy); presentation to users and stakeholders of social centres and health organizations; and presentation of the smart patients project and its products in scientific meetings.

Conclusion

The project was concluded on 31st October 2018 and all the objectives were successfully reached. In the upcoming years it is our intention to follow the experts and citizens who have been involved in the project in order to find out how the online training materials influenced the way of being/acting of the experts with their patients, and the citizens lifestyle as well as their empowerment in the management of health problems. Moreover, there have been some community interventions were the project and its material is presented to the stakeholders with the same purpose. Besides, it would be interesting to update and improve the training materials throughout time, in order citizens become increasingly empowered on health issues management and on their own health.

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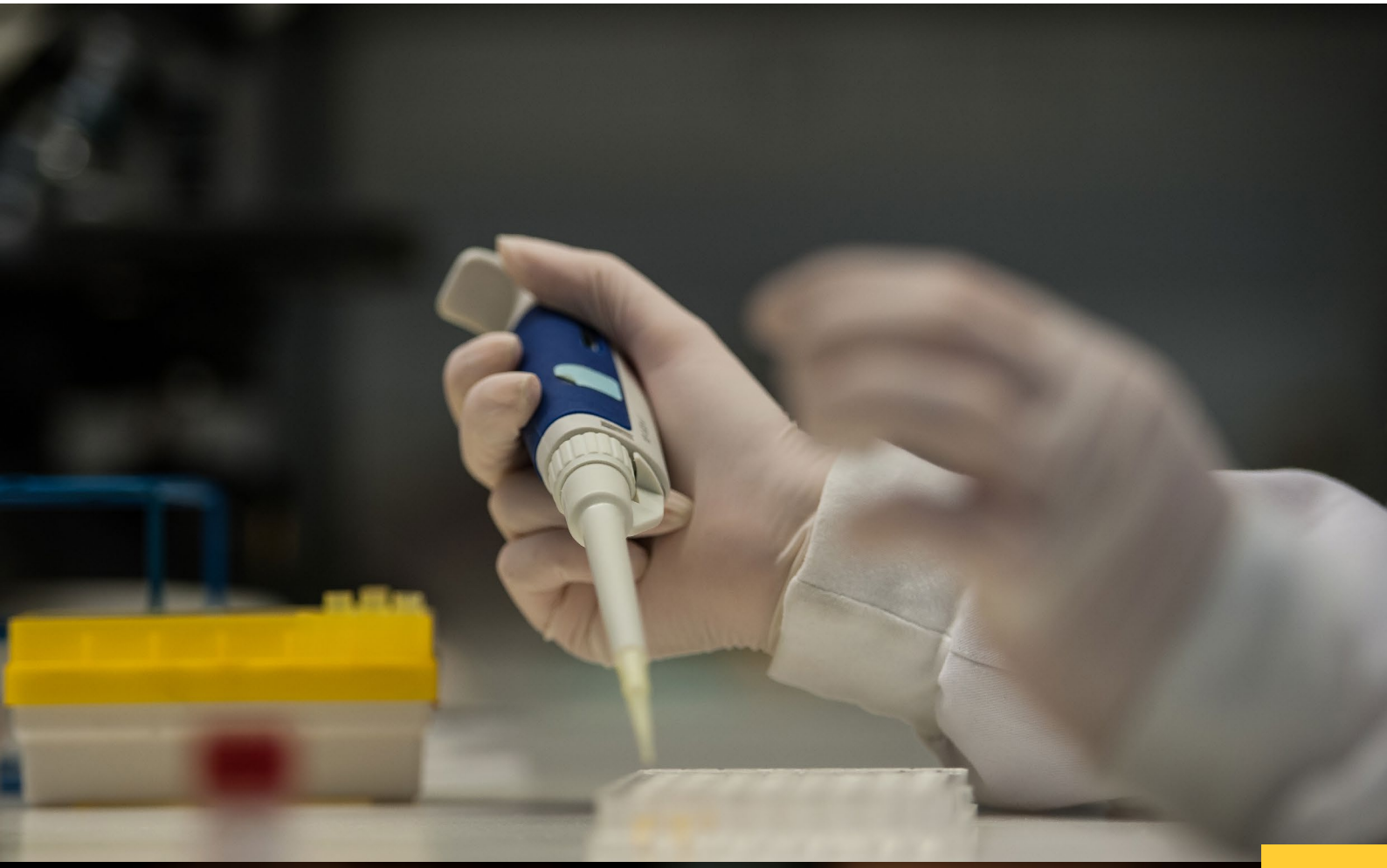


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NEW

THERAPEUTIC APPROACHES

BASED ON IONIC LIQUIDS

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Resumo

Os líquidos iónicos (LIs) definem-se, atualmente, como sais (com pelo menos um ião orgânico) estáveis acima do seu ponto de fusão.

Começaram a ser utilizados principalmente como solventes, mas rapidamente chamaram a atenção das Ciências da Vida, na medida em que algumas das características daqueles compostos podem ser relevantes em aplicações terapêuticas.

Os LIs podem mostrar propriedades físico-químicas mais interessantes ao nível de ingredientes farmacêuticos ativos como, por exemplo, hidrossolubilidade, para além do facto de os LIs (líquidos à temperatura ambiente e/ou à temperatura do corpo humano) não apresentarem polimorfismo, um aspeto que frequentemente limita as condições de uso e a eficácia terapêutica de ingredientes farmacêuticos ativos sólidos.

Esta linha de investigação procura através de uma escolha criteriosa dos iões a emparelhar afinar algumas dessas propriedades, e estudar a combinação de duas moléculas bioativas que tenham grupos ionizáveis de carga oposta, formando líquidos iónicos com efeito terapêutico dual.

Abstract

Ionic liquids (ILs) are currently defined as salts (with at least one organic ion) stable above their melting point.

They began to be used mainly as solvents, but quickly drew the attention of the Life Sciences, as some of the characteristics of those compounds may be relevant in therapeutic applications.

