UNIVERSIDADE D
COIMBRA

Sara Filipa Teixeira Vilela

Relatório de Estágio e Monografia intitulada "Nanotechnology in Photoprotection" referentes à Unidade Curricular "Estágio", sob a orientação do Dr. Amadeu Carvalho e da Professora Doutora Patrícia Sofia Cabral Pires e apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas

Setembro de 2022

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Coimbra, 9 de setembro de 2022

Sara Filipa Teixeira Vilela

(Sara Filipa Teixeira Vilela)

"Levo amigos e memórias,

o fado que me embala,

a torre em sua glória,

a guitarra que se cala...

Oh Coimbra!

Mil poetas te choraram,

ficarás para a eternidade,

oh Coimbra do Mondego,

capas, guitarras e saudade

dentro de mim em segredo."

Agradecimentos

Aos meus pais. Obrigada pelo amor e apoio incondicionais, por estarem ao meu lado em todos os altos e baixos, pelos abraços que tornaram o impossível possível, por toda a força que me deram, e por atenderem sempre o telemóvel. Nada do que sou hoje seria possível sem vocês a dar-me a mão. Obrigada por serem tudo e me darem tudo o que são.

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PARTE I

RELATÓRIO DE ESTÁGIO EM FARMÁCIA COMUNITÁRIA

Farmácia Vilaça

Abreviaturas

AINE	Anti-inflamatório Não Esteroide
ANF	Associação Nacional das Farmácias
COVID-19	do inglês, *Coronavirus Disease 2019*
DCI	Determinação Comum Internacional
DGS	Direção-Geral da Saúde
FFUC	Faculdade de Farmácia da Universidade de Coimbra
IMC	Índice de Massa Corporal
MICF	Mestrado Integrado em Ciências Farmacêuticas
MNSRM	Medicamentos Não Sujeitos a Receita Médica
MSRM	Medicamentos Sujeitos a Receita Médica
PIC	Preço Inscrito na Cartonagem
PVF	Preço de Venda à Farmácia
PVL	Produtos de Venda Livre
PVP	Preço de Venda ao Público
SINAVE	Sistema Nacional de Vigilância Epidemiológica
SWOT	do inglês, *Strengths, Weaknesses, Opportunities, Threats*
TRAg	Testes Rápidos de Antigénio

I. Introdução

Os cinco anos do ciclo de estudos do Mestrado Integrado em Ciências Farmacêuticas (MICF) na Faculdade de Farmácia da Universidade de Coimbra (FFUC) culmina no estágio curricular que é, para muitos, o primeiro contacto com a profissão. O estágio curricular permite a aplicação prática dos conhecimentos adquiridos durante todo o percurso e a expansão e aperfeiçoamento dos mesmos, preparando os alunos para exercer a profissão de farmacêutico como profissional de saúde, especialista do medicamento e agente de saúde pública ativo e responsável.

Tem-se verificado uma evolução do papel do farmacêutico ao longo dos anos, reforçando-se a valorização da profissão e a responsabilidade do ato farmacêutico e verificando-se que o farmacêutico comunitário é, num grande número de situações, o primeiro contacto da população com um profissional de saúde quando precisa de ajuda, facto que foi reforçado pela dificuldade de atendimento em centros de saúde e hospitais durante a pandemia.

A população está cada vez mais exposta a grandes quantidades de informação e o farmacêutico destaca-se como um agente de saúde pública próximo e disponível para corrigir, informar, atualizar e aconselhar o público de forma fidedigna e segura. O aumento de novas formas farmacêuticas e o surgimento das mais variadas gamas de produtos de saúde com diferentes objetivos, composições, posologias e indicações terapêuticas, obriga o farmacêutico comunitário a acompanhar a inovação e atualidade, de modo a proporcionar um atendimento o mais completo, acertado e esclarecido possível. O papel do farmacêutico é preponderante no aconselhamento farmacoterapêutico, selecionando os produtos de saúde mais adequados e explicando a sua posologia e função, advertindo para possíveis efeitos adversos e interações medicamentosas, aconselhando medidas não farmacológicas para melhorar estilos de vida e garantir o bem-estar geral do utente, e contribuindo para a adesão à terapêutica.

O meu Estágio Curricular realizou-se na Farmácia Vilaça, em Coimbra, entre os dias 10 de janeiro e 22 de julho de 2022, com a orientação do Dr. Amadeu Carvalho.

O presente relatório está redigido segunda as Normas Orientadoras da Unidade Curricular "Estágio" 2021/2022, de acordo com o sistema de análise SWOT (do inglês, *Strengths, Weaknesses, Opportunities, Threats*) e incide numa abordagem crítica e representativa do percurso realizado durante o período de estágio.

2. Farmácia Vilaça

A Farmácia Vilaça localiza-se na Rua Ferreira Borges 3000-179, na baixa de Coimbra, ostentando 110 anos de serviços farmacêuticos e aliando um passado rico em tradição à modernidade e inovação. A equipa técnica é constituída por três farmacêuticos: o Dr. Amadeu Carvalho, Diretor Técnico, o Dr. João Pais e a Dra. Marisa Ferreira.

A Farmácia Vilaça é constituída por dois andares onde se distribuem diversos locais de organização, nomeadamente o espaço principal de atendimento com dois balcões individualizados e exposição de produtos de saúde por secções: áreas distintas com produtos de venda livre (PVL) como dermocosmética, saúde capilar, área do bebé, espaço animal, proteção solar, saúde oral e perfumaria, entre outros. Estas secções encontram-se fora dos balcões, devidamente identificadas, sinalizadas e acessíveis ao cliente; por outro lado, os Medicamentos Não Sujeitos a Receita Médica (MNSRM) e os Medicamentos Sujeitos a Receita Médica (MSRM) não se encontram ao alcance do doente: parte dos MNSRM encontra-se exposta atrás do balcão, visível ao consumidor, enquanto outra parte, juntamente com os MSRM, se encontra armazenada no *robot*. A farmácia apresenta também gabinete privado para a realização de serviços farmacêuticos, laboratório de preparação de medicamentos manipulados, armários de armazenamento de medicamentos e produtos dispensados na farmácia, área de organização e arrumação de encomendas, escritório da Direção Técnica e instalações sanitárias. Na zona do *back office* encontra-se o *robot* de farmácia, BD Rowa™ Vmax.

Para além do funcionamento frequente de uma farmácia comunitária, a Farmácia Vilaça oferece serviços farmacêuticos de grande importância para os seus utentes, como a realização de testes de antigénio (TRAg) à COVID-19 (do inglês, *Coronavirus Disease 2019*), medição de tensão arterial, peso, altura, glicémia e colesterol, e cálculo do índice de massa corporal (IMC). Destacam-se ainda as consultas de dermocosmética com utilização da máquina de diagnóstico DermoPrime para observação de hidratação, poros, manchas, rugas, uniformidade, elasticidade, sebo e tipo de pele; rastreios auditivos; e rastreios de doença venosa crónica com auxílio do analisador hematológico Reflotron® Plus para medição de parâmetros bioquímicos.

O horário de funcionamento é das 8h30 às 20h de segunda a sexta-feira, e das 9h às 19h ao sábado, salvo em dias de serviço em que o horário é alargado durante 24 horas de

modo a garantir a dispensa de medicamentos e aconselhamento profissional em situações de emergência.

O sistema informático utilizado é o Sifarma2000®, uma ferramenta que permite a gestão e auxílio no atendimento nas farmácias comunitárias, desenvolvido pela Associação Nacional das Farmácias (ANF) e cuja gestão e manutenção é assegurada pela Glintt, uma empresa de Consultoria e Serviços Tecnológicos. Para comunicação e certificação dos resultados dos testes de antigénio à COVID-19 foi utilizada a plataforma *online* do Sistema Nacional de Vigilância Epidemiológica (SINAVE), através do preenchimento de um formulário eletrónico e, posteriormente, o Módulo de Atendimentos Sifarma®.

O público-alvo da Farmácia Vilaça é constituído por clientes fidelizados de grupos etários distintos e turistas, nacionais e internacionais.

Durante o meu estágio curricular na Farmácia Vilaça tive a oportunidade de realizar diversas tarefas como receção de encomendas e acondicionamento adequado de medicamentos e outros produtos de saúde, verificação de *stocks*, medição de parâmetros fisiológicos, registo e observação de testes rápidos de antigénio à COVID-19, atendimento e dispensa de produtos de dermocosmética, atendimento e dispensa de medicamentos e atendimento de receitas médicas em formatos distintos (eletrónica, manual), entre outras responsabilidades intrínsecas ao dia-a-dia do farmacêutico, designadamente o controlo de prazos de validade. Tive também a oportunidade de experienciar a rotatividade de horários, estando exposta aos distintos momentos da realidade da farmácia.

3. Análise SWOT

A análise SWOT é uma ferramenta vastamente utilizada em empresas que tem como objetivo executar uma análise crítica e uma gestão estratégica e ponderada. Esta análise é realizada a nível interno e externo, contando com a identificação de quatro vertentes: forças, fraquezas, oportunidades e ameaças.

Internamente, são avaliados os pontos fortes, ou forças (S – *Strenghts*) a preservar, e os pontos fracos, ou fraquezas (W – *Weaknesses*), a eliminar.

Externamente, o foco incide nas oportunidades (O – *Opportunities*) e nas eventuais ameaças (T – *Threats*), parâmetros que estão fora do controlo imediato da empresa mas que,

no entanto, não podem ser ignorados uma vez que formam o contexto em que a mesma se movimenta e impactam extensamente a sua *performance*.

Esta análise SWOT tem como objetivo a análise dos parâmetros acima mencionados ao longo do período de estágio curricular.

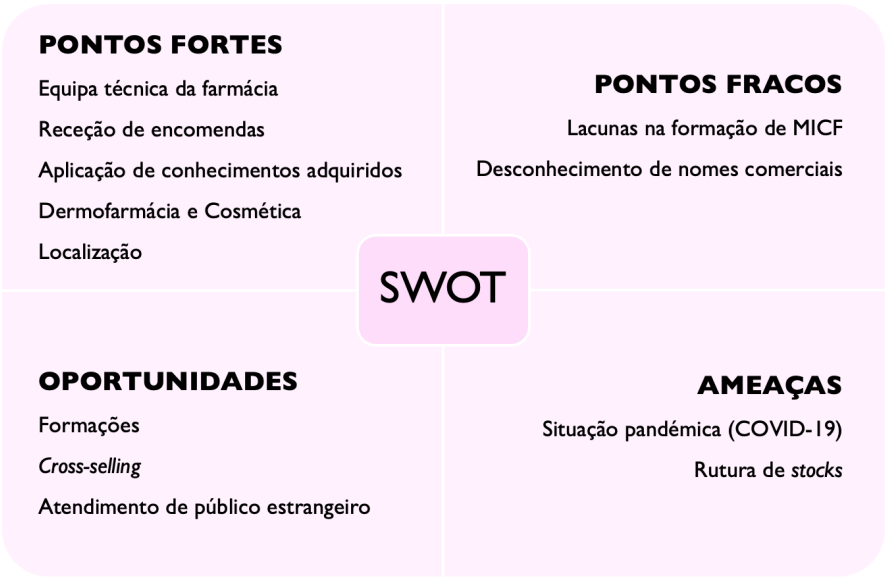

Figura 1 – Análise SWOT do Estágio Curricular em Farmácia Comunitária

3.1. Pontos Fortes

3.1.1. Equipa Técnica da farmácia

A Equipa Técnica da Farmácia Vilaça, constituída, como referido acima, pelo Dr. Amadeu Carvalho, o Dr. João Pais e a Dra. Marisa Ferreira, prima por um serviço de excelência com foco na saúde e bem-estar do doente, onde se destaca um aconselhamento farmacêutico notável.

