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LUANA DIAS CAMPOS

ESTUDO DA UTILIZAÇÃO E PERCEPÇÃO DOS BENEFÍCIOS DO COLÁGENO EM ALTERAÇÕES DERMATOLÓGICAS E ORTOPÉDICAS

STUDY OF THE USE AND PERCEPTION OF THE BENEFITS OF COLLAGEN IN SKIN AND ORTHOPEDIC ALTERATIONS

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Dissertação apresentada à Faculdade de Engenharia de Alimentos da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Alimentos e Nutrição.

Dissertation presented to the School of Food Engineering of the University of Campinas in partial fulfillment of the requirements for the degree of Master, in Food and Nutrition.

Supervisor/Orientador: Profa. Dra. Cinthia Baú Betim Cazarin

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RESUMO

O colágeno corresponde a um quarto da massa proteica total do corpo humano. São proteínas da matriz extracelular capazes de interagir com células por meio de várias famílias de receptores, regulando a proliferação, migração e diferenciação celular. Alterações na estrutura do colágeno, assim como sua degradação estão relacionadas à alterações da estrutura da pele, deterioração dos ossos e cartilagens e das funções cardiovasculares e respiratórias. A suplementação de colágeno é indicada para indivíduos com maior deterioração do tecido colagenoso encontrado em ossos, tendões, pele, cabelo, unhas, cartilagem e articulações. Entretanto, acredita-se que em geral, o consumo de colágeno se baseia em benefícios associados à manutenção e elasticidade da pele, do que aos benefícios associados à perda óssea e manutenção das articulações. Desta forma, o presente estudo teve como objetivo avaliar a percepção, conhecimento, atitude e práticas de consumidores de colágeno por meio de um questionário online e realizar uma pesquisa em relação à oferta deste produto/suplemento no mercado brasileiro (farmácias e online). O questionário da pesquisa foi disponibilizado através da plataforma Google Forms e o link de acesso, divulgado por redes sociais e-mail. Os dados foram analisados através de testes de análise estatística qualitativa, chi-quadrado, inferência estatística e estatística descritiva. No total, 275 participantes responderam à pesquisa, 73,3% da região Sudeste, 84,1% do sexo feminino, 49,8% com pós-graduação completa e com renda em sua maioria ente 1 e 6 salários mínimos. A maioria dos participantes relatou o consumo do produto por um período de 3 meses a 1 ano (31,6% e 28%), sendo 52,7% por automedicação. O período de consumo superior a três meses foi associado à percepção de benefícios à saúde ($p<0,001$). A percepção de benefício foi sentida por 69,1% dos consumidores, que apontaram com maior frequência benefícios em relação à saúde da pele 57,4% e articulações 36,8% como: melhora da hidratação, elasticidade, firmeza, efeito antienvelhecimento e aparência em geral e maior conforto nos movimentos articulares, melhora na mobilidade das articulações e diminuição das dores articulares, incluindo joelho e coluna. O conhecimento dos participantes não contemplou todos os benefícios que o suplemento oferece, sendo a associação do consumo com benefícios dermatológicos (41,9%) mais reconhecida do que benefícios ortopédicos e relacionados à perda de massa óssea (30,5% e 16,8%, respectivamente). O colágeno em pó foi a forma de apresentação do produto mais consumida (52,7%). De acordo com o levantamento de mercado os suplementos à base de colágeno vêm se diversificando ao longo dos anos com diferentes formas de apresentação do produto, sendo o pó a forma de apresentação com menor preço em comparação com cápsulas, comprimidos e gomas, e sendo as cápsulas os produtos mais presentes no mercado. O tempo de consumo de suplementos à base de colágeno superior a 3 meses parece ser fator essencial para sua obtenção de eficácia. Os benefícios dos suplementos à base de colágeno em relação à saúde da pele e articulações, descritos pelos participantes do presente estudo já são conhecidos pela literatura científica, e reforçam a consolidação necessária para o reconhecimento deste suplemento por diferentes sociedades médicas/ científicas.

Palavras-chave: colágeno, tratamento, benefícios, percepção do consumidor, pele, articulações