ILs can show more interesting physicochemical properties at the level of active pharmaceutical ingredients such as water solubility, in addition to the fact that ILs (liquids at room temperature and/or human body temperature) do not present polymorphism, an aspect which often limits the conditions of use and therapeutic efficacy of solid active pharmaceutical ingredients.

This line of research seeks, through a careful choice of the ions, to fine-tune some of these properties, and to study the combination of two bioactive molecules that have ionizable groups of opposite charge, forming ionic liquids with a dual therapeutic effect.

Introduction

Ionic Liquids (ILs) are a class of compounds that developed from traditional high temperature molten salts. Although many different early studies have been taken as the true hallmark of the beginning of the ILs era (Angell et al., 2012; Laus et al., 2005; Welton, 2018), the most consensual one is the work developed in 1914 by Paul Walden (Walden, 1914), who deliberately produced ethylammonium nitrate (Figure 1) as a liquid possessing ionic character.

Figure 1. ethylammonium acetate (1) and 1,3-dialkylimidazolium cations (2).

The introduction of ILs in the biosciences and in the pharmaceutical industry has been slow and subtle (Egorova et al., 2017; Ferraz et al., 2011; Shamshina et al., 2015). The pharmaceutical industry firstly regarded ILs as "greener" surrogates of volatile organic compounds (VOCs) used as solvents in the synthesis of active pharmaceutical ingredients (APIs) (Earle et al., 1999; Earle & Seddon, 2000; Ferraz et al., 2018; Welton, 1999). In this connection, and to assess how "green" ILs really were, their toxicity was evaluated, and soon it was recognized that ILs could be used against pathogenic microorganisms (Pernak et al., 2003; Prudencio et al., 2020). This prompted several groups to study antimicrobial activity of known ILs (Carson et al., 2009; Demberelnyamba et al., 2004; Pernak et al., 2001; Pernak et al., 2007), to prepare and test novel ILs based on APIs (Bica et al., 2010; Ferraz et al., 2012; Ferraz et al., 2016; Hough et al., 2007), or to use ILs as co-adjuvants or carriers in drug formulations (Cojocaru et al., 2013; McCrary et al., 2013; Zavgorodnya et al., 2017).

Nowdays, half of all drugs used in medicine are administered in the form of a salt and the formation and formulation of a suitable salt as a drug candidate is recognized as one of the essential steps in the pre-clinical phase of modern drug development.(Berge et al., 1977; Stahl, 2002) The number of examples of compounds with pharmaceutical activity in cationic or anionic form with a biocompatible or inert counter-ion is growing. (Sekhon, 2011) An example of this is the growing number of publications referring to the use of ILs based on active pharmaceutical ingredients. For example, it is reported in the literature that Ibuprofen-based LI (1-(2-hydroxyethyl)-1-3-methylimidazolium ibuprofenate) is about 100,000 times more soluble than ibuprofen.. (Viciosa et al., 2015) It should be noted that ibuprofen is a practically insoluble molecule in water, (Filippa & Gasull, 2013) which tends to decrease its clinical effectiveness.

Thus, it is reasonable to admit that one of the advantages of IL formation may be the increase in the aqueous solubility of existing drugs, among others. The formation of an ion pair also allows the formation of new APIs with possible activity against more than one disease.

Methods of Preparing Ionic Liquids

ILs are frequently produced from ammonium, phosphonium or sulphonates ions[2]. There are two main methods of preparing ILs: metathesis and acid base neutralization (Figure 2). We could also consider another method, for imidazolium cations that was developed by Earl and Seddon: the reaction of imidazole carbenes as strong bases (Earle, 2005).

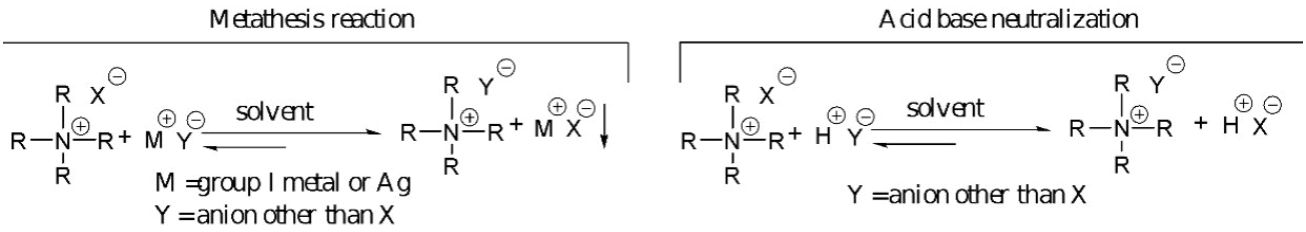

Figure 2. General procedure for the metathesis reaction and acid base neutralization.

There are several alkylammonium halides commercially available and they can be used directly in metathesis reactions [4]. When alkylammonium halides are not availabe, a quaternization reaction is required, when an organic halide salt is formed through the alkylation of a base by a haloalkane [4]. This method can also be used to prepare pyridinium and imidazolium halides (Scheme 2). Currently, the use of non-conventional methods like microwave[5, 6] and ultrasound techniques[5, 7] is being applied in the quaternization reaction with better results[5, 8].

This line of research use the acid-base neutralization method (Ferraz et al., 2020; Silva et al., 2020). This methodology avoids the contamination problem(Ohno & Yoshizawa, 2002). This procedure is also quite simple and through the use of equimolar mixing, it is possible to obtain the salts without the formation of by-products(Ohno & Yoshizawa, 2002). This method results very well with tertiary amines with halide acids or some organic acids.

Perspectives

Our line of work at the moment is developing new Ionic Liquids based on malaria drugs. Basic, because our long experience with these drugs but also because malaria is endemic to poor countries, there is a constant need to fuel the antimalarial drug pipeline with new options, classical antimalarials like primaquine, chloroquine and mepacrine have basic nitrogen-based groups can be easily paired with organic acids.