A equipa é motivada e proativa, organizada, acolhedora e profissional, e demonstrou prontidão e disponibilidade constante para o esclarecimento de dúvidas e questões ao longo de todo o meu percurso, auxiliando-me e elucidando-me sobre as formas corretas de proceder nas mais distintas situações, permitindo-me aumentar e aperfeiçoar os meus conhecimentos e capacidades, e evitar erros.

3.1.2. Receção de encomendas

A receção de encomendas, seguida pelo armazenamento e acondicionamento de vários produtos de saúde, foi a primeira tarefa do meu estágio curricular. Esta é feita através do uso do Sifarma2000® e com auxílio da fatura da encomenda em questão.

A receção de encomendas é uma excelente ferramenta de aprendizagem para alguém que, como eu, estava a experienciar um primeiro contacto profissional com medicamentos e bens de saúde, uma vez que requer atenção de vários detalhes indispensáveis, nomeadamente o prazo de validade, o preço de venda à farmácia (PVF), o preço de venda ao público (PVP), o preço inscrito na cartonagem (PIC), as condições de armazenamento e acondicionamento (por exemplo, produtos que necessitam de ser guardados de imediato no frigorífico de modo a assegurar a sua qualidade e viabilidade), e o estado geral da embalagem.

Após a receção, os produtos são armazenados em diferentes áreas de acordo com a organização da farmácia: produtos de saúde distintos estão ao alcance do consumidor, alguns MNSRM encontram-se visíveis na zona de atendimento, mas não acessíveis, enquanto outros MNSRM e MSRM são armazenados no *robot*.

Este processo de receção e organização é fundamental para uma familiarização com os diversos produtos, permitindo o contacto com diferentes formas farmacêuticas, diferentes apresentações, laboratórios e nomes comerciais, margens de lucro e preços – passos cruciais que facilitam a transição para o atendimento, aconselhamento e dispensa.

3.1.3. Aplicação de conhecimentos adquiridos

O MICF permite a aprendizagem de diversas valências e o contacto com as mais distintas áreas. Ao longo do nosso percurso académico, o conhecimento adquirido é em grande volume e maioritariamente teórico e o estágio curricular permite a aplicação do mesmo em situações reais e distintas.

Num contexto de farmácia comunitária, os conhecimentos adquiridos ao longo do curso e as bases fornecidas nas diferentes unidades curriculares são imprescindíveis e noções de farmacologia, interações medicamentosas, efeitos adversos, interpretação de parâmetros bioquímicos e medidas não farmacológicas, entre outras, são preponderantes aquando da tomada de decisões em aconselhamento farmacoterapêutico e dispensa de medicamentos nas mais diversas situações.

3.1.4. Dermofarmácia e Cosmética

A Farmácia Vilaça destaca-se pela vasta gama de produtos de dermofarmácia e cosmética, uma área com crescimento e importância inegáveis nos últimos anos. O aconselhamento que pude observar neste âmbito, juntamente com a existência de várias marcas que permitem um cuidado personalizado a cada tipo e estado de pele, ajudou-me a cimentar e amplificar o conhecimento adquirido ao longo do curso, deixando-me confortável para recomendar e explicar a utilização correta e beneficial destes produtos e a sua importância na saúde do utente em circunstâncias distintas e tendo em conta o gosto pessoal do consumidor.

Sendo esta uma área de especial interesse pessoal e com uma oportunidade de exploração limitada ao longo do nosso percurso académico, considerei uma grande vantagem ter a oportunidade de interagir frequentemente com a mesma durante o meu estágio.

3.1.5. Localização

A Farmácia Vilaça localiza-se num dos locais mais frequentados de Coimbra, rodeada de comércio local, cafés e restaurantes e facilidade de deslocação a pé, o que se torna convidativo tanto para habitantes locais como para turistas. Destes fatores resulta um leque de consumidores com necessidades e preferências distintas que enriqueceram grandemente a minha experiência.

Apesar da farmácia se encontrar num local próximo de outras, o que poderia ser considerado um ponto negativo, verifiquei que vários clientes, incluindo clientes habituais e alguns apenas de passagem, preferiam esperar para ser atendidos, ou até encomendar produtos para o dia seguinte quando estes estavam em falta, do que recorrer a serviços de outros estabelecimentos. Estas situações contribuíram para fortalecer a minha opinião de que o farmacêutico é um profissional que inspira segurança na população e que a atenção, tempo e cuidado dispensados no atendimento de cada utente são fundamentais para a criação de uma relação de confiança e fidelidade, o que se traduz numa melhoria do bem-estar do utente e é favorável para a farmácia.

3.2. Pontos Fracos

3.2.1. Lacunas na formação de MICF

A existência de uma única unidade curricular sobre preparações de uso veterinário, lecionada no último ano, revelou-se insuficiente para permitir realizar com segurança o aconselhamento e a cedência de produtos veterinários.

Os desparasitantes, tanto internos como externos, são os produtos de uso veterinário mais recorrentemente procurados e devem ser administrados tendo em conta o uso pretendido e o peso do animal, de modo a escolher a forma farmacêutica e posologia mais indicadas. Foi a observação do aconselhamento e recomendações por parte da equipa técnica da Farmácia Vilaça que me permitiu uma melhor compreensão destes procedimentos, proporcionando-me um maior à-vontade no acompanhamento destes casos.

3.2.2. Desconhecimento de nomes comerciais

Um desafio recorrente no dia-a-dia da farmácia comunitária é a existência de diversos nomes comerciais para a mesma substância ativa, uma vez que a grande maioria das pessoas que recorrem à farmácia estão familiarizadas com o nome comercial do medicamento que pretendem e se referem a este pelo mesmo. O contacto reduzido com os diversos nomes comerciais durante a nossa formação, onde os medicamentos são quase exclusivamente referidos pela sua Determinação Comum Internacional (DCI) podem, em algumas situações, dificultar e atrasar o atendimento.

3.3. Oportunidades

3.3.1. Formações

Durante o período de estágio tive a oportunidade de assistir a várias formações internas e sessões de esclarecimento nos âmbitos da dermocosmética, cessação tabágica e suplementação alimentar. Tive também a oportunidade de assistir a uma formação sobre proteção solar dinamizada pela Eucerin, realizada no Hotel Vila Galé.

Considero todas as oportunidades de formação essenciais para um melhor conhecimento dos produtos existentes no mercado e as suas indicações e recomendações, de modo a proporcionar o melhor e o mais completo atendimento e aconselhamento possíveis.

3.3.2. *Cross-selling*

O método *cross-selling* consiste em complementar o tratamento do doente, melhorando o serviço e o aconselhamento de modo a resolver o problema apresentado ao associar outros produtos (como, por exemplo, MNSRM ou produtos de dermocosmética) pertinentes a um primeiro solicitado pelo doente.

Esta técnica permite manter um equilíbrio entre as necessidades do utente e a rentabilidade da farmácia, algo cada vez mais pertinente com o surgimento de preços competitivos em locais de dispensa de MNSRM em grandes superfícies e com a situação pandémica.

3.3.3. Atendimento de público estrangeiro

A localização da Farmácia Vilaça permite o atendimento a uma grande variedade de utentes com necessidades distintas. Apesar de a pandemia da COVID-19 ter impactado negativamente o turismo nacional, com a diminuição gradual das restrições de segurança sentiu-se uma crescente afluência de público internacional na farmácia, procurando medicamentos, produtos de dermocosmética e realização de testes de antigénio à COVID-19.

A existência de diferentes termos científicos, nomes, dosagens e indicações terapêuticas existentes internacionalmente exige alguma pesquisa e muita atenção aquando do atendimento de público estrangeiro de modo a encontrar o produto equivalente em Portugal, ou o substituto indicado para as necessidades apresentadas. Nestes momentos de atendimento, verifiquei várias vezes a admiração dos consumidores no atendimento farmacêutico português, tendo ouvido, em diversas circunstâncias, agradecimentos e comparações a outros países, onde não é usual um aconselhamento tão cuidado e completo.

Este fator permitiu-me também trabalhar na minha comunicação de termos científicos e relacionados com a saúde em inglês e em espanhol, uma competência que considero como uma grande vantagem.

3.4. Ameaças

3.4.1. Situação pandémica (COVID-19)

A situação pandémica que assola Portugal desde março de 2020 impactou largamente a vida da população, causando grandes alterações em todos os aspetos.

Apesar de, ao longo do meu estágio, ter assistido a uma diminuição de restrições de segurança, na farmácia é sempre obrigatória a presença de dispensadores de álcool gel e o uso de máscara, tendo ainda estado presentes, durante cerca de metade do tempo, as placas de acrílico nos balcões.

As máscaras e as placas de acrílico que separam o farmacêutico do utente dificultam a interação entre ambos, impedindo a comunicação clara e concisa e exigindo várias repetições de perguntas, indicações e esclarecimentos, em tom de voz elevado.

As mudanças de regras constantes no que toca às restrições são outro fator que gera confusão e descontentamento nos utentes: as mudanças mensais das comparticipações de testes de antigénio à COVID-19 geraram particular insatisfação e o facto de as farmácias não serem avisadas destas mudanças com antecedência obrigou a uma constante consulta da legislação em vigor de modo a conseguirmos informar os utentes o mais rapidamente e com a maior clareza possíveis. A obrigação do uso de máscara na farmácia após o levantamento do seu uso em locais comerciais foi outro fator que levou a reivindicações frequentes, obrigando a uma explicação recorrente de que a farmácia é um espaço de saúde. Por outro lado, a remoção das placas de acrílico melhorou muito a comunicação e a proximidade com os doentes.

A pandemia levou ainda a um aumento visível das dificuldades financeiras da população, sendo os preços dos produtos frequentemente um fator decisivo no momento da compra.

3.4.2. Rutura de *stocks*

Ao longo do período de estágio, foi possível constatar a falta de alguns medicamentos e produtos de saúde solicitados, alguns dos quais por clientes habituais, nos armazenistas. Esta falta de disponibilidade impossibilita a dispensa da medicação e, em muitos casos, obrigou a que os doentes necessitassem de recorrer novamente ao médico para obter uma nova

prescrição, levando ao descontentamento dos mesmos e à sensação de impotência por parte da farmácia.

4. Casos Práticos

4.1. Caso Prático n.º 1

Mulher, na casa dos 40 anos, chega à farmácia com queixas de tosse, dores de garganta e congestão nasal, e acrescenta ainda que já realizou um teste rápido à COVID-19 para despistar a doença, apesar de não ter conhecimento de qualquer contacto de risco. Após inquirir sobre o tipo de tosse e a duração dos sintomas, informou-me que a tosse tinha começado por ser seca mas tinha evoluído para produtiva, e que sentia dificuldades em expelir a expetoração. Comunicou também que se encontrava assim há cerca de uma semana, o que lhe estava a provocar um cansaço evidente.

Uma vez que a doente referiu o facto de não conseguir expelir o muco, aconselhei a toma de 1 comprimido efervescente Aquilea Mucus por dia, cuja composição em N-acetilcisteína, própolis e vitamina C contribui para reequilibrar o nível ideal de muco nas vias respiratórias, funcionando também como imunoestimulante no combate a constipações e dores de garganta [1]. Uma vez que a Aquilea Mucus atua como fluidificante das secreções mucosas, permitindo a sua excreção, avisei a utente de que estes comprimidos não iam levar a que a tosse cessasse, mas sim resolver o problema subjacente à mesma, de modo a que esta aderisse à terapêutica com tranquilidade e segurança. Sugeri ainda que o comprimido fosse dissolvido em água e tomado de manhã, alguns minutos após o pequeno-almoço, de modo a auxiliar a eliminação da expetoração durante o dia e não afetar o período de descanso da noite.