ABSTRACT

Collagen accounts for a quarter of the total protein mass in the human body. It is an extracellular matrix protein capable of interacting with cells through several families of receptors, regulating cell proliferation, migration, and differentiation. Changes in collagen structure, as well as its degradation, are related to changes in the structure of the skin, deterioration of bones and cartilage, and deterioration of cardiovascular and respiratory functions. Collagen supplementation is indicated for individuals with more significant deterioration of collagenous tissue found in bones, tendons, skin, hair, nails, cartilage, and joints. However, it is believed that, in general, collagen consumption is based on benefits associated with skin maintenance and elasticity rather than benefits associated with bone loss and joint maintenance. Thus, the present study aimed to evaluate the perception, knowledge, attitude, and practices of collagen consumers through an online questionnaire and to carry out a survey regarding the offer of this product/supplement in the Brazilian market (pharmacies and online). The survey questionnaire was made available through the Google Forms platform, and the access link was disseminated through social networks and email. Data were analyzed using qualitative statistical analysis tests, chi-square, statistical inference, and descriptive statistics. In total, 275 participants responded to the survey, 73.3% from the Southeast region, 84.1% female, 49.8% with a complete graduate degree, and with an income mostly between 1 and 6 minimum wages. Most participants reported consuming the product for three months to 1 year (31.6% and 28%), with 52.7% self-medicating. A period of consumption longer than three months was associated with the perception of health benefits ($p<0.001$). The perception of benefit was felt by 69.1% of consumers, who most frequently mentioned benefits in terms of skin health 57.4% and joints 36.8% such as improved hydration, elasticity, firmness, anti-aging effect and appearance in general and greater comfort in joint movements, improvement in joint mobility and decrease in joint pain, including knee and spine. The participants' knowledge included only some of the benefits that the supplement offers, with the association of consumption with skin benefits (41.9%) being more recognized than orthopedic benefits and those related to loss of bone mass (30.5% and 16.8%, respectively). Collagen powder was the product's most consumed form of presentation (52.7%). According to the market survey, collagen-based supplements have been diversifying over the years with different forms of product presentation, with powder being the cheapest form of presentation compared to capsules, tablets, and gums, and capsules are the most present products on the market. Consumption time of collagen-based supplements for more than three months seems to be an essential factor for their effectiveness. The benefits of collagen-based supplements concerning skin and joint health, described by the present study's participants, are already known in the scientific literature and reinforce the necessary consolidation for recognizing this supplement by different medical/scientific societies.

Keywords: collagen, treatment, benefits, consumer perception, skin, joints

SUMÁRIO

1. CAPÍTULO I

INTRODUÇÃO GERAL, OBJETIVOS E ESTRUTURA DA DISSERTAÇÂO

1. INTRODUÇÃO GERAL

Onipresente em animais vertebrados o colágeno é um biomaterial (Bielajew, Hu & Athanasiou, 2020) que corresponde a um quarto da massa proteica total de humanos e outros vertebrados, sendo constituído por proteínas fibrosas insolúveis (Arseni, Lombardi & Orioli, 2018) que formam redes que reforçam os tecidos e fornecem matriz extracelular para as células. Essas estruturas possuem funcionalidades de enrijecimento de tensões que ajustam funções mecânicas dos tecidos e regulam o comportamento celular (Jansen, Licup, Sharma, Rens, MacKintosh & Koenderink, 2018), sendo ainda fundamentais para proporcionar elasticidade e resistência aos órgãos e tecidos (Arseni et al., 2018) e contribuem para as propriedades de organização e forma dos tecidos (Ricard-Blum, 2011), provendo rigidez e resiliência (Panwar, Butler, Jamroz, Azizi, Overall & Brömme, 2018).

Os colágenos são capazes de interagir com células por meio de várias famílias de receptores, regulando a proliferação, migração e diferenciação celular. Alguns colágenos possuem distribuição restrita nos tecidos e assim funções biológicas específicas (Ricard-Blum, 2011).

No corpo humano existem 29 tipos de colágeno (Kielty e Grant, 2002), sendo encontrados em uma variedade de tecidos como: pele, tendões e ligamentos, músculo esquelético, tecido adiposo, ossos, córnea, vasos sanguíneos, válvulas cardíacas, cartilagem articular, tecidos conjuntivos, entre outros (Bielajew et. al, 2020). A maior parte do colágeno no corpo humano (80 a 90%) está na forma I, II e III.

Na pele o colágeno tipo I é o mais abundante com 80% do conteúdo total, seguido pelo colágeno tipo III que representa 15% (Sibilla et al., 2015). Na matriz da cartilagem, o colágeno tipo II nos adultos representa mais que 90% do conteúdo total de colágeno, sendo seguido pelo colágeno tipo III que apresenta um conteúdo de cerca de 10% na cartilagem articular (Eyre et. al, 2006).

Alterações na estrutura dos colágenos e sua degradação estão relacionadas ao enrugamento da pele, deterioração dos ossos e cartilagens e as funções cardiovasculares e respiratórias (Panwar et al., 2018). Os grupos com maior risco de deterioração do tecido colagenoso são: pessoas acima de 40 anos (devido à idade), esportistas e praticantes de atividades intensas (devido a uso excessivo, impacto) e outras circunstâncias como excesso de peso, menopausa, queimaduras, cirurgia implantes dérmicos ou dentais e tratamentos oncológicos agressivos (**Figura 1**)

(Figueres Juher & Basés Pérez, 2015). Sendo assim, a suplementação de colágeno hidrolisado é indicada para pacientes com maior risco de degradação de tecido colagenoso.

Figura 1: Grupos de risco para deterioração do tecido colagenoso. Fonte: Figueres Juher et al., (2015). A figura foi parcialmente criada utilizando Servier Medical Art, disponibilizado por Servier, licenciado por aCreative Commons Attribution 3.0 licença não portada (https://creativecommons.org/licenses/by/3.0/) e Freepik (https://br.freepik.com/).

Comprovadamente o consumo de colágeno hidrolisado pode trazer muitos benefícios para o corpo humano como melhora na saúde da pele (Barati et al., 2020; Grand View Research, 2020; Lupu et al., 2020, Gradisteanu Pircalabioru, Chifiriuc, Albulescu & Tanase, 2020; Proksch, Segger, Degwert, Schunck, Zague & Oesser, 2014) e da dor articular (Clark et al., 2008; Czajka et al., 2018; Lugo et al., 2013; Lupu et al., 2020; Zdzieblik, Brame, Oesser, Gollhofer & König, 2021). O consumo de colágeno hidrolisado pode potencializar a regeneração dos tecidos colagenosos, prevenindo e tratando doenças degenerativas do colágeno (osteoartrite e osteoporose) e também a deterioração dérmica (Figueres Juher et al., 2015).