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EFFECTS OF

NOISE FREQUENCY

ON PERFORMANCE AND WELL-BEING

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Award: SHO2019 Best Paper Award, International Symposium on Occupational Safety and Hygiene 16th April 2019

Abstract

In a previous study we found that intermittent sounds, simulating alarm sounds, have a relevant effect on workers' performance and wellbeing. As the frequency of these sounds can influence subjects performance and well-being, a new study testing the effect of intermittent sound patterns with different frequency was carried out. Five noise conditions were simulated and tested through an experimental study with 16 undergraduate students. The influence of each condition on participants' attention and short-term memory was assessed with the serial recall and response inhibition tests. Discomfort, stress and annoyance were accessed using visual analog scales. No significant differences were found between the noise conditions in what regards to subjects performance. However, higher discomfort, stress and annoyance perceptions were found in condition with intermittent sounds at 3000 Hz. This study provided important insights about the influence of different noise frequencies on subject's performance and well-being.

Introduction

Ergonomics is concerned with the understanding of interactions among humans and other elements of a system. People in systems operate within a particular environment, which can have impact on their health, comfort and performance. Occupational noise is a health hazard present in several workplaces, with physiological impacts, including noise-induced hearing loss. However, occupational noise has been also related to negative effects on workers' well-being and performance. In fact, it is an important physical hazard pointed and studied in the field of cognitive ergonomics. It has been related to negative effects on stress, well-being and mental processes, such as perception, impaired attention and memory (Monteiro et al., 2018; Sousa et al., 2019; Golmohammadi et al., 2022).

The influence of occupational noise on workers' performance has been a matter of study, in particularly in the last years decade (see e.g., Khajenasiri et al., 2016; Nassiri et al., 2013; Monteiro et al., 2018). The features of occupational noise, in particular sound pressure levels, the type of noise and its frequency can be related to several non-physiological effects.

The study of the influence of occupational noise on workers' performance by this research team, has been started in 2015, were the sound pressure levels from a fast food restaurant were characterized and its effect on performance were analysed. We have investigated the effects of three noise conditions on attention and short-term memory, as well as on subjects' perceptions of discomfort, stress and annoyance. This first study ended in 2017, and the results were published in Monteiro et al. (2018a; 2018b). Since alarms frequency can have influence on the obtained results, and considering the importance to create alternative solutions to food establishments, where alarm signs are regular and several mistakes with the clients' requests observed, the influence of intermittent sound patterns with different frequency on performance and well-being were analysed in Sousa et al. (2019).

Methodology

A total of 16 undergraduate school student, 8 males and 8 females, were part of this study. The participants had a mean age of almost 22 years old (±0.7; min=21; max=23).

In a laboratory context, five noise conditions were simulated and tested: Standard Condition (C0); Industrial noise with alert sounds at 500 Hz(C1); Industrial noise with alert sounds at 1000 Hz (C2); Industrial noise with at alert sounds at 2000 Hz(C3); Industrial noise with alert sounds at 3000 Hz(C4). The noise levels were fixed at 45±0.3 dB(A) in C0, and in 68±0.5 dB(A) in the other conditions.

The influence of noise on participants' attention and short-term memory was assessed with the serial recall and response inhibition tests. Discomfort, stress and annoyance were accessed using visual analog scales (100 mm in length; "Not at all..." to 100="Extremely...").

Results and discussion

No significant differences were observed between the different noise conditions for Serial Recall and Response Inhibition tests ($p>0.05$). Similar results were obtained for the stimulus perception and perceptions of the interference of stimulus ($p>0.05$). These results were not expected, in particularly considering results from previous studies. One possible explanation can be related to the small time of this experiment for each trial and also for the resting time. We want to continue this experiment, but these issues should be rethink, reducing also the arousal effect. The inclusion of tasks with different workloads can be also important in future experiments.

In what regards to discomfort, stress and annoyance results shows significant differences between the conditions under analysis for these variables ($p < 0.05$). Higher levels were found in condition C4 (Industrial noise with alert sounds at 3000 Hz). In what regards to discomfort, stress and annoyance results showed significant differences between the conditions under analysis for these variables ($p < 0.05$). Higher levels were found in condition C4 (Industrial noise with alert sounds at 3000 Hz). These results were expected, since high sounds frequencies are frequently related to higher discomfort, perception and sensitive (Ménard et al., 2008; Kumar et al., 2008). Results also denoted a relationship between the annoyance, stress, discomfort and interference, similar to what was previously identified in Monteiro et al. (2018a).

Conclusions

We start this research looking for alternate solutions for occupational noise in fast food restaurants, were alert sounds emitted by machinery are frequent. Despite no significant differences were found in subject's performance when they were exposed to intermittent sounds with different frequencies, it was identified an important impact of higher frequency stimulus on subject's discomfort, stress, and annoyance, which increasing fatigue with the time of exposure. Additional research about the influence of noise in workers' performance is needed, including field studies.

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BIOMOLECULES IN THE RELATIONSHIP OF

CANCER *AND* OBESITY

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Resumo

A obesidade tem sido associada a várias causas principais de morte e morbidade, incluindo neoplasias malignas. Esse aumento da prevalência tem sido acompanhado por um aumento mundial nas taxas de incidência de melanoma cutâneo nas últimas décadas, assim como de gliomas, os tumores cerebrais malignos primários mais comuns em adultos (Almeida et al., 2019). Embora a etiologia da obesidade seja estabelecida, os mecanismos implicados permanecem obscuros (Coelho et al., 2016). O melanoma é refratário às terapias convencionais, e o uso da radioterapia como terapia adjuvante em pacientes com melanoma cutâneo é ineficaz, por isso é extremamente importante entender a modulação antioxidante do melanoma em um ambiente de obesidade (Coelho et al., 2017; Oliveira et al., 2016). Além disso, o potencial metastático de alguns tipos de câncer é reduzido ou inibido pela obesidade, o que gera grandes preocupações sobre o prognóstico de pacientes com metástase (Fonseca et al., 2021). Todos os estudos divulgam modelos interessantes para o estudo da biologia desses tumores em um ambiente obeso, que podem ser explorados na busca de biomarcadores, marcadores de prognóstico e abordagens terapêuticas.