Para a dor de garganta, recomendei pastilhas Septolete Duo limão e mel para dissolver na boca, contendo cloridrato de benzidamina e cloreto de cetilpiridínio, indicadas para tratamento anti-inflamatório, analgésico e antissético de irritações na garganta: 3 a 4 pastilhas por dia, no máximo durante 7 dias [2].

Para a congestão nasal, 2 a 3 nebulizações diárias do *spray* nasal Rinerge, com cloridrato de oximetazolina, indicado para o alívio rápido e prologado da congestão nasal associada à constipação. Acrescentei que este *spray* deveria ser apenas utilizado durante, no máximo, 5 dias e reforcei a importância da higiene nasal com água do mar [3].

Como reforço do sistema imunitário e contribuição para a redução do cansaço e fadiga, recomendei ainda 2 comprimidos diários de Bromilase®, um suplemento alimentar com bromelaína, alfa-amilase, vitaminas B12 e D3 e selénio, que também contribuem para a melhoria do estado geral do doente com o seu efeito anti-inflamatório [4].

Terminei o aconselhamento a reforçar a importância do descanso e da ingestão de líquidos e relembrando que, caso não surgissem melhorias após o tratamento ou surgissem novos sintomas, como estados febris, deveria procurar cuidados médicos.

4.2. Caso Prático n.º 2

Mulher, na casa dos 20 anos, recorre à farmácia devido a queixas de sensibilidade vaginal e secura vulvar. Refere que não apresenta dor, ardor ou comichão recorrente, mas que se sente extremamente incomodada no dia-a-dia. Acrescenta também que já tinha recorrido a outra farmácia onde lhe foi recomendado um lubrificante íntimo de aplicação interna que, no entanto, não tinha resolvido o problema uma vez que a sensação era maioritariamente externa, e cujo uso a deixava desconfortável.

Comecei por recomendar a lavagem diária com o gel de limpeza Lactacyd Pharma Sensitive, sem fragrância e com pH 3,5, indicado para adolescentes e mulheres com tendências a alergias, com o intuito de melhorar a sensação de sensibilidade e desconforto, tanto externa como interna [5].

Recomendei também a aplicação do gel hidratante Melagyn® Hidratante Vaginal, após a lavagem, que contém componentes como ácido hialurónico e aloé vera, de modo a hidratar e acalmar a secura e irritação sentidas na região vulvar [6]. Uma vez que a doente apresentava essa preocupação, reforcei o facto deste gel ser um hidratante, especificamente para ser utilizado na zona externa.

Reforcei também que caso os sintomas não melhorassem, ou piorassem, deveria consultar um médico ginecologista.

4.3. Caso Prático n.º 3

Entra na farmácia um utente, homem, na casa dos 30 e nacionalidade americana, com queixas de dor de ouvido e desconforto auricular geral. Após algumas questões, revela que

não apresenta dores de garganta ou de cabeça associadas, exclui a possibilidade de entrada de água e acrescenta também que, por vezes, sente comichão.

Aconselhei a utilização das gotas auriculares Otoceril, com clorobutanol hemihidratado, cloretona e benzocaína, indicado para a dissolução e remoção do cerúmen do canal auditivo externo e ação antissética local. Expliquei ao doente que deveria tapar o canal auditivo com algodão e aplicar 3 a 5 gotas durante 5 dias [7].

Recomendei também a utilização de Bloxoto® solução otológica, um dispositivo médico com ação lubrificante, emoliente, protetora e calmante utilizado como auxílio do tratamento de irritações e inflamações do canal auditivo causadas por patógenos externos ou fatores ambientais, e reforçando que auxilia ainda a prevenção de otites e inflamações. Expliquei que deveria colocar 3 a 4 gotas por dia no ouvido afetado, no máximo durante uma semana [8].

Reforcei a importância da lavagem auricular, recomendando a água do mar hipertónica Audispray Adult [9].

4.4. Caso Prático n.º 4

Um utente, homem, na casa dos 20, recorre à farmácia e solicita os comprimidos orodispercíveis Imodium® Rapid, indicados no tratamento sintomático de diarreias agudas e crónicas.

Uma vez que o Imodium® Rapid é apenas indicado para o tratamento sintomático e que se deve proceder, sempre que possível e apropriado, ao tratamento da causa subjacente à diarreia, adverti o utente para o facto de que este medicamento deve apenas ser utilizado em casos de emergência [10] e recomendei a utilização de MegaFlora®, em cápsulas ou saquetas, que contribui para o equilíbrio microbiológico do intestino e das funções digestivas [11]. Após isto, o utente respondeu que, naquele momento, não se encontrava com diarreia e que apenas pretendia utilizar o medicamento como prevenção, o que imediatamente me fez questionar a razão. O utente explicou então que se encontrava em época de exames, uma altura de grande *stress* emocional, e que temia não conseguir comparecer às avaliações com o nível de concentração necessário devido ao desconforto digestivo e intestinal causado pela ansiedade.

Identificada a razão, recomendei, ao invés do Imodium® Rapid, a toma de 2 comprimidos de Sedatif PC®, utilizado em estados ansiosos e emotivos e situações de *stress*,

3 vezes ao dia, durante este período de ansiedade intensificada [12]. Reforcei ainda a importância do repouso e de um regime alimentar adequado.

4.5. Caso Prático n.º 5

Uma turista estrangeira, na casa dos 60 anos, entra na farmácia e solicita ibuprofeno 400 mg, em comprimidos. Apesar de ser um pedido usual na farmácia, perguntei em que local era a dor que esta pretendia tratar, de modo a perceber se podia prestar algum auxílio adicional. A isto, a senhora respondeu que apresentava algumas dores nas pernas, que considerava normais uma vez que tinha caminhado mais do que o costume, mas o que realmente a preocupava, e a razão dos comprimidos que pediu, era o inchaço nos membros inferiores.

Constatando que a senhora não apresentava dores que a preocupassem, ou em que um anti-inflamatório não esteroide (AINE) como o ibuprofeno seria recomendado, inquiri a utente sobre o edema e condições subjacentes que pudessem levar ao mesmo; a utente explicou que tem observado o edema principalmente após longas viagens de autocarro e que, apesar de não lhe causar dor, lhe causa desconforto, dificuldade a andar e sensação de pernas pesadas; respondeu também que não apresenta nenhuma condição cardíaca que pudesse levar a acumulação de líquidos e que tem urinado com a frequência usual.

Procedi então a recomendação de Venopress®, um suplemento alimentar em comprimidos que contém diosmina micronizada e hesperidina, aconselhando a toma de 1 comprimido por dia. O Venopress® é indicado para o tratamento de edema e peso nas pernas [13].

Para uma redução mais célere da sensação de desconforto e peso nas pernas, recomendei a aplicação de FisioVen bioGel para massagem duas vezes ao dia, após lavagem. O FisioVen bioGel contém extratos liofilizados de azevinho e castanheiro-da-índia e mucilagens de alteia que proporcionam um aumento na elasticidade e tonificação da epiderme, enquanto a massagem potencia a circulação do sangue [14].

Por fim, recomendei a elevação dos pés em momentos de repouso e a lavagem dos membros inferiores com água fresca.

5. Considerações Finais

O estágio em farmácia comunitária revelou-se uma das experiências mais desafiantes e enriquecedoras do meu percurso no MICF, permitindo-me consolidar conhecimentos, aprimorar capacidades, desenvolver novas competências e entender a realidade do funcionamento de uma farmácia comunitária.

Ao longo do estágio curricular, tornou-se claro o papel fundamental do farmacêutico como profissional de saúde e agente de saúde pública. Este papel vai muito além do conhecimento científico em torno do medicamento que, embora fundamental, não basta para exercer a profissão de modo exemplar e competente: ser farmacêutico inclui domínio de *soft skills*, capacidade de trabalho em equipa, organização, gestão e espírito crítico, nunca esquecendo a importância da empatia e da criação de relações com a comunidade, assentes no interesse, no cuidado e na confiança.

Agradeço a todos os membros da Farmácia Vilaça por me transmitirem os seus ensinamentos e contribuírem para o meu crescimento enquanto profissional de saúde e enquanto pessoa. Termino esta etapa do meu percurso académico com uma admiração acrescida pela profissão farmacêutica, um sentido de responsabilidade reforçado e a intenção de permanecer em constante aprendizagem e contribuir para a valorização do ato farmacêutico e para a saúde e bem-estar da população.

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PARTE II

MONOGRAFIA

"Nanotechnology in Photoprotection"

Resumo

A fotoproteção tornou-se essencial no dia-a-dia com a consciencialização emergente do público no que toca aos vários efeitos da exposição desprotegida da pele a radiação ultravioleta, nomeadamente eritema, fotoenvelhecimento e carcinogénese. O método de proteção solar mais comum é a aplicação tópica de protetor solar: os protetores solares são preparação cosméticas que contém filtros UV cuja principal função é proteger a pele ao bloquear a radiação ultravioleta. Os filtros UV podem ser inorgânicos ou orgânicos.

A nanotecnologia é uma área altamente investigada e diversa focada em materiais com tamanhos abaixo de 100 nm e apresenta um papel crescente na indústria cosmética, principalmente em formulações de protetores solares. As partículas em nanoescala apresentam propriedades físico-químicas novas, complexas e únicas que geram várias aplicações úteis, portanto protetores solares contendo filtros UV em tamanhos nano oferecem benefícios numerosos, tais como aumento de estabilidade, textura e propriedades de espalhamento melhoradas, transparência e efeito duradouro.

Na União Europeia, os protetores solares que contêm filtros UV em tamanho nano são regulados pelo Regulamento (CE) n.° 1223/2009 do Parlamento Europeu e do Conselho de 30 de Novembro de 2009, que autoriza o uso de dois filtros inorgânicos em tamanho nano, nano-óxido de zinco e nano-dióxido de titânio, e de dois filtros orgânicos em tamanho nano, nano-metileno bis-benzotriazol tetrametilbutilfenol e nano-tris-difenil triazina.

Assim, a aplicação da nanotecnologia aos filtros UV presentes nos protetores solares tem-se demonstrado vantajosa e essencial para obter uma formulação mais eficiente e estável, e uma utilização mais confortável, estética e agradável para o consumidor.

Palavras-chave: Cuidados de pele, filtro UV, fotoproteção, nanomaterial, nanotecnologia, protetor solar, radiação ultravioleta.

Abstract

Photoprotection has grown into an essential of everyday life with the emergent public awareness concerning the multiple effects of unprotected ultraviolet radiation exposure on the skin, namely erythema, photoaging and carcinogenesis. The most common sun protective measure is topical sunscreen application: sunscreens are cosmetic preparations containing UV filters which fundamental function is to protect the skin from ultraviolet radiation by blocking it. UV filters can be inorganic or organic.

Nanotechnology is a highly researched and diverse area focused on materials with size below 100 nm and presents a rising role on the cosmetic industry, especially on sunscreen formulations. Particles on nanoscale present new, complex and unique physicochemical properties that have produced several helpful applications, therefore sunscreens containing nanosized UV filters offer numerous benefits, such as increased stability, improved textural quality and spreading properties, transparency and long-lasting effects. Despite its benefits, nanoparticles' penetration across the skin barrier and unintentional entry routes into the body arise toxicological concerns.

In the European Union, sunscreens containing nanosized UV filters are regulated by the Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 that authorizes the use of two nanosized inorganic filters, nano-zinc oxide and nano-titanium dioxide, and two nanosized organic filters, nano-methylene bis-benzotriazolyl tetramethylbutylphenol and nano-tris-biphenyl triazine.