Há vantagens de consumir o colágeno hidrolisado em relação ao colágeno nativo. O colágeno hidrolisado é altamente digerível facilitando a absorção de suas unidades monoméricas e distribuição pelo corpo. Sua estrutura é constituída por peptídeos com baixo peso molecular, ricos em aminoácidos glicina, prolina e hidroxiprolina (Sibilla, Godfrey, Brewer, Budh-Raja & Genovese, 2015). Esses peptídeos são considerados com melhor bioatividade do que suas contrapartidas maiores (Hong, Fan, Chalamaiah & Wu, 2019).

O colágeno além de nutrir, pode ser usado como medicamento, sendo desta maneira considerado um produto nutracêutico, ou seja, um produto/ substância que apresenta benefício fisiológico ou fornece proteção contra doenças crônicas. Produtos nutracêuticos podem ser utilizados para melhorar a saúde, retardar o processo de envelhecimento, prevenir doenças crônicas, aumentar a expectativa de vida ou apoiar a estrutura e função do corpo (Nasri, Baradaran, Shirzad & Rafieian-Kopaei, 2014).

Os peptídeos de colágeno podem apresentar diferentes estruturas, comprimentos e composição de aminoácidos, dependendo da fonte utilizada para a produção (Bolke, Schlippe, Gerß & Voss, 2019). O tipo de colágeno, as condições e a fonte de extração afetam a solubilidade e a atividade funcional do produto, podendo determinar as aplicações posteriores do colágeno (Schmidt et al., 2016).

O colágeno e os produtos derivados do colágeno são usados de forma ampla e para uma variedade de aplicações nas indústrias alimentícia, farmacêutica, cosmética (Liu, Nikoo, Boran, Zhou & Regenstein, 2015) (Schmidt et al., 2016), na entrega de medicamentos e na engenharia de tecidos (Browne, Zeugolis & Pandit, 2012), devido a suas propriedades nutricionais e funcionais (Liu et al., 2015).

Em 2019 a demanda do mercado global de colágeno foi estimada em 920,1 toneladas (Grand View Research, 2020). No período de 2020 a 2027 a partir do cálculo da Taxa Composta de Crescimento Anual (CAGR) estima-se um aumento da demanda de 5,9%. Os cuidados em saúde foram estimados como maior demanda de colágeno dentro do seguimento global, em 2019 e estima-se que mantenha esta posição até 2027 (estimativa de 48% do total de volume de mercado), tendo esse crescimento se apoiado no reparo de tecidos e aplicações odontológicas (Grand View Research, 2020).

A demanda por produtos contendo colágeno é esperada devido à sua crescente aplicação, mudanças nas preferências e estilos de vida dos consumidores, aumento da renda disponível e aumento da conscientização sobre saúde e cuidados pessoais (Grand View Research, 2020).

1.1 Caracterização e Digestão do Colágeno

A fibrila de colágeno é o bloco de construção básico de tecidos ricos em colágeno. Ela possui espessura entre cinquenta a centenas de nanômetros (**Figura 2**), sendo utilizada em materiais compostos com uma variedade de estruturas como na dentina em combinação com minerais, no tendão e córnea combinada a proteoglicanos, entre outros. Essas estruturas podem apresentar propriedades

isotrópicas, anisotrópicas e mecânicas diferentes dependendo do arranjo da fibra (Fratzl, 2008).

O colágeno hidrolisado pode ser adquirido a partir de resíduos agroalimentares (ossos, tendões e pele). Suas características serão determinadas pelo tipo de extração. Como os colágenos se co-localizam em vários tipos de tecido, a obtenção de amostras de apenas um tipo de colágeno é dificultosa (Hulgan e Hartgerink, 2022). Já o colágeno tipo II é geralmente extraído da cartilagem bovina ou suína (Cao e Xu, 2008), podendo ser extraído da cartilagem do esterno do frango como o Colágeno nativo não desnaturado de frango tipo II (UC-II).