Abstract

Obesity has been associated with various major causes of death and morbidity including malignant neoplasms. This increased prevalence has been accompanied by a worldwide increase in cutaneous melanoma incidence rates during the last decades, as well as gliomas, the most common primary malignant brain tumors in adults (Almeida et al., 2019). Although obesity aetiology is established, the implicated mechanisms remain unclear (Coelho et al., 2016). Melanoma is refractory to conventional therapies, and radiotherapy usage as an adjuvant therapy in cutaneous melanoma patients is ineffective, so it is extremely important to understand the antioxidant modulation of melanoma under an environment of obesity (Coelho et al., 2017; Oliveira et al., 2016). Moreover, the metastatic potential of some types of cancer is reduced or inhibited by obesity, which drives major concerns on the prognosis of metastasized patients (Fonseca et al., 2021). All of the studies disclose interesting models for the study of these tumors' biology under an obese environment, that can be explored for the search of biomarkers, prognostic markers and therapeutic approaches..

Obesity prevalence has significantly increased, leading to a public health concern and worldwide branded as "the modern epidemic". The prevalence of obesity in Europe has increased by approximately 30% over the past 10 years and this phenomenon is corroborated by data from several other countries. It has long been recognized that excess adipose tissue increases the risk of cardiovascular disease, type 2 diabetes and metabolic syndrome, but only in the past few decades it became widely accepted that augmented body adiposity is a risk factor for several types of malignancies. Additionally, obesity can lead to worsened prognosis, poorer treatment outcome, and increased cancer-related deaths. Melanoma arises from the malignant transformation of melanocytes, the pigment-producing cells of the skin, hair and eyes. Its incidence rates have increased in the last decades worldwide from 3% to 7% annually. These statistics suggest a doubling of rates every 10–20 years, raising melanoma to the most rapidly increasing cancer in Caucasians. Several reports showed positive associations between increased body fat and the risk of cutaneous melanoma

later in life, suggesting that the increasing incidence of melanoma may be related to the enlarged obesity prevalence. In vivo adiposity-related stimulation of melanoma growth has been demonstrated. Tumour-associated macrophages and endothelial cells have been pointed out as possible mediators in the growth-promoter effect of adipose tissue towards melanomas. In fact, tumour stroma comprises many different cell types, including fibroblasts, adipocytes, immune, and endothelial cells that, along with the extracellular matrix, are key players in cancer development and progression. However, we hypothesize that adiposity might also exert a direct effect over melanocytes without the involvement of stromal cells in a paracrine or endocrine manner. In the paper entitled "Effect of Adipocyte Secretome in Melanoma Progression and Vasculogenic Mimicry", it is explored the biological role of adipocytes secretome in B16-F10 and MeWo melanoma cell survival and plasticity (Coelho et al., 2016).

Moreover, and considering malignant melanoma, lungs are main target organs for metastization and their immune response is a key modulator of this mechanism. The concept that the metastatic potential of some types of cancer is reduced or inhibited by obesity, known as the obesity paradox, drives major concerns on the prognosis of metastasized patients. The aim of the study "Lower melanoma pulmonary metastatic burden in obese mice: role of FGF-21" was to investigate how high-fat diet (HFD)-induced obesity affects melanoma metastization. C57Bl6/J mice were fedwith HFD or standard diet for 180 days and inoculated intravenously with B16F10 melanoma cells. Upon 21 days of inoculation, lung tissue of overweight and lean mice was assessed for histology and immunohistochemistry assays. Adipokine antibody arrays were performed in mice serum. In vitro RAW 264.7 macrophage cultures were established and incubated with FGF-21 and/or lipopolysaccharide (LPS). Conditioned media was added to B16F10 cells for viability quantification. HFD-fed mice presented a reduced number of metastases with lower proliferative rates. The high content of inflammatory foci observed in noninoculated obese mice was significantly decreased upon B16F10 inoculation, concurrent with a slight fibrosis reduction. Plasma levels of fibroblast growth factor-21 (FGF-21), an endocrine regulator, were elevated in noninoculated HFD mice and the expression of FGF receptor 1 (FGFR-1) was significantly upregulated after inoculation. FGF-21 reduced melanoma viability in LPS-stimulated macrophages. Altogether, these findings suggest that higher amounts of FGF-21 are able to counterbalance the proinflammatory eff¬ects associated with obesity, protecting the lungs from melanoma metastization.

Melanoma has poor prognosis with a median survival rate between 6 and 9 months. Currently it remains one of the most challenging cancers due to its

refractory behavior to conventional therapies. While early-stage melanoma can be detected and effectively removed through surgery, melanoma with high metastatic potential is difficult to treat and more prone to develop resistance to available therapies, such as chemotherapy and radiation. Although the diagnosis of melanoma is straightforward, there are many disagreements regarding treatment and surveillance In order to surpass some of the limitations addressed to melanoma treatment, preventive or adjuvant methods like dietary factors are nowadays a relevant field of research. Despite the knowledge about melanoma biology, pathogenesis and developed therapies, is extremely important to understand the effect of these dietary compounds in redox modulation of melanoma under an obesity environment, especially the effect of antioxidant vitamins A, C and E or the effect micronutrient such as selenium salts. These antioxidant compounds are hypothesized to reduce the risk of developing melanoma because of their properties. Thus, in the review "Melanoma and obesity: Should antioxidant vitamins be addressed?" it is provided a systematic and up-to-date scientific discussion for the better understanding of the contribution of antioxidant compounds like vitamins A, C, E and selenium salts and their potential role against melanoma (Oliveira et al., 2016). Nowadays micronutrients are a trendy field of research. These dietary factors, such as vitamins may be useful on melanoma prevention, acting as anti-cancer agents possibly by suppressing the reaction/ light-induced erythema of human skin, preventing the development or progression of melanoma in general, inhibiting growth, proliferation, inducing apoptosis and differentiation of human and murine melanoma cell lines population, decreasing inflammatory environment associated with melanoma development in an obesity context and by restraining toxic effects of ROS released during inflammation. Despite all the research and investigation some data still remain controversial, and more studies are needed in order to understand dietary factors in particular these antioxidant vitamins and their potential role in melanoma therapy.