Thus, the application of nanotechnology to UV filters present in sunscreens has proved to be advantageous and essential to obtain a more efficient and stable formulation, and provide a more comfortable, aesthetic and pleasant use for the consumer.

Keywords: Nanomaterial, nanotechnology, photoprotection, skincare, sunscreen, ultraviolet radiation, UV filter.

Acronyms

α-MSH	α-Melanocytic Hormone
•OH	Hydroxyl radical
AP-1	Activator protein-1
CPD	Cyclobutene pyrimidine dimer
DNA	Deoxyribonucleic acid
DOPA	Levodopa
EC	European Commission
EU	European Union
EUON	European Union Observatory for Nanomaterials
FDA	Food and Drugs Administration
INFARMED	(from Portuguese, Autoridade Nacional do Medicamento e Produtos de Saúde) National Authority for Medicines and Health Products
IR	Infrared
MBBT	Methylene Bis-Benzotriazolyl Tetramethylbutylphenol
MMP	Matrix metalloproteinase
mtDNA	Mitochondrial DNA
NF-$_k$B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NM	Nanomaterial
NP	Nanoparticle
PP	Photoproduct
ROS	Reactive oxygen species
SB	*Stratum basale*
SC	*Stratum corneum*
SCCS	Scientific Committee on Consumer Safety
SG	*Stratum granulosum*
SL	*Stratum lucidum*
SPF	Sun protection factor
SS	*Stratum spinosum*
TBPT	Tris-biphenyl triazine
UV	Ultraviolet
UVR	Ultraviolet radiation
VL	Visible light
W/W	Weight per weight

1. Introduction

A cosmetic is, by definition, "any substance or mixture of substances intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odors" [1] and include a wide range of products. Cosmetics that are specifically applied on the epidermis are designated skincare products[2].

The role of cosmetics and the value placed on a youthful and healthy appearance [2] [3] have faced considerable changes in the eyes of society, influenced by culture and values. Currently, the use of cosmetics has an important role in everyday life for personal hygiene and wellness, with an increased market revenue [2] that is translated in a multibillion-dollar industry targeted around anti-aging products [3] [4].

Nanotechnology is an extensively researched and promising area in cosmetics that spawns advancement and innovation in formulations and delivery systems. Its application has been shown to add useful new features and overcome customary limitations related with traditional cosmetics products, improving consumer satisfaction and product effectiveness [5].

With the emergent acknowledgement of the acute and chronic effects of exaggerated and unprotected ultraviolet radiation (UVR) exposure on skin, the search for safe sun protective measures is critical, the most practiced being sunscreen application [6] [7]. Sunscreen formulations usually combine two or more ultraviolet (UV) filters to overcome absorption spectrum shortcomings of individual ingredients and provide a higher sun protecting factor (SPF) [6] [7].

The European Union (EU) market allows for the use of four UV filters in their nanosized form in sunscreen formulations: zinc oxide (ZnO), titanium dioxide (TiO_2), methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT) and tris-biphenyl triazine (TBPT)[1].

2. Skin anatomy, physiology and function

Skin is the largest organ of the body in weight (15% of total body) and surface area (approximately 1.7 m^2) [8], composed by multiple layers with several key features [2] [8] [9] [10]. Its

heterogenous, dynamical and complex [2] [8] [9] [10] arrangement of different cells, extracellular matrix's elements and vascular, nervous and appendage structures is essential so that the skin can successfully partake in its tasks [10].

Skin's most important function is as a barrier against external threats (mechanical, chemical and microbial) [9] [10]. It also prevents fluids' loss, provides mechanical support, offers protection from harmful radiation, regulates body temperature and preserves the body's homeostasis [9] [10] [11]. Moreover, it's the sensory organ for touch, pain, heat, cold and emotional sensation, mediates immunological function, participates in vitamin D synthesis and aids both endocrine and exocrine functions [10].

The skin consists in three essential structured layers: epidermis, dermis and hypodermis [8] [9] [10] [12], all of which present significant differences when it comes to their anatomy and function [9].

2.1. Epidermis

Epidermis is the superficial layer and acts as physical barrier to the external environment and works to prevent loss of water from the skin [8] [9] Histologically, it is classified as a stratified squamous epithelial layer [11].

The epidermis is mainly composed by keratinocytes which are organized in five different strata [11] and are in a constant state of transition [2] [8] [12], from the deeper layers to the superficial, connected by desmosomes, tight junctions and adherent junctions [2]. Keratinocytes protect the skin against the external environment, work as a barrier for shearing forces, prevent the water absorption from the outside and avoid water and electrolyte loss [13].

The five epidermis layers are as follows: *stratum basale* (SB) (in contact with the dermis), *stratum spinosum* (SS), *stratum granulosum* (SG), *stratum lucidum* (SL) (when present), *and stratum corneum* (SC) (in contact with the external environment) [2] [9] [11] [13].

The SB, the innermost layer, is connected to the dermis by a two-layered membrane known as dermal-epidermal junction that forms the interface between epidermis and dermis [12] [13] and is responsible for the provision of nutrients to the epidermis, the exchange of oxygen, nutrients and toxic substances between the two layers [13] and provides resistance against mechanical shear forces [9]. The SB presents cuboidal to columnar cells (that constantly

produce keratinocytes [8] with stem cell-like properties), Merkel cells and melanocytes [8]. It has two layers: the most superficial layer, lamina lucida, and the deeper one, lamina densa [12].

The Merkel cells' membrane interacts with the skin's free nerve endings and have a sensory function as mechanoreceptors and transducers of fine touch [8] [12] [13]. These cells are particularly noted in the palms, feet, finger pads, toes' plantar surface and in the oral mucosa [14].

Melanoblasts (which are undifferentiated cell precursors spread across the skin, hair follicles, eyes, meninges, heart and cochlea) differentiate into melanocytes [15]. Melanocytes are dendritic pigment producing cells, derived from the neural crest [13] [15] [16] that synthesize melanin [15]. In the epidermis, a melanocyte is surrounded by thirty-six keratinocytes, which forms an epidermal melanin unit [15] [16]. Melanocytes are present in the same number in every individual: what varies is their activity and size of the melanosomes, the melanin-containing organelles that are responsible for pigmentation of the hair and skin [12] [13]. Melanin's synthesis, distribution and role are described ahead.

The SS consists in four to ten layers [8] [13] of polyhedral cells with central oval nucleus and tonofilaments on its cytoplasm [13] that extend outward. Langerhans cells, which are antigen processing and presenting cells, can be found on this layer [12]. Langerhans cells act as the skin's first line of immunological defense [13] and their number decreases with UVR exposure, leading to a consequent decrease in the immunologic activity of the skin [12].

From the SS, keratinocytes migrate to the SG, the granular layer, so named due to the visible keratohyalin granules [12] [13] produced by the non-dividing differentiating keratinocytes [8]. On the SG, cells gradually lose their organelles and become more compact, going on to form the outermost epidermal layer [12].

The SL, a thin clear layer, lies between the SG and the SC and is not always present. It can be found in thicker skin, such as the palms and the soles and presents keratocytes with eleidin, which have opaque membranes and a dense cytoplasm [13] [17]. Eleidin is a transformation product of keratohyalin [17].

At the SC, keratinization is completed, and the keratinocytes are attached via desmosomes and surrounded by lipids secreted from the lamellar granules [12]. These non-viable terminally differentiated keratinocytes are known as corneocytes [9]. Every twelve corneocytes are organized in clusters that represent the first physical barrier against

penetration and impact [11] [18] [19]. This construction is responsible for the protective and moisture-control barrier functions of the skin [12].

The SC structure is commonly described by the brick-and-mortar model [11] [18] [19] [20] where the "bricks" refer to alternate staggered corneocytes, and the "mortar" to the lipid matrix surrounding them, that contains intact and degraded corneodesmosomes (the desmosomes found on the SC) [11] [18] [19] as well as ceramides, cholesterol and long-chain free fatty acids, the fundamental components of the "mortar" [19].

SC composition primarily includes water, keratin, keratin-filaggrin complex, inner envelope proteins, outer envelope lipids, involucrin, loricrine, cholesterol, cholesterol esters, cholesterol sulphate, ceramides, free fatty acids and triglycerides [11]. This composition is responsible for its pH range and for maintaining an optimal environment for enzymes [11]. pH varies between 4.5 and 5.5 [9] [11] on the surface and it's close to neutrality at the SC-SG interface [21] [22]. The term "acid mantle" refers to the SC's characteristic acidic nature under physiological conditions [9] [19] [20] and illustrates its protective quality since originally the acid mantle was only considered as a mechanism against invading organisms [19]. The skin mantle and pH gradient's formation are regulated by lactic acid secretion, sebum triglycerides' excretion and the presence of free fatty acids in the intercorneocyte lipids and membrane transporters [11].

It's now known that the pH gradient contributes to antimicrobial defense, permeability barrier homeostasis, integrity and cohesiveness and processes of desquamation [11] [22] for pH is critical to various biochemical processes since the difference in extracellular and intracellular H^+ concentration establishes ionic, electric and osmotic driving forces, affecting cellular functions and enzymes' activity [19].

Langerhans cells and Merkel cells can also be found on the SC [9] [12] [13].

2.2. Dermis

The dermis consists of two layers of connective tissue, which blend with no boundary [8]: the papillary dermis and the reticular dermis. The papillary dermis, the upper part, is formed by loose connective tissue, and the reticular dermis, the lower part, by dense connective tissue [13]. Structurally, it consists mostly of collagen and elastin fibers in a proteoglycan-based matrix [8]. The main type of cell present is the fibroblast, but mast cells, macrophages [2] [9], circulating immune cells and sensory stimuli receptors [9] (Meissner's corpuscles, Pilo-Ruffini corpuscles

and Pacinian corpuscles) [8] can also be found. Fibroblasts produce collagen [23] [24], proteoglycans, glucosaminoglycans [8] [24], hyaluronic acid [8], fibronectin and laminin – which together constitute the extracellular matrix [8] [24]. Fibroblasts are also responsible for reepithelization during wound healing [24].

The dermis provides support to the epidermis [2], protection against mechanical damage, water retention and thermal regulation. Collagen fibers provide tough mechanical support to the skin while elastic fibers contribute to the elastic recoil. Its blood vessels work as nutrient supply and maintain the body temperature [13] [9].

2.3. Hypodermis

The hypodermis is the deepest layer of skin, mostly constituted by adipose tissue, vessels and nerves. The hypodermis's adipose tissue works as a reserve of energy due to fat storage [9]. It is made of fat lobules separated by fibrous transverse septa and rich in vasculature and is fundamental in skin protection, temperature control and cushion [8]. The hypodermis also provides mechanical and physiological support [9].

2.4. Accessory structures

Apart from the layers, the skin presents accessory structures [10]: hair, nails, sweat glands (both apocrine and eccrine) and sebaceous glands [9] [10]. They participate in thermoregulatory and sensory functions, social communication through the secretion of pheromones, assist on the regulation of electrolyte balance and strengthen the epidermal barrier with substance release [8].

Hair follicles are distributed all over the body, except on the palms and the soles [10] [13], and protect the skin from mechanical offenses, facilitate homeothermy, have sensory function and participate in social communication [25]. Nails, translucid hardened keratin plates, protect the fingertips and aid in the acts of grabbing and catching objects [10].