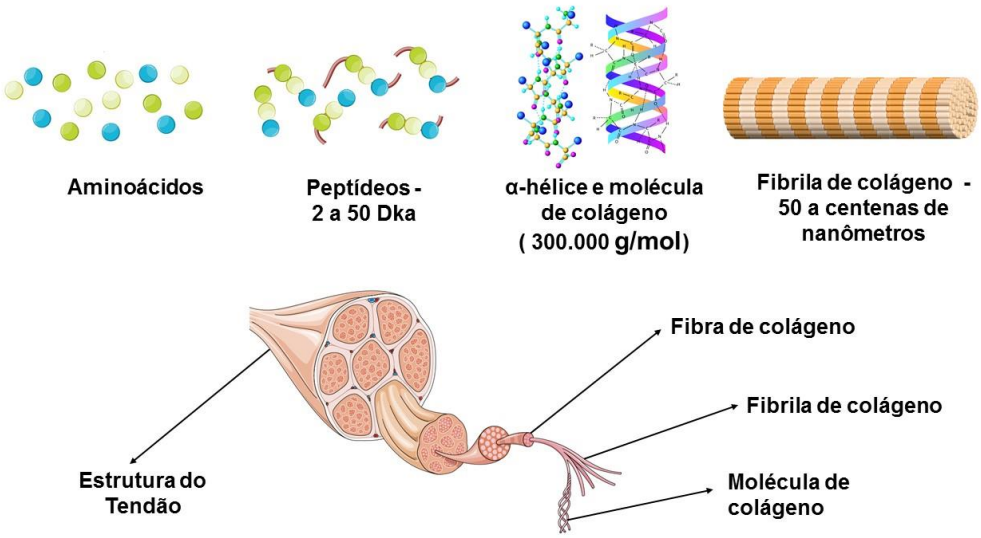

Figura 2: Composição e tamanho das estruturas que compõe o colágeno. Fonte: Sorushanova et al., 2019; Brasil 2021. A figura foi parcialmente criada utilizando Servier Medical Art, disponibilizado por Servier, licenciado por aCreative Commons Attribution 3.0 licença não portada (https://creativecommons.org/licenses/by/3.0/), Shutterstock.com e Adobe Stock (https://stock.adobe.com/br/).

A digestão do colágeno é semelhante a digestão de outras proteínas, porém descobertas recentes relatam algumas diferenças no processo descritas abaixo.

Durante o processo de digestão humana as ações de enzimas gástricas em proteínas resultam na liberação de aminoácidos e peptídeos de diferentes tamanhos no intestino delgado. Neste órgão a ação de enzimas exopeptidases degradam estes peptídeos remanescentes em aminoácidos, porém peptídeos contendo prolina, hidroxiprolina possivelmente podem apresentar resistência a esta ação, resultando em maior número destes peptídeos no lúmen (Sato, 2018; Udenigwe et. al, 2021).

A absorção de aminoácidos ocorre através de transporte passivo por difusão e transporte ativo (canais sódio e próton dependentes). Já peptídeos apresentam diferentes mecanismo de absorção no intestino delgado como: mecanismos enantio-seletivos através de transportador de peptídeos 1 (PEPT1), difusão passiva através das junções celulares e transporte ativo, através de canais sódio e próton dependentes (Daniel, 2004; Adibe, 2003; Frenhani e Burini, 1999; Urao et. al, 1997).

A simulação da digestão *in vitro* não reflete totalmente as condições após ingestão oral em seres humanos (Udenigwe et. al, 2021), porém seus resultados podem propor o isolamento e identificação de possíveis peptídeos derivados de alimentos no corpo humano. Esta abordagem é mais simples e fácil comparada a identificação e isolamento de peptídeos no sangue e órgãos (Sato, 2018). Desta forma estudos *in vitro* podem proporcionar uma perspectiva sobre a digestão de colágeno.

Ao estudar a digestão de colágeno *in vitro* Xu et al. (2021) associaram a solubilidade de colágeno tipo II não desnaturado insolúvel natural (IC II) e colágeno tipo II não desnaturado solúvel em pepsina (SC II) com o pH gástrico, descrevendo padrões diferentes de fibras após o processo de digestão gástrica, com o primeiro apresentando a liberação de algumas fibras curtas da tripla hélice e o segundo apresentando algumas fibras ligeiramente mais finas e curtas com uma pequena porção da tripla hélice destruída. Tais autores sugeriram *"A solubilidade de IC II pode ser melhorada em maior extensão sob valores de pH mais baixos, enquanto SC II pode manter sua estrutura de hélice tripla sob condições de pH mais altos". Desta maneira* o consumo de SC II após a refeição em pH mais elevado foi proposta para manutenção de sua estrutura.

Sousa et al. (2020) descreveram em seu estudo após analisar proteína de colágeno no processo de simulação de digestão *in vitro* que no final da digestão intestinal não foi encontrado proteínas intactas, mas sim parcialmente hidrolisadas. Os autores encontraram ainda peptídeos resistentes à digestão indicando hidrólise incompleta da proteína.

Sequências diferentes de peptídeos foram descritas por Larder e colaboradores (2021) ao simular o processo de digestão superior de duas fontes de colágeno hidrolisado (CH) de origem bovina (grupos CH-LH e CH-OPT). O grupo CH-LH apresentando 300 sequências peptídicas não encontradas em CH-OPT, e este apresentou 574 sequências não observadas em CH-LH, ambos compartilharam 138 sequências comuns. Tais dados estão relacionados à capacidade antioxidante dos produtos e a seu peso molecular que apresentou diferença em picos de peptídeos de alto e baixo peso molecular. O grupo CH-OPT apresentou no colo

ascendente aumento produção de H_2S, diminuição de NH_4 e aumento da produção de ácidos graxos de cadeia curta (ácidos propiônico, butírico e valérico), efeitos probióticos dependentes de CH que ainda precisam ser estudados. A pesquisa de Ofengenden et al., (2018) sugere que as mudanças das condições enzimáticas afetam o perfil de peptídeos hidrolisados e regulam diferencialmente suas atividades biológicas.

1.2 Identificação de peptídeos de colágeno bioativos

Reguladores biologicamente ativos, os peptídeos bioativos são um grupo de moléculas encontradas nas estruturas proteicas originais e que se tornam ativas após sua clivagem (Sánchez e Vásquez, 2017; Akbarian et al., 2022). A preparação de peptídeos bioativos de colágeno de baixo peso molecular vem despertando grande interesse de fabricantes, pesquisadores e consumidores, mas ainda necessita resolutividade para alguns desafios (Hong et al., 2019).