Radiotherapy is frequently used to treat the majority of malignancies and has a direct impact in the proliferative phenotype of both normal and cancer cells. Radiation induced ionization of regulatory proteins and DNA might render the cells unviable and culminate in cellular death. Ionizing radiation can also indirectly cause cellular damage. The formation of highly reactive oxygen and nitrogen radicals increases the intracellular oxidative stress, depleting the antioxidant defenses, which subsequently react with many cellular components (DNA, proteins, lipids) leading to unrecoverable damage. However, melanoma is known to be radioresistant, which discourages the use of ionizing radiation as an adjuvant therapy in melanoma patients. Recently, the use of radiation in higher

delivered doses, hypofractionated and in combination with immunotherapy has led to some positive outcomes in melanoma metastasis treatment and palliation. Nonetheless, obesity, particularly high visceral adiposity, presents a problem in treatment planning and delivery of radiation to internal metastases. Generally, higher body adiposity is associated with both cancer initiation and progression. Obesity itself is a risk factor for several types of neoplasms, including melanomas. High adiposity can be a contraindication for (and may limit the extent of) cancer surgery since it contributes to the inadequate dosing of chemotherapeutic drugs and complicates the planning and delivery of radiation. Adipocytes secrete a ariety of factors that exert effects at both local and systemic levels. The grand majority of these factors are cytokines, chemokines and inflammatory mediators, but a role in growth regulation as a new aspect of adipokines has been revealed by novel adipocyte-released molecules. Fat-derived molecules stimulate melanoma progression and aggressiveness and act as mediators of proliferation in melanoma cells. Resistance to oxidative stress appears to be a key mechanism of tumor radioresistance. Obesity is linked to a more pro-oxidative status, with a concomitant systemic increase in reactive oxygen species (ROS), acting as an additional source of oxidants. For the current study, we hypothesized that adipocytes might lead to two antagonistic outcomes towards melanocyte radiosensitivity. Although the fat-derived growth factors might protect melanocytes from radiation-induced loss of survival by stimulating their overall proliferation, the adipocyte-generated oxidants can further increase the oxidative burden, aggravating the radiation-induced damages. In the study entitled "Adipocyte Secretome Increases Radioresistance of Malignant Melanocytes by Improving Cell Survival and Decreasing Oxidative Status" cell cultures were irradiated at standard doses to investigate the action of the adipocyte secretome in melanoma radioresistance (Coelho et al., 2017).

Gliomas, a wide term which comprises all tumors arising from the supportive tissue of the brain, represent 30% of all brain tumors and 80% of all malignant brain tumors. They are the most common primary malignant brain tumors in adults. Prognosis is extremely poor, with a median survival time of approximately 12 to 15 months and is almost invariably fatal. This tumor represents about 12–15% of all primary brain tumors and about 60–75% of all astrocytomas. Gliomas increase in frequency with age and affect, preferentially, men. Genetic factors in glioma etiology are poorly understood; less than 5% of glioma cases are familial in origin, with only a few described by rare genetic syndromes. In 2001, different studies from the International Agency for Research into Cancer (IARC) and the World Cancer Research Fund (WCRF)

have reported a relationship and established a link between obesity and cancer risk. Excess adiposity is related with an increase the incidence and/or death rates from a wide variety of human cancers, being the most common colon, rectum, esophagus, kidney, pancreas, gallbladder, ovary, cervix, liver, prostate and certain hematopoietic cancers. Overweight and obesity are important risk factors for developing cancer and also for cancer related mortality. It is important to understand the pathophysiological mechanisms involved in the link between obesity and cancer, in order to target future preventive and therapeutic strategies for cancer in obese people. Despite its high morbidity, the etiology of glioma remains largely unknown. Among several risk factors, lifestyle was also recently identified as a major risk factor for the development of primary glioma. Consequently, there might be a relationship between the increase and dysfunction of adipose tissue. Obesity, favored by the modern lifestyle, acquired epidemic proportions nowadays, and accelerated weight gain, in adults, is associated with increasing incidence of all central nervous system tumors, mostly glioma. At the present time, it is not clear which factors might be involved in this relation. Genes that influence obesity are highly expressed in the brain and could also mediate glioma susceptibility. Some studies analyzed body weight in relation to survival in glioma demonstrating higher death rates in patients with an excess body weight. Obesity, and in particular visceral obesity, plays a major role in the pathogenesis of several metabolic disorders. Recently two large sample studies have established that obesity has no clear relationship with the occurrence of glioma. The study presented in "Adipocyte proteome and secretome influence inflammatory and hormone pathways in glioma" aimed to develop an in vitro rodent model for the study of the influence of adipokines secreted by adipose tissue in glioma biology (Almeida et al., 2019). We propose a model in which GL261 cells, a mouse glioma cell line, is cultured in the presence or absence of 3T3-L1 mature adipocytes conditioned medium. The 3T3-L1 pre-adipocytes were differentiated under controlled experiments and the adipokines and inflammation chemokines pattern expression were examined by proteome microarrays in the mature adipocytes conditioned medium were grown.

Our studies disclose some paradoxical relationship between obesity and cancer. They have also been able to develop an interesting in vitro and in vivo models for the study of melanoma and glioma biology under an obese environment, that can be explored for the understanding of cancer cells biology, for the search of biomarkers, prognostic markers and therapeutic approaches.

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FATTY MESS

Fat Diet-Induced Obesety in Melanoma Metastasis

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Resumo

O melanoma é o cancro de pele mais agressivo, caracterizado por alto potencial metastático e baixa sobrevida. O excesso de peso e a obesidade foram identificados como fatores de risco para muitos tipos de cancro. No entanto, existem neoplasias em que a obesidade está associada a prognósticos mais favoráveis, o denominado "paradoxo da obesidade".

Dados preliminares obtidos pelo nosso grupo de investigação revelaram que a obesidade atua como uma faca de dois gumes no melanoma: potencializando o crescimento e a vascularização/angiogénese do tumor primário, mas simultaneamente diminuiu o potencial metastático, reduzindo o crescimento do tumor secundário.