Sweat glands produce and secrete sweat [10], an acidic solution containing low sodium and chlorine concentrations and high concentration of potassium, urea, ammonia, lactate and some amino acids. It is produced by stimuli (thermal, mental or gustatory) [13]. The sweat contributes to moisture the skin and maintain body temperature and its secretion works as a cooling and excretion mechanism. Sweat glands can be classified in apocrine and eccrine: apocrine glands, controlled by sympathetic nerve fibers, can be found in the armpits, eyelids,

ear canals, areolas and nipples, wings of the nostril, perianal region and some parts of the external genitalia; the remaining body surface is covered in eccrine sweat glands, particularly in palms and soles, innervated by sympathetic nerves [10].

Sebaceous glands open into hair follicles [13] and secrete sebum [10], a light-yellow oily viscous fluid constituted by triglycerides, squalene, free fatty acids, wax, sterol esters and free sterols [9]. The sebum lubricates the skin and hair [10] and provides moisture balance [9]. Sebaceous glands are absent from palms and soles and are prominent on the face, front of the chest, back and scalp [13].

Features such as variations in skin thickness according to anatomical site and the presence of appendages can affect the skin's functional properties [8] [9].

3. Types of radiation and their effects on the skin

Solar radiation is composed of several types of electromagnetic radiation emitted by the sun but only a part reaches the earth surface. The full spectrum consists of the visible (Vis), UV, and infrared (IR) wavelengths [26]. The majority is UVR. There are three distinct types of UVR: UVA (320-400 nm), UVB (280-320 nm) and UVC (100-280 nm) [3] [27] [23] [28] the last one being the shortest wavelength and thought to be the most damaging type of UVR [3]. UVC is, however, completely absorbed in the stratosphere by the ozone [3] [23] while UVA and UVB actually reach the surface of the earth in approximated percentages on 95% and 5%, respectively [3] [23].

UVA, that can be characterized as UVA1 (340-400 nm) and UVA2 (320-340 nm) [3] [23] penetrates the dermis [3] [23] [27] [28] while UVB, that has higher energy than UVA [23], is absorbed by the epidermis [27].

Skin aging is classified as intrinsic and extrinsic aging, also known as chorological aging and photoaging, respectively [23] [28] [29]. Unlike chronological aging, that is predetermined by one's biological predisposition, photoaging largely depends on the degree of sun exposure, the main source of UVR, and melanin production. This means that people with a history of intensive sun exposure, that have fair skin and that reside in sunny geographical areas experience greater amounts of UVR and consequently, more severe photoaging [30].

Hereupon, photoaging consists of the changes that occur in sun-exposed skin [3] [23] [28] resulting in a process in which the skin undergoes changes in epidermal thickness, dermal

elastosis, collagen degradation, increase in pigmentation and increase in mutagenesis of keratinocytes, fibroblasts and melanocytes [3] [31]. It disturbs tissue homeostasis, increases risk of skin cancer and accelerates onset age-related phenotypes [23] [32]. Photoaging it's characterized by deposition of elastic material, atrophy, roughness, telangiectasia, wrinkling [28] [32], irregular pigmentation, benign or malignant neoplasms and functional decrement [3] [28] [32], volume loss [3], melasma and yellowing and uneven skin tones [28].

These features are commonly observed on the face, neck, dorsal hands and chest since these are the less photoprotected body areas [28]. The clinical signs of photoaging differ according to various factors such as skin phototype, intensity of the exposure, presence of photodermatoses, wavelength, biologic deoxyribonucleic acid (DNA) repair capacity [27] [28] [33], ethnicity, age and gender [28].

As UVB exposure acts only on the epidermal cells [33], it causes mostly cyclobutene pyrimidine dimmers (CPDs) and photoproducts (PPs) [30] [33], and is associated with keratinocyte and melanocyte damage [33] [34], sunburn, erythredema, photoaging [3] [23] [27] [28], mutagenesis and skin cancers [28]. Severe UVB irradiation results in decreased hyaluronic acid hence aged skin being associated with loss of moisture which is one of the most noticeable histological and chemical changes observed: the loss of skins capacity to retain water [28].

On the other hand, UVA indirectly leads to DNA damage by production of reactive oxygen species (ROS) [30] which generation is predominately initiated by UV rays in the UVA spectrum range with some overlap with the UVB range [33] [35]. ROS are a class of oxygen composes or oxygen containing substances [31] mainly produced, in the skin, by keratocytes and fibroblasts [34]. ROS are generated via respiratory chain reactions as a byproduct of normal mitochondrial metabolism [35] but can be introduced extrinsically by a variety of factors where UVR and visible light (VL) exposure are included [35].

Their presence in small amounts has been proven to be beneficial [31] however excessive ROS can directly damage cells [31] [35] by initiating a complex reaction cascade that causes oxidative damage to cellular components that further leads up to mitochondrial dysfunction, cellular structural integrity decrease and extracellular matrix degradation [35].

The unbalanced condition that causes the body tissues to not be able to counteract sources of ROS, both endogenous and exogenous, is called oxidative stress [29]. Oxidative stress leads to inflammatory reactions such as acute erythema and chronic damage that can

result in premature skin aging and skin cancer [30]. The human body has innate defense mechanisms as protection from free radicals, such as antioxidative enzymes and non-enzymatic antioxidative molecules, which reduce and neutralize them [29] [35] [36]. UVR exposure leads to the depletion of the skin's antioxidants [30] and consequent increases of ROS production and decreases in the antioxidant defense mechanism that ultimately result in an imbalance that progressively damages cellular structures [29].

UVA radiation is absorbed by cellular chromophores and reacts with DNA and molecular oxygen resulting in DNA modifications [33] due to phosphodiester bond breaks, pyrimidine dimmers, single-strand breaks and DNA-protein crosslinks [30]. It also results in ROS production, including the superoxide anion ($O_2^{-\bullet}$) and the singlet oxygen ($^1O_2$), which can further lead to the generation of highly toxic hydroxyl radicals ($^{\bullet}OH$) [35].

ROS activate cytoplasmic signal transduction pathways related to growth differentiation, tissue degradation and cellular senescence [30], which is a state of irreversible growth arrest cells can enter in response to DNA damage and as a way to prevent cancer development [23]. ROS then can cause permanent genetic changes in tumor suppressor genes and protooncogenes [30] and prompt skin cells to enter in a premature state of cellular senescence. These effects can consequently lead to accelerating aging phenotypes [23] [28] [31], oxidative damage and melanoma development [3] [23] [27] [28]. Increased ROS production also affects mitochondrial DNA (mtDNA) which on its turn contributes to increase ROS production, potentially creating a vicious cycle [33].

ROS also induces the activation of transcription factors in skin cells, including activator protein-1 (AP-1) that increases matrix metalloproteinases' (MMPs) production and upregulation, which causes collagen breakdown and elastin degradation in the extracellular matrix and a shutdown of its synthesis [30] [31]. MMPs are also implicated in abnormal elastin accumulation in the superficial dermis [30]. In addition, ROS activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$_k$B) which affects the expression of multiple inflammation mediators, indirectly promotes additional ROS and MMPs production, further degrading collagen and elastin [31]. Collagen destruction is an hallmark of photoaging [30].

UVR and photoaging lead to excessive proteolytic activity, disturbing the skin's three-dimensional integrity. The imperfect repair of dermal degradation is repeated with every UVR exposure which leads to the accumulation of solar scarring that ultimately results in visible photoaging [30].

Evidence begins to appear about IR (700 nm – 1 mm) and VL's (400-700 nm) important roles in photoaging and photodamage which have not been recognized and valued [3]. This is especially significant in the blue light range (380-700 nm) [3] since it can generate ROS, proinflammatory cytokines and MMPs, as much as potentiate UVR effects [3] [28]. IR can penetrate the skin and directly affect cells [28].

Therefore, and even though the sun is fundamental to sustain human life [27], the excessive skin exposure to UVR prompts an abundance of adverse effects (Figure 2), both acute and chronic, that demand photoprotective measures [27].

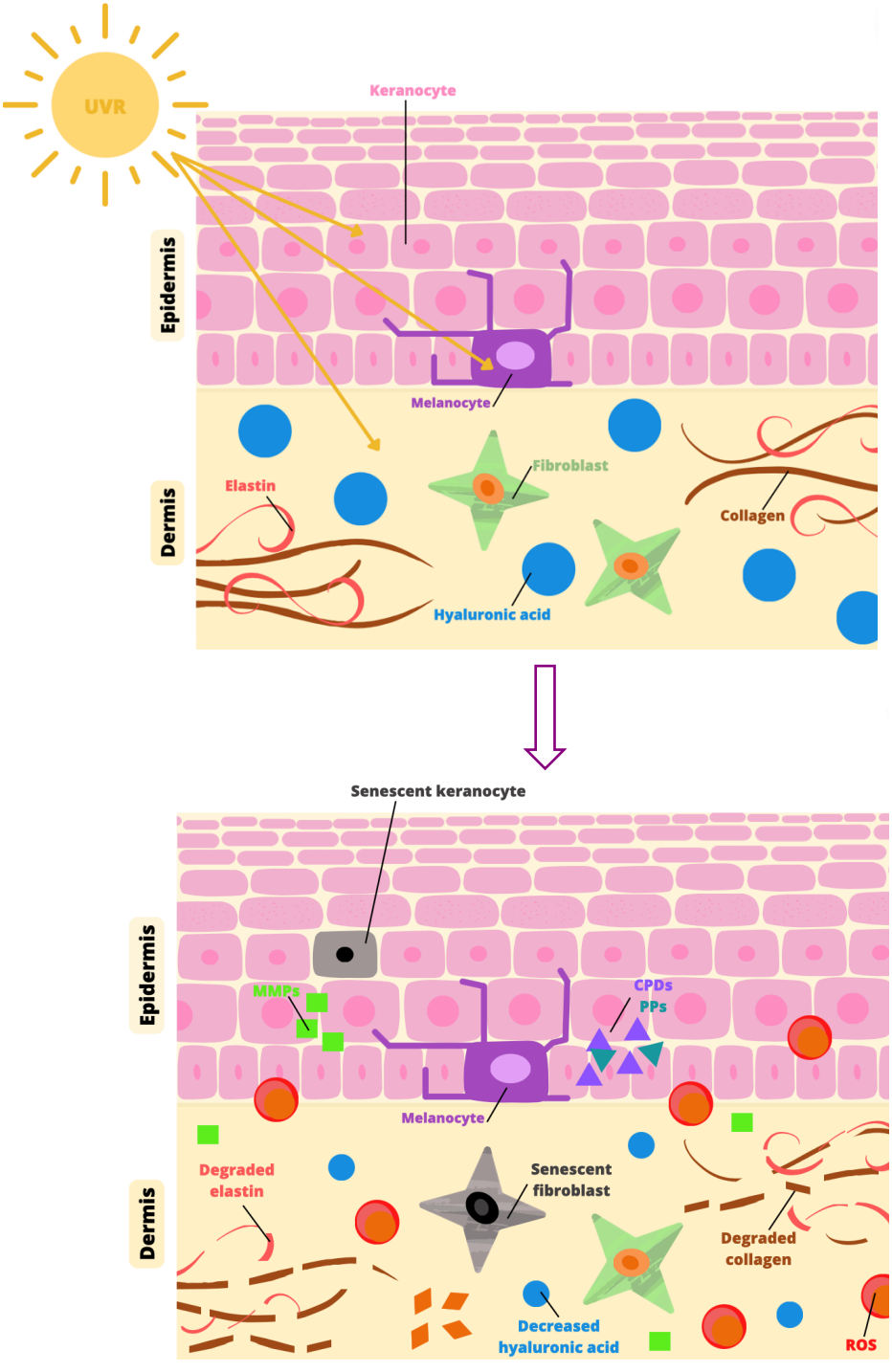

Figure 2 – UVR-induced effects on the skin

4. Photoprotection

The melanin molecule, as mentioned before, plays a critical role in skin, eyes and hair pigmentation and offers photoprotection by absorbing UVR, serving as a physical barrier to reduce UVR penetration through epidermal layers [15] [16] [37]. There are two types of melanic pigments: eumelanin (brown-black color) and pheomelanin (yellow-red color) [15] [16]. Skin pigmentation is one of the most noticeable and variable phenotypes in humans [16].