Segundo Zhao et al. (2021), os peptídeos de colágeno apresentam benefícios para a saúde, porém ainda há necessidade de obtenção de mais detalhes referentes a sua eficácia e mecanismos de ação. A produção em larga escala, triagem e purificação desses peptídeos apresenta grandes desafios, visto que os aminoácidos e sua sequência possuem efeitos na atividade dos peptídeos bioativos.

Estudos em relação a digestão e absorção de peptídeos de colágeno apresentam grande relevância visto a gama de funções em que peptídeos podem estar relacionados como: ação antiplaquetária (Ye et al., 2020), efeitos prebióticos e antioxidantes, aumento da enzima conversora de angiotensina e atividade inibitória dipeptidil peptidase IV (Larder et. al, 2021), inibição da atividade de acetilcolina (Zhao et. al, 2021) indutor de biomineralização, bioativo para regeneração óssea (Lee et. al, 2007), antimicrobiano, capacidade de redução de colesterol, hipoglicemiante, antihipertensivo, anticancerígeno (Nasri, 2019).

1.2 Dados Mercadológicos e Regulamentares do colágeno

Em 2019 o mercado global de colágeno foi estimado em US$ 4.562,4 milhões, com 35,1% de participação da Europa. Estima-se que entre 2020 e 2028 a Ásia seja a região mais lucrativa com Taxa Composta de Crescimento Anual de 9,7%. Assim como em 2019, em 2020 os cuidados em saúde também foram o maior segmento de aplicação (Grand View Research, 2020).

Algumas das principais empresas que operam no setor de colágeno são: CGelita AG, Nitta Gelatin, NA Inc., Darling Ingredients Inc., Weishardt International, Nippi Collagen NA Inc., Rousselot B.V., Collagen Matrix; Inc, Koninklijke DSM N.V., CONNOILS LL, Advanced BioMatrix; Inc. (Grand View Research, 2020).

Um estudo realizado no interior de São Paulo descreveu produtos de colágeno comercializados em farmácias na forma de pó e cápsulas (Domingos Junior et al., 2019; Rosatto et al., 2020), porém encontramos na literatura o desenvolvimento de outras formas de apresentação desta substância, como alimentos enriquecidos com colágeno: barras de cereais (Ferreira et al., 2021), balas (Barbosa et al., 2018) e iogurtes (Chuproski et al., 2020), entre outros.

Segundo Brasil (2021) “um produto à base de colágeno em pó com a finalidade de suplementar a alimentação com colágeno, deverá ser regularizado como Suplemento Alimentar”. Além de suplemento alimentar o colágeno é classificado como nutracêutico (Kwatra, 2020), e ingrediente bioativo para produtos nutricosméticos (Asserin et al., 2015).

A Agência Nacional de Vigilância Sanitária (ANVISA) (Brasil, 2021) classifica os suplementos alimentares em seis categorias compreendendo medicamentos e alimentos, são elas: (a) suplementos de vitaminas e minerais; (b) substâncias bioativas e probióticos; (c) novos alimentos; (d) alimentos com alegações de propriedades funcionais; (e) suplementos para atletas; (f) complementos alimentares para gestantes e nutrizes; e (f) medicamentos específicos isentos de prescrição.

Ao consultar o registro de alguns produtos (Brasil, 2021) no site da Agência Nacional de Vigilância Sanitária (ANVISA), como por exemplo, as marcas Max Titanium®, Lavitan®, Imecap®, IntegralMédica®, Sanavita®, entre outras, nota-se que os produtos estão descritos na categoria Alimentos sendo classificados como suplementos alimentares no subgrupo Novos Alimentos e Novos Ingredientes. A Agência Nacional de Vigilância Sanitária (Brasil, 1999) define essa categoria como *“alimentos ou substâncias sem histórico de consumo no País, ou alimentos com substâncias já consumidas, e que, entretanto, venham a ser adicionadas ou utilizadas em níveis muito superiores aos atualmente observados nos alimentos utilizados na dieta regular”.*

Algumas nomenclaturas sobre colágeno são descritas pela ANVISA como: Colágeno Tipo II, Colágeno hidrolisado (IN nº 28/2018), Colágeno de frango com colágeno tipo II não desnaturado, Colágeno tipo II não desnaturado (IN nº76/2020) Peptídeos bioativos de colágeno hidrolisado com peso molecular médio de 2kDa e colágeno (IN nº102/2021).

A ANVISA determina, alegações autorizadas para os produtos que estejam de acordo com suas especificações de conteúdo no produto, consumo mínimo da substância para funcionalidade descrita na alegação, dose máxima consumida e contaminação permitida nos produtos. Alguns dados são descritos abaixo. As normativas e portarias são descritas na tabela 1.

A autorização da utilização do termo substância bioativa é descrita para o colágeno, o colágeno tipo II, o colágeno tipo II não desnaturado, o colágeno de frango com colágeno tipo II não desnaturado e peptídeos bioativos de colágeno hidrolisado com peso molecular médio de 2 kDa. Com exceção do colágeno tipo II não desnaturado, do colágeno e de peptídeos bioativos de colágeno hidrolisado com peso molecular médio de 2kDa, não há definição de quantidade necessária do suplemento/ ingrediente para o uso desta alegação em rótulo. Não havendo também dose máxima de ingestão.