Neste projeto exploratório, propomos explorar e aprofundar o impacto das dietas ricas em gordura e da obesidade na etiologia do melanoma.

Abstract

Melanoma is the most aggressive skin cancer characterized by a high metastatic potential and poor survival rate, leading to major morbidity/mortality. Overweight, obesity and diet composition have been identified as risk factors for many types of cancers. However, there are cancers where obesity is associated with favorable outcomes and this has been coined the "obesity paradox".

Preliminary data obtained by our research group disclosed paradoxical findings unveiling that obesity act as a two-edged sword in melanoma: potentiating primary tumor growth, and vascularity/angiogenesis, but at the same time decrease metastatic potential, thus preventing secondary tumor growth.

In this exploratory research project, we propose to further explore and deepen the impact that fat-rich diets and obesity partake in melanoma etiology.

Skin cancer is by far the most common of all cancers. Melanoma accounts for only about 1% of skin cancers but causes the large majority of skin cancer deaths. Several risk factors are known to contribute to melanoma development: sun/UV radiation, a family history of melanoma, high number of nevi, the degree of skin pigmentation, a suppressed immune system, among others.(Jiang et al., 2015) The risk of melanoma increases with age but, unlike other solid tumors, melanoma is not uncommon among those younger than 30.(Jiang et al., 2015) In fact, it's one of the most common cancers in young adults, accounting for the third-highest number of deaths across all cancers.(Apalla et al., 2017)

The incidence of cutaneous melanoma is consistently rising and obesity has been postulated as one of the causes for the increased incidence of melanoma. Obesity has been identified as risk factor for several types of cancer, however the association with melanoma incidence is not as strong.(Clement et al., 2017) Nevertheless, several reports showed positive associations between

adiposity and the risk of melanoma later in life suggesting that the increasing incidence of melanoma may be related, in part, with the enlarged obesity prevalence. Additionally, there is evidence supporting that feeding behavior and diet composition might be associated with melanoma etiology.(Karimi et al., 2016) Calorie restriction demonstrate a wide range of beneficial effects able to help prevent malignancies and increase the efficacy of cancer therapies. Concomitantly with melanoma expansion, the development of a supporting network of blood supply is vital to sustain tumor growth. Melanomas are highly vascularized tumors and angiogenesis has been correlated with poor overall survival and increased rate of relapse.(Kimura & Sumiyoshi, 2007) Contrastingly, the deregulated tumor microenvironment leads to a tortuous vascular network culminating in a low abundance of nutrients and oxygen within the tumor milieu. However, melanomas can generate an angiogenic-independent tumor microcirculation – socalled vasculogenic mimicry – to increase perfusion. Tumor cell-lined vascular networks sustain a redundant blood supply, with a viable blood flow between vasculogenic mimicry void spaces and the endothelial vasculature. The presence of these mimetic channels by the tumor itself stands a predictor of poor prognosis, but little is known about the biological relevance of this phenomenon.(Zhang et al., 2019) Adipocytes, obesity and fat-rich diets are well-known promoters of primary melanoma growth in preclinical models. High fat diet (HFD)-fed and overweight C57Bl/6 mice exhibit larger B16F10 tumors with increased microvessel density and higher-caliber capillaries. (Coelho et al., 2016; Fonseca et al., 2021) We have previously published reports on adipocytes ability to paracrine enhance B16F10 melanocytes proliferation, migration adhesion, invasion, antioxidant defenses and treatment resistance.(Coelho et al., 2016, 2017) Moreover, we demonstrated that adipocyte-released molecules induce melanoma cells to rearrange, on in vitro 3D cultures, into vessel-like structures typically reported for endothelial cells, endorsing the potential adipocyte secretome inducer effects of tumor vasculogenic mimicry.(Coelho et al., 2016) In fact, preliminary data obtained in a pilot study from our research group disclosed that not only the number and caliber of capillaries was elevated in overweight B16F10 tumor-bearing animals, but the increase in microvascular density was accompanied by a parallel higher number of vasculo-mimetic channels in vivo.(Fonseca et al., 2021) Therefore, we hypothesized that obesity could be exacerbating the vasculogenic mimicry microcirculation pattern in melanomas, endorsing a potential role of obesity towards the vasculogenic mimicry phenotype. Surprisingly, we also unveiled an unexpected antagonistic outcome of obesity in melanoma metastasis. Despite the increased volume of primary B16F10 tumors found in HFD-fed animals, the number of lung metastases in overweight animals injected with circulating

B16F10 cells was significantly lower than their lean counterparts. Obesity-associated changes apparently decrease B16F10 lung-tropism and metastatic potential thus restraining secondary tumor growth. Molecular characterization of adipose-associated serum factors revealed that HFD-fed mice exhibited remarkably large amounts of fibroblast growth factor (FGF)-2, FGF-21 and vascular endothelial growth factor (VEGF), with a concomitant overexpression of the FGFR-1 receptor by melanoma cells, highlighting possible new molecular mechanisms linking obesity and melanoma.(Fonseca et al., 2021)

The relative risk of obesity-associated cancer is now well established for 13 different malignancies.(Lauby-Secretan et al., 2016) Counterintuitively, adiposity appears to be protective and associated with favorable outcomes in other types of cancer, holding the "obesity paradox" hypothesis.(Pamoukdjian et al., 2019) For melanoma, numerous reports support fat-rich diets role as melanoma growth promoters. Actually, calorie-restriction is known to inhibit B16F10 cell tumorigenesis and slower melanoma growth while concomitantly enhancing pulmonar colonization in vivo. Our data point towards the inverse relationship, where HFD acts as a two-edged sword in melanoma: supporting primary tumor growth and vascularity, but at the same time decreasing melanoma metastatic spread.

Altogether, the strength of the association between adiposity and melanoma in human studies remains inadequate. It is our conviction that the "obesity paradox" hypothesis lies in between melanoma primary tumor versus secondary metastasis growth. Adiposity promotes cutaneous melanoma onset and growth, while protecting disease spread, therefore, undermining meta-analyses and other cohort studies estimates of the melanoma obesity-associated risk. Nevertheless, sufficient evidence exists to support ongoing and planned research studies to further acquire in-depth knowledge to attain a clearer understanding of this rationale.