The synthesis and distribution of melanin, which occurs on melanosomes, is called melanogenesis [15] and is a very complex process with multiple pathways and regulatory agents [13] [16]. Melanin is formed from the conversion of tyrosine to levodopa (L-DOPA) by the tyrosinase, located only in the melanosomes' membrane, following enzymatically catalyzed cascading reactions. Eumelanin results from the oxidative polymerization of the 5,6-dihydroxyindole: the hydroxylation of the L-tyrosine at the L-DOPA is catalyzed by the tyrosinase and by various tyrosinase-related proteins; pheomelanin is formed from through the oxidative polymerization of the cysteinyldopa [15].

Through their extensions, the melanosomes of melanocytes in the epidermal melanin unit are transferred to the keratinocytes that surround them in order to distribute it uniformly, ensure a homogeneous pigmentation and create a screen that covers the keratinocytes' nucleus [13] [15] [16]. This transfer takes place when the pH of the extracellular environment increases from 5.0 to 6.8. Keratinocytes take over melanosomes through phagocytosis, a UVR-dependent process regulated by the α-melanocytic hormone (α-MSH). An increase of melanin synthesis, proliferation and distribution occur by way of α-MSH and UV exposure, stimulating pigmentation which increases the skin's resistance to sun burns [15].

The ratio between eumelanin and pheomelanin determines the difference in pigmentation: if the quantity of pheomelanin produced is higher than the quantity of eumelanin, the skin presents a lighter in color and a higher susceptibility to sun burns [15] [16]. The type of melanin produced depends on the melanogenic enzymes' function and on the substrates' availability. Eumelanin is photoprotective since it limits the extent of UV penetration and scavenges the ROS. On the other hand, pheomelanin, besides being weakly protective against UV, is phototoxic and can enhance UV-induced ROS production [16] [37].

The quantity of synthesized melanin is genetically determined and varies according to ethnicity, but it's also influenced by intrinsic (molecules secreted by keratinocytes, fibroblasts,

inflammatory cells and endocrine cells) and extrinsic (UV radiation and chemical products) factors [15]. pH is also important in the skin pigmentation regulation since melanosomes derived from light skinned melanocytes are more acidic than melanosomes derived from dark skin, which present a more neutral pH. Since the activity of tyrosinase is enhanced by a neutral pH, it represents a key parameter in the melanogenesis [16].

Even though the traditionally recommended methods to proper photoprotection are seeking shade, wearing protective clothing and brimmed hats [3] [27] [38] and sunglasses [3] [38], the application of sunscreen has been widely used as the vital method of photoprotection for many years now [3] [38] [39].

There are four interconnected requirements for good UV protection: technology, assessment of performance, standards for UV protection and compliance. Technology reduces the amount of UVR that reaches the skin and is, at its core, the UV filters in the formulation of the sunscreen. Technology affects the interaction of the components with the skin and if the formulation is not pleasant the compliance will be reduced. The assessment of the sunscreen's performance focuses on the quantity and the quality of UV protection and their standards must fulfill the criteria of different evaluation commissions (in the EU, the European Commission (EC)) for SPF and UVA-protection. Finally, compliance by the sunscreen user is considered the most important factor, influenced by the other three, since the uniform and regular application [40] [38] with the right quantity is vital for a correct and effective photoprotection [40] and to prevent photoaging and pigmentation in all skin types. Sunscreen users should apply appropriate amounts in order to obtain the recommended concentration of 2 mg/cm^2 [38].

Photoprotection efficacy indicators, namely SPF, allow for UV filters to be evaluated according to their provided level of photoprotection [41]. The SPF of a sunscreen is the measure of how much the product shields the sun's shorter wave UV rays and its simplicity appeals to consumers which is noticed by its heavy marketing on sunscreens [40]. SPF was recognized as the standard for sun protection measuring in 1978 by the Food and Drugs Administration (FDA) [3]. In European countries, SPF testing is standardized by the European Cosmetic Toiletry and Perfumery Association since 1994. [42].

Recently it has become increasingly clear that photoprotection as a mean towards slowing down skin aging is a much more complex situation since the solar spectrum is formed by many wavelengths beyond UV that play its part in photoaging [28] [38], specifically in

pigmentary disorders in dark skin and erythema in lighter skin. Protection against IR radiation is also required to prevent skin aging [38]. The role of VL in photoaging is less clear however it has been shown to induce long-lasting pigmentation in dark-skinned individuals suggesting its interaction with the same melanin precursor as UV [28]; the use of broad-spectrum sunscreens that include protection against VL significantly minimizes hyperpigmented areas when compared to sunscreens containing only UV filters [38]. To add protection against all exposome factors that contribute to skin aging, broad-spectrum sunscreens should ideally include additional skin care benefits such as antioxidants which prevent the extracellular matrix's degradation and skin pigmentation [28].

According to these findings, it's generally accepted that topical sunscreen application prevents and delays senescent cells' accumulation but further studies are required to fully validate it [23]. Despite recent advances, better protection against UVA1, VL and IR is still required [38] and ecological and toxicological concerns have been brought up about the consequences of regular use of sunscreen products [28].

5. UV filters

Even though the first commercial sunscreens were only available around the 1920-1930s, the concept of a photoprotective topical product has been around since the ancient Egypt, in 4000 BC [3] [41].

Sunscreen products include any preparation intended to be placed in contact with the human skin in order to, exclusively or mainly, protect it from UVR by absorbing, scattering or reflecting radiation. Sunscreen products are cosmetic preparations, according to Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009, available in several cosmetic product forms [1].

Commercial sunscreens are complex multicomponent mixtures of various substances, organic and inorganic, dispersed in a combination of solvents [43]. Sunscreen products contain in their formulations UV filters to block radiation, usually more than one. Besides the filters, they contain many other substances, such as emollients, preservatives or stabilizers, emulsifiers, fragrances, coloring compounds [44] and additives like antioxidants [3].

Since the effects of increased ROS, MMPs and DNA damage resulting from solar radiation are well acknowledged, the addition of antioxidants on sunscreen formulations helps to prevent and diminish free radicals and oxidative stress. To be effective, the antioxidants

must be present in high concentration, stable on the final formulation and able to penetrate the SC while still existing in enough concentration on the epidermis and dermis. An example of a fairly used antioxidant in sunscreens is vitamin C [3].

In Europe, there are relatively few authorized UV filters, which can become a problem when formulating a sunscreen that ensures a high level of protection and follows broad-spectrum efficacy recommendations above a 370 nm wavelength [41]. All sunscreens available in the EU market should protect against both UVA and UVB radiations [42]. To be effective, UV filters must be retained on the skin's top surface as a protective film, where they should remain photostable during the UV exposure period [6] [7].

UV filters can be divided in two types: inorganic, also known as physical or mineral filters, and organic, also known as chemical filters [27] [44].

Inorganic filters act by absorbing, reflecting and scattering the radiation and are highly effective immediately after application [27], providing a wide range of UVR blockage [7] (Figure 3).

Organic filters are molecules with a chemical structure that absorb the damaging UVR which is later released as thermal energy or emitted at higher wavelengths (Figure 3) [27] [43] [45]. They're classified as UVA, UVB or wide-spectrum absorbers depending on their chemical structure [7]. The key requisites are for these molecules to not undergo chemical changes or induce unwanted toxicity upon UVR exposure [43]

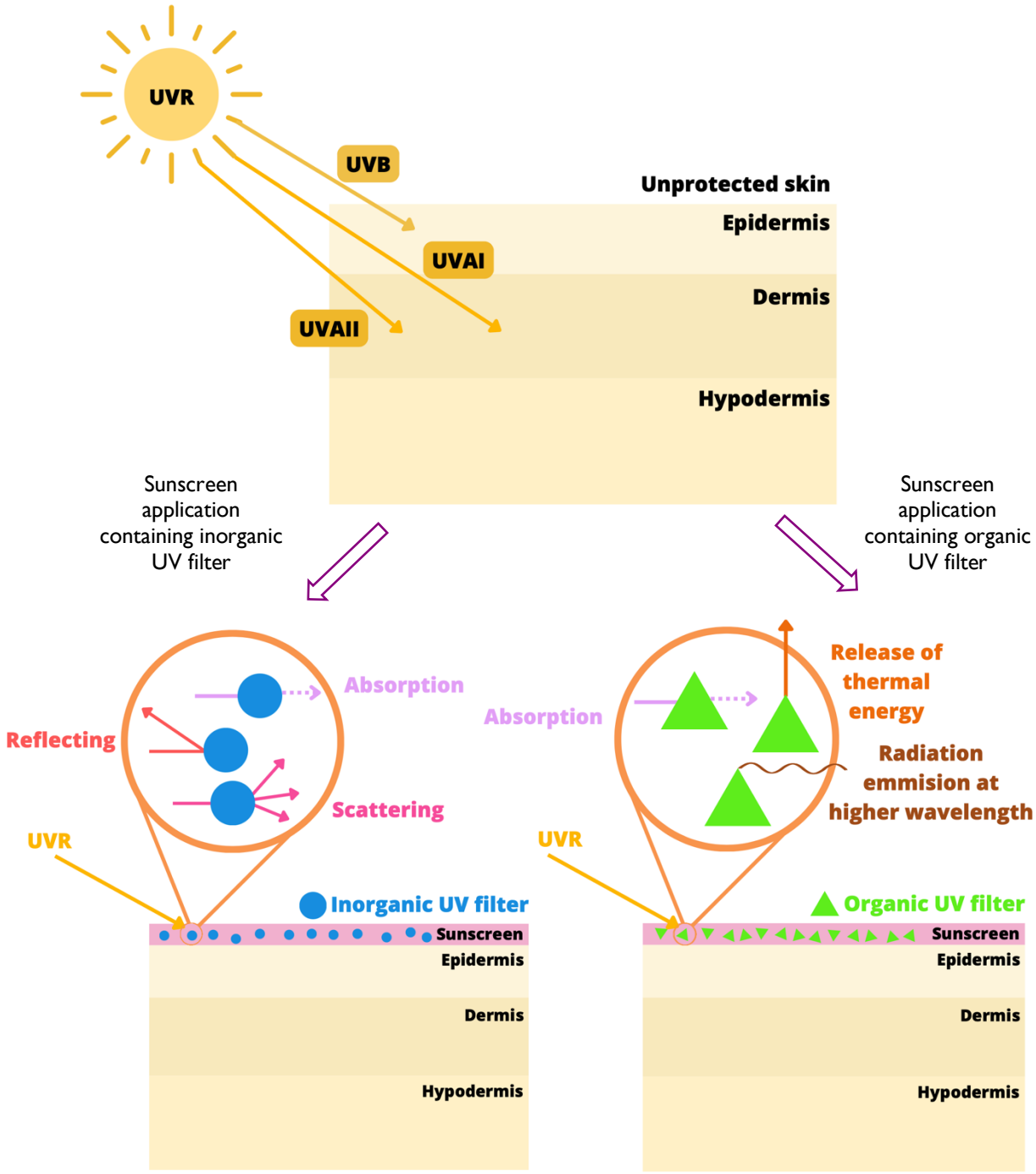

Figure 3 – Action mode of inorganic and organic UV filters

All the UV filters allowed in sunscreen products sold in the EU market are listed in the Annex VI of Regulation (EC) No 1223/2009 on cosmetic products along with the concentration limits and additional restrictions that have been positively assessed by the Scientific Committee for Consumer Safety (SCCS) and approved by the EC. This includes the authorized nanosized UV filters: nano-ZnO, nano-TiO_2 (Table 1), nano-MBBT and nano-TBPT (Table 2) [1].