Para produtos à base de colágeno tipo II não desnaturado a Agência Nacional de Vigilância Sanitária (Brasil, 2021) descreve a utilização da alegação *"O colágeno tipo II não desnaturado auxilia na manutenção da função articular"* restrita a utilização aos produtos que contenham a quantidade mínima do ingrediente igual a 10 mg de colágeno total e 1,2 mg de colágeno tipo II não desnaturado. Estes produtos não possuem a ingestão máxima determinada e devem conter a seguinte descrição "*Este produto não deve ser consumido por gestantes, lactantes e crianças".*

A Instrução Normativa (IN) 102 de 2021 da ANVISA estabelece como limites mínimos para o consumo de colágeno de 11,5 microgramas e de peptídeos bioativos de colágeno hidrolisado com peso molecular médio de 2kDa de 2,5 gramas. Estabelecendo alegação para o último de: *"auxiliam na manutenção da saúde da pele*". Ambos os produtos não possuem ingestão máxima determinada, e também devem possuir o alerta em sua rotulagem: *"Este produto não deve ser consumido por gestantes, lactantes e crianças."*

A identidade e qualidade de colágenos comestíveis são regidos pelo regulamento técnico, descrito na Portaria nº 384 de 2021 do Ministério da Agricultura, Pecuária e Abastecimento/Secretaria de Defesa Agropecuária. A IN nº160 de 2022 estabelece os limites máximos tolerados de contaminantes em alimentos, determinando apenas limite para a contaminação de colágeno por cromo. Já a Resolução nº 240 de 2018 da ANVISA determina a dispensa de registro sanitário para suplementos alimentares.

Quadro 1: Regulamentações Brasileiras que regem a produção/ comercialização de colágeno.

Fonte, Categoria e Número	Finalidade
Brasil, Resolução nº 16, de 30 de abril de 1999	Aprova o Regulamento Técnico de Procedimentos para registro de Alimentos e ou Novos Ingredientes, constante do anexo desta Portaria.
Brasil, Instrução Normativa Nº 28, de 26 de julho de 2018	Estabelece as listas de constituintes, de limites de uso, de alegações e de rotulagem complementar dos suplementos alimentares.
Brasil, Resolução da Diretoria Colegiada – RDC Nº 240, de 26 de julho de 2018	Altera a Resolução – RDC nº 27, de 6 de agosto de 2010, que dispõe sobre as categorias de alimentos e embalagens isentos e com obrigatoriedade de registro sanitário.
Brasil, Instrução Normativa Nº 76, de 5 de novembro de 2020	Dispõe sobre a atualização das listas de constituintes, de limites de uso, de alegações e de rotulagem complementar dos suplementos alimentares.
Brasil, Portaria Nº 384, de 25 de agosto de 2021	Aprova os Regulamentos Técnicos que fixam os padrões de identidade e qualidade para gelatina, gelatina hidrolisada e colágeno comestíveis.
Brasil, Instrução Normativa N° 102, de 15 de outubro de 2021	Altera a Instrução Normativa nº 28, de 26 de julho de 2018, que estabelece as listas de constituintes, de limites de uso, de alegações e de rotulagem complementar dos suplementos alimentares.
Brasil, Instrução Normativa - Nº 160, de 1° de julho de 2022	Estabelece os limites máximos tolerados (LMT) de contaminantes em alimentos.

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2. OBJETIVOS

2.1 Objetivo Geral

Avaliar a percepção, conhecimento, atitudes e práticas dos consumidores em relação ao consumo do colágeno.

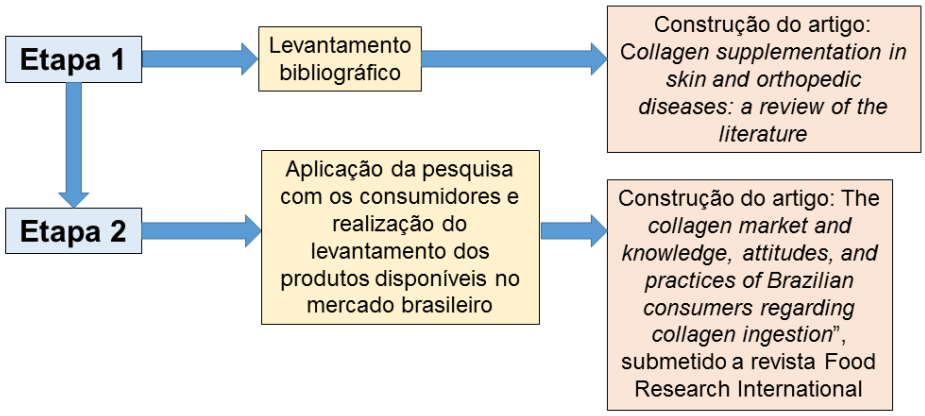
2.2 Objetivos Específicos

- Realizar revisão bibliográfica sobre a produção, tipos e benefícios do uso do colágeno na saúde, com foco no tratamento de alterações na pele e nas articulações.
- Identificar as características dos produtos de colágeno disponíveis no mercado.
- Avaliar a percepção, conhecimento, atitudes e práticas dos consumidores em relação ao consumo do colágeno e correlacionar estes dados com dados socioeconômicos.