Herein, and in accordance with our previous work, we aim to challenge the obesity paradox in malignant melanoma by taking advantage of the extensive expertise of the research team in the murine syngeneic B16F10 melanoma model, the most commonly used metastatic melanoma model for preclinical studies, and gathering together a team of researchers with solid knowledge in diet-induced obesity models, cancer metabolism and angiogenesis.

Our approach will improve the diet-induced obesity B16F10 melanoma model and comprises the development of a Luciferase and GFP dual-reporter melanoma cell line. Therefore, diet-induced obese C57Bl/6 mice inoculated with B16F10-Luc-GFP melanoma cells will be used as an in vivo model to

study the effects of obesity and fat-rich diets in melanoma development and metastasis. Briefly, we will transfect the B16F10 cells with Luciferase and GFP transgenes and create an auto-reporter melanoma cell line. Luciferase-expressing B16F10 cells will definitely enable in vivo noninvasive monitoring of primary melanoma growth and allow us to track the B16F10 cell metastatic spread. In fact, the C57Bl/6 - B16F10 melanoma model system is ideal to study by whole-body live imaging, given the high tissue contrast between tumor tissue and the surrounding parenchyma. Moreover, the GFP transgene will allow us straightforward visualization and analysis of tumors and metastasis in ex vivo tissues by conventional fluorescence microscopy and flow cytometry.

C57Bl/6 animals will be submitted to a diet challenge. The C57Bl/6 mouse model is a particularly good model mimicking the complications that are observed in human obesity. When fed ad libitum with an hyperlipidic diet, obesity, hyperinsulinemia, hyperglycemia and hypertension establish in these mice. Animals fed ad libitum with a normal-fat diet however, do not develop any metabolic abnormalities. Additionally, calorie restriction with a high-fat diet effectively attenuates obesity-related markers in rodents. Therefore, our diet-induced obesity model will include two diets with different fat contents that will be provided to two groups of animals: a HFD with 45% of kcal from fat and a NFD with 13% of fat by calories, respectively. To further improve the diet challenge, a third group of animals (ICD) will receive the HFD in a pair-fed system, guaranteeing they get the same daily amount of calories as their NFD counterparts. By examination of the pair-fed ICD animals, we will also be able to conclude whether the effect of diet in melanoma growth and metastization is due to excess consumption of calories or to an overload of dietary lipids. Afterwards, mice will be engrafted with B16F10-Luc-GFP cells to grow primary and metastatic melanomas in vivo. Subcutaneous inoculation of B16F10-Luc-GFP cells will induce primary skin melanomas, while intravenous injection of B16F10-Luc-GFP cells will directly introduce melanoma cells into the blood flow and lead to the development of distant metastases.

In vivo monitoring of orthotopic tumor development and disease dissemination will be performed by bioluminescent imaging of luciferase-expressing B16F10 cells, providing us with detailed information of tumour growth, volume and metastasis location/organ tropism of metastatic cells. Contrast-enhanced X-ray micro-computed tomography of tumor-bearing animals, will provide a highly detailed three-dimensional analysis of the vascular network within the primary melanomas and allow the quantification of the relative tumor blood perfusion and tumor neovascularization. Angiogenesis and vasculogenic mimicry will be evaluated by postmortem

analysis of tumor and metastasis sections. GFP expression by melanoma cells allied to immunofluorescence staining of CD31-positive endothelial cells will allow us to discriminate true endothelium-lined vessels from the tumor cell-derived vasculature. Overexpression of FGF-2, FGF-21 and VEGF, found in obese mice serum in our previous study, are known to be involved in angiogenesis and metabolic cues.(Coelho et al., 2016; Fonseca et al., 2021) In order to pinpoint the molecular bases of melanoma progression induced by the distinct diets, the expression of FGFR1 and FGFR2, as well as VEGFR1 and VEGFR2 will be investigated by RT-qPCR in both primary melanomas and distant metastasis. Receptors activity will further be examined by Western blotting using antibodies against total and phosphorylated (active) receptor forms. Depending on the findings, these signaling pathways will further be investigated, namely by examining Erk and Akt downstream effectors. The circulating levels of FGF-1, FGF-2 and FGF-21 and VEGF-A and -B ligands will be performed in mouse serum by ELISA.

We anticipate that, by the end of the project, further evidence supporting the obesity paradox in melanoma will be disclosed. It is expected that HFD-animals on one hand will bear considerably larger primary tumours with enhanced vascular networks but, on the other hand, will simultaneously exhibit lessened metastatic disease burdens. We also foresee that a calorie-restricted feeding regimen will reverse the deleterious effects of fat-rich diets in melanoma progression, hence ICD animals will present a primary disease burden closer to lean animals. Additionally, we expect to identify alterations in serum FGF/VEGF levels and FGFR/VEGFR expression and signalling that are distinctly modulated by HFD-feeding, which might contribute to further unravel the obesity paradox in melanoma.

Altogether, the main purpose of the current project is to help clarify the obesity paradox in melanoma, adding up to accumulating evidence and epidemiologic data and further strengthen the association between obesity and malignant melanoma progression. Nevertheless, this proposal might disclose a paramount dietary influence of fat-rich diets in melanoma progression and aggressiveness, concomitantly promoting beneficial and deleterious consequences with direct implications in disease prognosis, treatment outcomes and overall survival. Ultimately, this project will emphasize the importance of taking into consideration the role of adiposity in clinical practice to develop individualized treatment plans, with personalized therapeutic regimens, maximizing melanoma therapy success.

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DESENVOLVIMENTO, AVALIAÇÃO E QUANTIFICAÇÃO DE

BIOMOLÉCULAS

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Abstract

The synthesis of new biomolecules, the evaluation of their potential biological activity or therapeutic application, as well as the monitoring of intervening biomolecules in pathological contexts is of great interest to the scientific, medical and pharmaceutical community[1,2,3].