Table 1 – EU-approved nanosized inorganic filters [1] [2]

Ultraviolet filter	Maximum concentration (%)	Protection against
TiO_2 (nano)	25 [1]	UVB
ZnO (nano)	25 [2]	UVA, UVB

[1] In case of combined use of Titanium Dioxide and Titanium Dioxide (nano), the sum shall not exceed the limit given on the maximum concentration column.
[2] In case of combined use of Zinc Oxide and Zinc Oxide (nano), the sum shall not exceed the limit given on the maximum concentration column

Table 2 – EU-approved nanosized organic filters [1] [46] [47] [48] [49]

Ultraviolet filter	Maximum concentration (%)	Protection against
MBBT (nano)	10 [1]	UVB, UVA
TBPT (nano)	10	UVB, UVA

[1] In case of combined use of Methylene Bis-Benzotriazolyl Tetramethylbutylphenol and Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (nano), the sum shall not exceed the limit given on the maximum concentration column.

6. Nanotechnology in sunscreens

Nanotechnology can be described as a diverse scientific discipline [10] and a highly studied revolutionizing technology [5] that encompasses the design, production, manipulation and application of materials that display a size below 100 nm [4] [5] [39] with the purpose of overcoming their own limitations by granting them new or upgraded properties [4] [10].

In the EU, a nanomaterial (NM) in cosmetics refers to "an insoluble or bio-persistent and intentionally manufactured material" that has "one or more external dimensions, or an internal structure, on the scale of 1 to 100 nm" [50] [51].

Nowadays, the application of NMs is widespread in different industrial settings, from wastewater treatment to medicine [52]. One of the first industries to implement the use of nanotechnology-based materials was the cosmetic industry [51] [53] and is currently a global leader in its incorporation in the development of new products [53]. In an industry that constantly pursues innovative and groundbreaking technology, nanotechnology arises as a pioneering strategy [4].

Nanostructures are present in a great variety of cosmetic formulations regarding solar protection, beauty care, dental care, hair care, skin care and deodorants [4]. Amongst the many

uses of nanoparticles (NPs) in cosmetic products, its use in photoprotection is noteworthy since the incorporation of nanotechnology into sunscreen formulations has led to growing advantages, effectiveness and improved cosmetic appeal [39].

Inorganic NPs are comprised of metal or metal oxides and generally behave like insoluble particles, not being expected to change or disintegrate after skin application. They're non-toxic, hydrophilic, biocompatible and highly stable, suitable for large-scale manufacturing due to their reproducible synthesis and tunable properties, leading them to being well-established in the cosmetic industry [2] [51]. Nano-ZnO and nano-TiO_2 are the inorganic UV filters approved by the EC [1].

The main drawback of inorganic filters used to be their cosmetic acceptability since the chalky white coat left on the skin after sunscreen application was considered aesthetically unacceptable, especially for individuals with dark skin tones [27]. With the introduction of nano-sized inorganic filters, the formulations show superior dispersion and cosmetic result since reducing the particle size improves spreadability and provides transparency [2] [51] [53].

Nanotechnology is also used to improve the performance of organic UV filters [51]: nano-TBPT and nano-MBBT are the nanosized organic UV filters approved in the EU market [1] and are essential to assure a bigger concentration of these filters in sunscreen formulations and, consequently, superior photoprotection [2].

A marketed example of NP use in sunscreen is Bioderma's Mineral Fluid SPF 50+ that uses nano-ZnO and nano-TiO_2 as UV filters [54] which allows for a formulation that offers effective protection against both UVA and UVB radiation [2] [39], displaying no skin irritation and offering transparency after application [2] [4]: prime advantages of nanotechnology use in sunscreens. It's a sunscreen advertised under the premise of being 100% mineral and suitable for intolerant and sensitive skin, allergic to chemical filters and perfumes, with an ultra-light and fluid texture and colorless application [54].

On Table 3 below are mentioned some examples of commercially available sunscreens containing NPs [2] [53].

Table 3 – Examples of commercially available photoprotection products containing NPs

Commercial name	Company	Nanotechnology	Protection against
Avène Suncare Cream SPF 50+	Pierre Fabre	Nano-MBBT	UVA, UVB
Avène SunsiMed	Pierre Fabre	Nano-MBBT	UVA, UVB
Eucerin Actinic Control MD SPF 100	Beiersdorf AG	Nano-TiO_2	UVB
Eucerin Sensitive Protect Sun Fluid Mattifying SPF 50+	Beiersdorf AG	Nano-TiO_2	UVB
ISDIN Fotoultra 100 Spot Prevent Fusion Fluid SPF 50+	ISDIN SA	Nano-TiO_2	UVB
Mineral Fluid SPF 50+	Bioderma	Nano-ZnO, nano-TiO_2	UVA, UVB
Photoderm Aquafluide SPF 50+	Bioderma	Nano-MBBT	UVA, UVB
Photoderm AR SPF 50+	Bioderma	Nano-MBBT	UVA, UVB
Piz Buin Allergy Facial Cream Sun Sensitive Skin SPF 50+	Johnson & Johnson	Nano-MBBT	UVA, UVB
Soltan® Facial Sun Defense Cream	Boots (Optisol)	Nano-TiO_2	UVB
Sunissime Global Anti-Ageing Eye Care SPF 50+	Laboratoires Lierac SAS	Nano-ZnO, nano-TiO_2	UVA, UVB
TINOSORB® A2B	BASF	Nano-TBPT, nano-MBBT	UVA, UVB

7. Nanofilters skin penetration

Due to its barrier function, the skin's SC plays an important role in protecting it from penetration of substances [2]. The knowledge of skin penetration pathways is fundamental to assess delivery systems, chemical safety and possible interactions [9]. It's known that other factors besides molecule size affect skin penetration and they're generally divided in three categories: application site's location and skin condition, penetrating molecule's physicochemical properties and dispersing vehicle's physicochemical properties [11].

The primary mechanism of permeation across human skin is diffusion [55]. The delivery of active ingredients through the skin can be carried out through different pathways: the transepidermal intracellular route, the transepidermal intercellular route and the transappendageal (or transfollicular) route [56].

The transepidermal route includes the intracellular and the intercellular permeation: the intracellular is the shortest pathway through the corneocyte layers and the lipid matrix;

when the penetration occurs in a tortuous way through the intercellular lipid matrix it's called the intercellular route. Permeation through the transappendageal route occurs via the hair follicles and the sweat and sebaceous glands and provides an easy diffusion path in parallel to the transepidermal route [55]. It's generally accepted that compounds' predominant pathway for permeation is the intercellular route. The appendage route only represents around 0.1% of total absorption area [2] [55].

The diffusion of active ingredients across skin layers is influenced by the active ingredient's molecular weight, the absorption channels, solubility, polarity [56] but, and most importantly when formulating cosmetics, through the use of special ingredients known as penetration enhancers which, after contact with the SC, promote the actives' diffusion or change partitioning in the SC, making the transport of active agents into deeper layers of the skin possible. Fatty acids, cyclodextrins and surfactants are some examples of penetration enhancers [57].

The skin area where the formulation is to be applied, the local skin variations in thickness, condition, integrity and appendages' density across the body and the skin's hydration are also imperative aspects to consider [56]. Skin type, age and sex hormones also influence permeability. Thereby it's concluded that absorption can be favored or limited according to body site and so it should be taken into consideration when it comes to the comparison of experimental data [11].

NPs penetration across the skin barrier is a highly controversial matter, mostly due to the possible nanotoxicological implications. The NP size plays a critical role in this process, along with composition, colloidal stability and vehicle properties [2] [53].

It has been observed that NPs penetrate skin using the same three pathways mentioned above [2] but there are some uncertainties regarding NPs' ability to penetrate through the SC, arising toxicological concerns [51]. It's also important to establish whether its absorption through the skin happens in NP form or in a dissolved state [58]. The properties that can influence NMs interactions with the SC and their potential depositions in appendages and deeper skin layers are size, shape, surface charge and properties (for example, functional groups and coatings) and aggregation state. The vehicle in which they are suspended also influences the substance's properties and affects permeability [53].

The small size of NPs rises concerns over its possible passage through cell membranes, reaching sensible organs and interacting with cells, DNA and proteins [56] which could lead to possible toxicity processes from the interaction of NPs and biological systems such as ROS production, oxidative stress induction and long-term inflammations [10]. However, data suggests that NPs mainly accumulate on the skin surface and upper SC layers [10] [59].

Cosmetic products intended for dermal application are designed to be applied on healthy skin but sunscreens may be applied to sunburnt (inflamed) skin. According to the 11th Revision of EU Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, testing of dermal/percutaneous absorption (*in vivo*, *in vitro* or in human subjects) should be performed on intact skin however it safeguards that, despite the nonexistent protocol on dermal absorption through damaged skin (where sunburnt is included), information from such studies can be considered supporting information [58].

UVR exposure can facilitate the loosening of epidermal cells' intercellular connections, potently enabling the permeation of exogenous substances through the skin. Senzui *et al.* (2010) and Miquel-Jeanjean *et al.* (2012) studied nano-TiO_2 particles' ability to penetrate intact and compromised skin models when applied in sunscreen formulations. When it comes to UVR exposure and combination of damaged and UVR exposed compromised skin models, they didn't detect the NP's presence in the perfusate from either the intact or the compromised skin [59].

8. Nano-ZnO and nano-TiO2

In the late 1990s, nanosized particles of TiO_2 and ZnO were integrated into sunscreen products on a large scale, allowing a decrease on the skin's excessive whitening and therefore increasing consumers' willingness [61] [62]. In the 1980s, nano-TiO_2 and nano-ZnO patents were filed, specifying the benefits they brought to UV protection and perfected cosmetic appearance, and technical and engineering breakthroughs allowed for NP's mass production. In the 1990s, there was a big increase of nanosized TiO_2 on sunscreen formulations, followed by nanosized ZnO exploitation later on the decade [61].

Nanosized TiO_2 e ZnO exist in three different states: primary particles, aggregates and agglomerates. The primary particles typically range from 5 to 20 nm and are the first stage of NP production. Due to the strong attraction forces between the crystals, the primary particles cluster together which leads to the formation of aggregates, that are tightly bound and have a

bigger size, usually between 30 and 150 nm. Aggregates represent the smallest unit to occur in a final sunscreen formulation. Because of drying and heat treatment processes during manufacturing, the aggregates form agglomerates, loosely-bound and with sizes above 1 μm, which would be the size of nano TiO_2 and ZnO powder. Agglomerates are not efficient for UV protection and therefore must be broken into aggregates [61] [62].

The UV absorption profiles of TiO_2 and ZnO are fundamentally dependent on the aggregate size of metal oxides: SPF varies in the formulations containing the same concentration of inorganic filters with different particles' sizes [61] [62]. TiO_2 particles with average aggregate size of 100 nm present effective UVA and UVB protection while particles with size of approximately 50 nm offer higher UVB protection and lower UVA protection. There is significant scattering in the visible region with larger particles but the whitening effect of the sunscreen is still much less meaningful than other sunscreens. With the 50 nm size, there is less scattering which results in a more transparent formulation however, to achieve a broad spectrum of protection, it must be combined with other UVA filters. Compared with 50 and 100 nm aggregates, 20 nm aggregates offer considerably less protection against UVA and UVB. Therefore, choosing optimal size of the inorganic particle and maintaining it in the final sunscreen formulation are crucial factors to obtain the desired UV absorption profile and protection [39]. To maintain optimum final aggregate size, nanosized TiO_2 and ZnO are stabilized by dispersing agents, preventing agglomerate formation and maintaining the fine size [2] [39].