3. ESTRUTURA DA TESE

Esta dissertação foi desenvolvida em etapas aqui detalhas como, capítulo I – artigo de revisão submetido à revista Heliyon – "C*ollagen supplementation in skin and orthopedic diseases: a review of the literature*", construído com o objetivo realizar uma revisão de literatura sobre as evidências científicas sobre os efeitos benéficos do consumo de colágeno no tratamento de doenças dermatológicas e ortopédicas. Após aprofundamento científico sobre a área deste estudo, a pesquisa central desta dissertação foi elaborada com a metodologia conhecimentos, atitudes e práticas associados a dados sociodemográficos, sendo a partir destes dados elaborado o capítulo II, estruturado no formato de um artigo: "*The collagen market and knowledge, attitudes, and practices of Brazilian consumers regarding collagen ingestion*", submetido a revista Food Research International. Por fim, no capítulo III consta a discussão geral da dissertação e no capítulo IV a conclusão geral.

Figura 3: Estrutura da dissertação



4. CAPÍTULO II

Artigo publicado na revista Heliyon

COLLAGEN SUPPLEMENTATION IN SKIN AND ORTHOPEDIC DISEASES: A REVIEW OF THE LITERATURE

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ABSTRACT

Collagen is one of the main components of the extracellular matrix of the dermis and articular cartilage and influences the body's mechanical, organizational, and tissue formation properties. Produced from food industry by-products, it is considered a nutraceutical product widely used as an ingredient or supplement in food, pharmaceutical, and cosmetic industries. This study aimed to conduct a literature review on the scientific evidence regarding the beneficial effects of collagen consumption in the treatment of skin and orthopedic diseases. Literature data have shown that hydrolyzed collagen supplementation promotes skin changes, such as decreased wrinkle formation; increased skin elasticity; increased hydration; increased collagen content, density, and synthesis, which are factors closely associated with aging-related skin damage. Regarding orthopedic changes, collagen supplementation increases bone strength, density, and mass; improves joint stiffness/mobility, and functionality; and reduces pain. These aspects are associated with bone loss due to aging and damage caused by strenuous physical activity. Thus, this review addresses the economic and health potential of this source of amino acids and bioactive peptides extracted from food industry by-products.

Keywords: skin, joint, bone metabolism, senescence, aging.

INTRODUCTION

The development of science, improvements and innovations in the field and industry of food and access to sanitation and education contribute to increase human life expectancy. However, access to these factors is not uniform worldwide, making it a privilege of developed countries, where life expectancy is higher than 80 years old while in some African countries, in 2019, life expectancy ranged from 53 to 76 years old[1]. The increase in life expectancy carries with it senescence, promoting progressive and cumulative functional and structural changes in the human body[2].

Collagen is a very important protein in the aging process, since it influences the structural, mechanical, organizational, and tissue-building properties of the body[3]. This protein interacts with cells by several families of receptors, regulating their proliferation, migration, and differentiation, and some types of collagen have a restricted distribution in tissues and, therefore, a specific biological function[4]. Besides being a source of amino acids, collagen products can perform a biological activity in extracellular matrix cells by their bioactive peptides, which justifies their application in dietary supplements and pharmaceutical preparations[5].

Collagen is extracted from industrial by-products, such as bones, cartilage, tendons, and the skin of cattle, pigs, chickens, fish, or other marine organisms, and may undergo a hydrolysis process to obtain bioactive peptides[6-8]. The variables and methods applied in protein hydrolysis influence the composition of the peptides present in the final product and can impact the molecular weight, the amino acid composition, and the solubility and functionality of the product[6-7, 9]. The molecular weight of collagen peptides can range from 0.3 to 8 kDa[10] and low-molecular-weight peptides usually have better bioactivity compared with higher-molecular-weight peptides[11]. According to Sibilla et al.[10], the advantage of using collagen hydrolysates over native collagen is their high digestibility rate, which contributes to increased absorption, distribution, and use in the human body.

The greatest beneficial effects of collagen peptides occur in populations with collagen degradation or at greater risk of developing this type of condition, such as bone and cartilage loss resulting from aging, or even from strenuous

physical activity, joint impact, excess weight, hormonal changes, trauma, burns, aggressive cancer therapy, and skin and dental implants[12]. Therefore, collagen can be considered a nutraceutical product, since, besides its nutritional function (amino acid supply), it promotes physiological benefits and protection against some diseases. Notably, collagen is a low-tryptophan protein, an essential amino acid for humans. The study by Bordin and Naves[13] showed that replacing 20% to 25% of this protein in the diet of male Wistar rats decreased feed efficiency and the bioavailability of high biological value proteins(casein) existing in their diet. However, Paul, Lesser, and Oesser[14] observed that adding up to 54% of collagen peptides to the standard American diet does not change dietary protein quality (PDCAAS equal to 0.75). The authors also indicate that collagen is a source of conditionally essential amino acids (glycine and proline), which are important in some physiological situations.

Considering the beneficial properties and clinical relevance of using hydrolyzed collagen for health promotion, this study aims to perform a literature review on the beneficial effects of the consumption of collagen peptides on skin and orthopedic changes. We searched articles from the PubMed and ScienceDirect databases using the following keywords: collagen, collagen supplementation, collagen supplement, dermatological alterations, and orthopedic diseases. We selected studies published from 2000 to 2022, including all research that has evaluated the effects of collagen (native or hydrolyzed) supplementation in clinical trials or experimental protocols without the addition of any other nutrient or substance.