In the validation of synthesis, extraction and biological interaction methods, chromatographic methods play a fundamental role in the identification and quantification of these biomolecules of interest, whether these are potential new drugs, biomarkers or environmental indicators[4].

In order to contribute to the identification and quantification of biomolecules with potential (bio) technological application, new chromatographic methodologies have been developed, namely based on liquid chromatography, using HPLC-DAD[5,6].

In the development of new biomolecules, the bioactivity of compounds with potential application has been studied, such as Quinoxaline derivatives5, 6, 7. In addition to the antimicrobiological action, the effect of this family of compounds in the modeling of oxidative stress in pathological context has been evaluated [7].

The synthesis of new biomolecules, the evaluation of their potential biological activity or therapeutic application, as well as the monitoring of intervening biomolecules in pathological contexts is of great interest to the scientific, medical and pharmaceutical community[1,2,3].

The study of quinoxaline and its derivatives has become a subject of interest in recent years due to their wide variety of biological activities as well as therapeutic applications. Since they are rare in nature, synthetic quinoxalines are included in various antibiotics such as echinomycin, levomycin and actinomycin, well-known to inhibit the growth of Gram-positive bacteria and are also active against transplant tumors[3].

In search of alternatives to antimicrobial agents currently in use, and in order to respond to the landscape of loss of efficacy due to the emergence of resistance, several research groups are evaluating several families of compounds, among them the quinoxaline derivatives family, which presented several other potential biological applications[3,4].

Modifying quinoxaline's structure is possible to obtain a wide variety of compounds with different biological properties.

In the last two decades, several quinoxaline derivatives have been tested and presented antimicrobial activity, as antifungal and antibacterial agents. The antibacterial activity observed covers both Gram-negative and Gram-positive bacteria, including Mycobacterium species. There are also data pointing to activity against multidrug resistant Mycobacterium tuberculosis. Several studies have been described, concerning synthesis and biological activity of

a large amount of quinoxalines. Some quinoxaline 1,4-di-N-oxide derivatives have been shown to inhibit M. tuberculosis to a rate of 99 to 100% . Antifungal activity for quinoxaline derivatives has been tested against Candida albicans. Researchers also reported quinoxaline derivatives high antifungal activity. There are quinoxaline derivatives that present anti-protozoan activity, especially anti-amoebic, against Plasmodium and Leishmania species.

Quinoxaline derivatives present other biological properties. Anticancer activity has been already studied, and results obtained are very promising. Recently, our research group has demonstrated anti-proliferative activity in several cancer cell lines.

Some of the compounds studied by our group presented potential as new drugs for antimicrobial activity chemotherapy since the MIC's determined present low values and cellular viability tests show the complete elimination of the bacterial strain. In addition, the cellular viability tests for an eukaryotic model, indicate low toxicity for the compounds tested[5].

In the validation of synthesis, extraction and biological interaction methods, chromatographic methods play a fundamental role in the identification and quantification of these biomolecules of interest, whether these are potential new drugs, biomarkers or environmental indicators6. For this purpose, our group has identified, developed and validated new analytical chromatographic methods, based on HPLC-DAD chromatography[6,7].

Molecules modified by interactions with reactive oxygen species (ROS) in the microenvironment, and those changed in response to increased redox stress, are considered biomarkers of oxidative stress. The nitration of tyrosine (Tyr) residues in proteins is associated with nitrosative stress. L-Tyr and protein associated Tyr are the target of various reactive-nitrogen species (RNS), resulting in the formation of free 3-nitrotyrosine (3-NT) and protein-associated 3-NT. It forms after the substitution of a hydrogen by a nitro group (NO_2) in the ortho position of the phenolic ring of the Tyr residues. Studies have suggest that 3-NT is likely to have a deleterious effect on protein function and less likely to be important in normal cellular function. The nitration of proteins is a common process that occurs under physiological conditions and the concentration of 3-NT in plasma of healthy humans is on the threshold of the nM-to-pM range.A significant increase in the extent of this process results in increased 3-NT levels in biological samples and has been associated with a wide range of diseases. A wide range of methods for 3-NT detection and quantification were developed during the last years, all of them presenting positive and negative features. Our investigation group developed a new method that exhibited a good specificity,

with no interference observed with 3-NT structural relatives, namely Tyr. This method revealed good precision and accuracy. Additionally, the same method, with detection at 356 nm, also allowed the successful detection and quantification of 3-NT in a wide variety of biological matrices. Therefore, and unlike other developed methods for 3-NT quantification, our HPLC-based method was successfully applied to a wide range of biological matrices, exhibiting a great performance in all of them and allowing the effective quantification of 3-NT[7].

The modeling of oxidative stress in pathological context has been proven to be very relevant. In order to apply our new method to different pathologies, the evaluation of oxidative stress in a tumoral environment was performed, combined with the potential antitumour activity of the quinoxaline derivatives studied, has well as their ability to promote radiation cellular sensitivity[8]. In this study, we investigated the oxidative status of quinoxaline-1,4-dioxides derivatives in modulating melanoma and glioma cell lines, based on previous results from the research group and their capability to promote cell damage by the production of ROS. Overall, the results obtained emphasized the influence of quinoxaline-1,4-dioxides derivatives on the in vitro modulation of oxidative stress in malignant melanocytes and brain tumor cell lines. Quinoxaline-1,4-dioxides derivatives sensitize radiation action, decrease antioxidant cell defenses, specifically glutathione synthesis and modify the intrinsic radio resistance performance of cell lines. However, more in-depth studies for these quinoxaline derivatives are required to undoubtedly confirm and support these preliminary results and their influence in these major pathways to understand the potential radiation chemo sensitizing action of quinoxaline derivatives[8].

In synthesis, the development of new potential drugs, as well as the validation of their biological activity may be an important tool to fight growing and threatening diseases. Also, the development of analytical methodologies, namely those based on chromatographic techniques as HPLC-DAD, help investigators to validate biological mechanisms, evaluate diseases' environments and elucidate potential new targets. In this sense, we try to help to meet this goal with our contribution.

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