Nano-ZnO shows a broad absorption spectrum across both UVA and UVB but is more efficient as UVA filter. In the other hand, nano-TiO_2 mainly absorbs light in the UVB region. As referenced above, this ability is highly dependent on particle size: 40-60 nm is considered the optimal size range to achieve acceptable UV protection with good transparency [2].

Nano-ZnO and Nano-TiO_2 confer superior photoprotection when compared to previous generations of inorganic sunscreens [7] and the smaller size increases the consumers' cosmetic acceptability mainly since they're considerably less visible after application, a critical quality the initial sunscreen formulations containing mineral filters lacked [62].

8.1. Benefits and safety concerns

The combination of ZnO and TiO_2 unveils an effective protection against UV with optimal characteristics like transparency, spreadability, improved texture and no skin irritation

[4]. When compared to organic filters, nanosized inorganic UV filters are more photostable, safer and more environmentally friendly [2].

Since nanosized ZnO and TiO_2 reflect a small portion of particles from the incident light, they show ideal transparency which results in the main celebrated transparent effect [2] [4]. This non-greasy, clear formulation doesn't degrade with UV exposure [62], what is a fundamental trait in products which use is commonly associated with high temperatures, as sunscreens.

They are also shown to prevent penetration of UV blockers into the SC and consequently obstruct skin irritations [4].

Nano-TiO_2 and nano-ZnO's use raised concerns about possible toxicity due to its potential to generate ROS during UV exposure, since some forms of ZnO and TiO_2 present photocatalytic activity when exposed to UVR [62]. These concerns regard a potential penetration in the SC, which could ultimately enter the dermis and the blood supply [62], however, according to the SCCS, nano-TiO_2 and nano-ZnO show lack of penetration through the skin and are considered unlikely to lead to systemic NP exposure and reach viable cells/organs, or to cause toxicity and skin/eyes irritation (via dermal application or oral exposure) when applied on healthy skin. Therefore, the use of nano-TiO_2 and nano-ZnO in sunscreen formulation is not considered to pose a risk of adverse effects following dermal application [63] [64].

It's important to consider that these potential risks can be reduced or fully eliminated through techniques that coat the surface on NPs, that provides an extra layer of protection during the manufacturing processes, and the skin's natural antioxidant mechanism to neutralize ROS. It's also important to point out TiO_2 and ZnO overall safety record since they both been used in various products, such as toothpastes, lotions, baby powders and antidandruff shampoos, for decades [61] [62].

The toxicity concerns by inhalation exposure are arising when considering nano-ZnO and nano-TiO_2 manufacture for sunscreens since the lungs are unable to clear NPs, creating potential accumulation of increased concentrations in the alveolae and possible absorption into the bloodstream which could lead to internal organ damage [62]. The SCCS doesn't recommend nano-TiO_2 and nano-ZnO use in sprays [64] [65] since some nano-TiO_2 particles

have been shown to lead to carcinogenic effects after inhalation [63] [65] and nano-ZnO has shown lung inflammation post inhalation (Table 4) [64].

Table 4 – Most relevant safety concerns regarding inorganic NMs in sunscreen formulations [53] [63] [64] [65]

NM	Safety Concerns	SCCS Opinion	Justification
Nano-ZnO	Lung inflammation post inhalation	Positive for the use as UV filter in sunscreens (until 25% concentration)	Lack of evidence for oral and skin absorption that, if present, would be resolved by the continuous dissolution of zinc ions
		Negative for spray products	
Nano-TiO_2	Lung inflammatory response and potential carcinogenicity after inhalation exposure	Positive for use until 25% concentration and for coated TiO_2	Absence of dermal absorption after application to healthy skin
		Inconclusive for spray products	

9. Nano-TBPT and nano-MBBT

TBPT was the first filter added to Annex VI of the Regulation (EC) No 1223/2009, since it came into force in 2013 [41]. Nano-TBPT is a very effective, photostable broad-spectrum organic filter suitable for sunscreen products and anti-aging face care products [5] [51].

MBBT was approved as a cosmetic UV active in 2000 and its nanoform was authorized by EC decision in 2018 [66]. Nano-MBBT works as a broad-spectrum filter and can be used up to 10% weight per weight (w/w) concentrations for dermally applied cosmetic products [5] [51].

It has shown superior performance by combining absorption (90%) with scattering (10%) abilities and display higher attenuation when compared to the micronized compound [2].

9.1. Benefits and safety concerns

Most organic filters are oil-soluble or oil-miscible and therefore incorporated in the oily phase of the sunscreen formulation, according to their solubility. The oily phase volume is, however, normally reduced, limiting the UV filters' possible maximum concentration. The production of nano-TBTP and nano-MBBT aids the increase of loading capacity of organic

filters into the water phase of the sunscreen formulation, increasing their possible concentration [2] [67].

Additionally, the absorption spectrum of nanosized TBPT and MBBT can enlarge filter applicability [2] since nano-TBPT and nano-MBBT absorption in the UVA and UVB regions increase with a decreasing particle size [46] [48].

According to the SCCS, dermal exposure to formulations containing TBPT with particle around 81 nm, as well as oral exposure, results in low absorption and there has been no systemic effect observed. However, there's uncertainty surrounding its safe use in spray application due to possible inhalation exposure, thus spray products containing TBTP are not recommended until further information on safety inhalation exposure is provided (Table 5) [48].

Based on SCCS's opinion, MBBT doesn't pose a risk when applied on healthy and intact skin, showing very low dermal absorption, however it can lead to possible irritation effects and potential bioaccumulation in selected tissues. Inhalation toxicity is the primary concern since microfine MBBT shows inflammatory effects in the respiratory tract (Table 5) [46].

Table 5 – Most relevant safety concerns regarding organic NMs in sunscreen formulations [53] [48] [46]

NM	Safety Concerns	SCCS Opinion	Justification
Nano-TBPT	Inhalation exposure can lead to strong lung inflammatory response	Positive up to 10% concentration for uncoated median particle with size > 80 nm	Lack of dermal absorption in insoluble particulate form
		Inconclusive for spray application	
Nano-MBBT	Inhalation toxicity	Positive in concentrations up to 10%	No concern for systemic effects in dermal application
		Inconclusive for spray application	

10. Regulatory landscape

As previously mentioned, in the EU the cosmetic products' main regulatory framework is the Regulation (EC) No 1223/2009 that establishes the rules that must be fulfilled by any marketed cosmetic product to ensure internal market functioning and human health

protection [1]. In Portugal, the legal policies around cosmetic products are explained in the Decree-Law No 189/2008, from September 24th [68].

Regulation (EC) No 1223/2009 states that any sunscreen available on the market must be safe for human health under its normal and foreseeable use conditions, and considering its presentation, labeling, use and disposal instructions, and other indications or information provided by the responsible person and defined within this Regulation. Within the EU, only sunscreens with a designated responsible person can be placed on the market. The responsible person ensures compliance with the Regulation's obligations, safeguarding good manufacturing practices, safety assessments and safety reports [1].

Any sunscreen on the market has its own product information file, kept for ten years following the date of its last marketed batch, containing the product's description, safety report, manufacturing method's depiction, statement of compliance with good manufacturing practices, justified nature/effect and proof of effect claimed, and dates of testing, agents or suppliers related to the development and safety of the sunscreen and its ingredients. This product information file must be accessible to the Member State's competent authority [1]. In Portugal, the competent authority is the National Authority for Medicines and Health Products (INFARMED, I.P.).

Prior being marketed, every sunscreen's information must be electronically communicated to the EC. In this notification, the presence of substances in the form of NMs must be submitted along with its identification and its reasonably foreseeable exposure conditions [1].

UV filters, as well as NMs, are addressed in Chapter IV: Restrictions for Certain Substances. Within EU market, according to Article 14, sunscreens can't contain UV filters other than the ones listed in Annex VI and in accordance with the laid down conditions. Article 16 addresses NMs directly but doesn't apply to the ones regulated under Article 14, as is the case of UV filters. Besides the regular formal notification to the EC, sunscreens containing NMs must be communicated to the EC six months before being placed on the market, displaying the identification of the NM, specifying its particle size, physical and chemical properties, estimate quantity in the cosmetic product, toxicological profile, safety data particularly related to the sunscreen and reasonably foreseeable exposure conditions [1].

Any concerns regarding the safety of the NM, at any time, can be submitted to the SCCS for its Opinion. The SCCS offers Opinions on health and several safety risks of non-food consumer products and services, including cosmetic products and their respective ingredients [60].

As provided by Article 19, a sunscreen available on the market must present a container and packaging with the following information: name and address of the responsible person, nominal content at packaging time in weight or volume, date of minimum durability (unless the minimum durability is of more than 30 months, where the durability after open is indicated instead), specific use precautions, batch number or reference of identification, function, list of ingredients, impurities and subsidiary tech [1].

The 11th revision of the SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation, released in 2021, states that the safety assessment of a sunscreen is based on the safety of its ingredients, which on its turn is based on the exposure level and toxicological data, requiring suitable safety data for each ingredient that meets the NM criteria [58]. The EC holds regulations towards the NMs used in cosmetics and requires safety studies [4]. The SCCS performs a suitable characterization of the NM [53], which includes tests regarding nano-characteristics [51] [39]. The key parameters to be evaluated and evaluation methods are dependent of the composition, properties and predicted use of the NM [53] which include: chemical identity, chemical composition, agglomeration, crystallographic structure, particle size, size distribution, morphology, shape, structure, surface area, concentration, stability, solubility, density, morphology, porosity, impurities and potential exposure routes [39] [53] [51].

The European Union Observatory for Nanomaterials (EUON), funded by the EC with the purpose of providing research, policies and safety information about the current NMs on EU market [69], developed two databases accessible to consumers: NanoData and eNanoMapper [4].

11. Final considerations

The adverse effects of UV exposure on the skin are well known, carefully studied and increasingly relevant [38] [70], being the prime responsible for photoaging, skin cancers development and other damaging consequences [23] [71] – therefore photoprotection continues to be encouraged and emphasized [38] [70].

Amongst the different ways against the nefarious consequences of different UV wavelengths, sunscreens have grown to be cemented as essential photoprotection tools [38] [70]. Sunscreen use has been shown to protect against DNA damage, minimize oxidative stress, decrease inflammation and improve the skin's overall appearance [23] [38].

Nanotechnology is considered a tool of major importance towards scientific growth in various fields and the cosmetic industry is in the vanguard of nanotechnology use [4]. Since NMs were first introduced in the cosmetic industry, the market for nanotechnology has been consistently increasing worldwide due to its significantly advantageous cosmetic functions, superior skin penetration, biocompatibility and stability [4] [51] [53].

NMs can be used in a vast collection of cosmetic products and their use is noteworthy in sunscreen formulations [4]. The understanding of the UV properties in relation to particle size allowed for the incorporation of nanosized organic and inorganic filters into sunscreen formulations which led to more effective and cosmetically pleasant products [61], improving sun protection and general consumer's satisfaction [2]. Sunscreen is, and will be, a fundamental part of the photoprotective measures [61] and its regular use is recommended.

Regarding NMs safety, a series of parameters are assessed to deem them appropriate for cosmetic formulations and skin application [4] [53]. The main safety concerns considering NMs use appear from skin penetration and possible accidental exposure through an unwanted route [53] but current research argues in favor of NMs general safety [46] [48] [61] [63] [64] [65] [72].

Overall, the incorporation on nanotechnology in sunscreens represents a promising and viable path towards obtaining the finest and most beneficial formulations [4].

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