STRUCTURE AND CHARACTERIZATION OF COLLAGEN

In mammals, 25% to 35% of the total protein mass corresponds to collagen [10]. To date, 29 types of collagen [15] have been described so far. In the human body, this protein can be found in bones, tendons, ligaments, hair, skin, and muscles[16]. Types I, II, and III correspond to 80% to 90% of the total collagen found in the human body[15] and type I is the most abundant in the skin (80%).Type III collagen corresponds to 15%[10]. In cartilage, type II collagen predominates (90–95%) in the formation of the extracellular matrix.

Other types of collagen (I, IV, V, VI, IX, and XI) contribute to the formation and stabilization of the type II collagen fibril network[17]. The sequence of amino acids and covalent structures found in the molecule, as well as post-transcriptional modifications in amino acid side chains by hydroxylation, glycosylation, and cross-linking, characterize the collagen structure[11]. The collagen molecule has a trimetric nature, allowing combinations of pro-α chains. The triple-helix structure is a common feature in collagen, which can vary its incidence from 96% for type I collagen to 10% for type XII collagen[4]. A single type of collagen can have multiple isoforms and supramolecular structures with multiple α chains, which increases the diversity of the existing family [4]. For example, type I collagen is mostly a heterotrimer of two α1 chains and one α2 chain, but it can also be a homotrimer of three α1 chains. Types II, III, and VII are exclusively homotrimers whereas type IV has six different α chains available for combination and production of several isoforms[15].

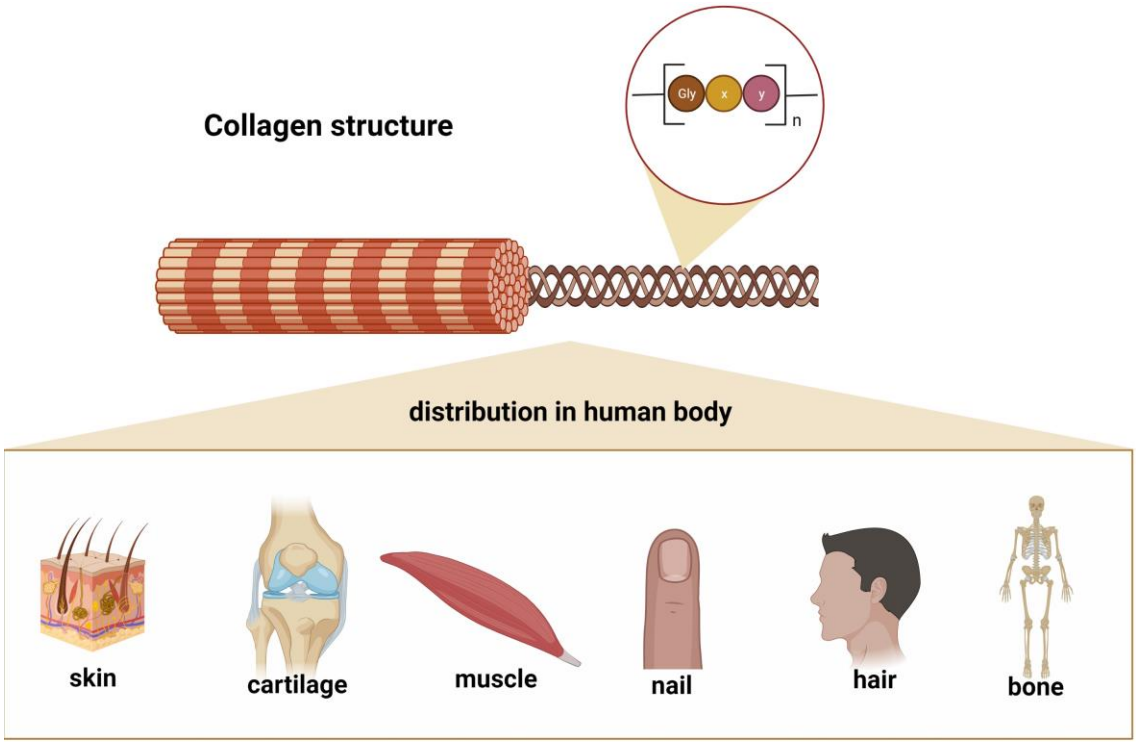

Figure 1. Chemical structure and organization of collagen. The sequence of amino acids $[Gly – X – Y]_n$ with and without interruptions is a characteristic of the collagen family and the amino acids proline and its hydroxylated form (hydroxyproline) occupy the X and Y positions. n: number of times that this sequence appears in the protein structure. Created by the authors using BioRender.com.

Besides the triple helix, the collagen family has two common characteristics: the repetition of amino acids $[Gly – X – Y]_n$ with and without interruptions, with the amino acids proline and its hydroxylated form (hydroxyproline) occupying the X and Y positions (**Figure 1**)[15].

DIGESTION AND ABSORPTION OF COLLAGEN

Similar to all proteins ingested as food or food supplement, when collagen is digested in the gastrointestinal tract, it releases amino acids and peptides in the small intestine to be absorbed. The degradation of the polymeric structure of collagen is the first step of digestion, and forms peptides, especially dipeptides, tripeptides, or free amino acids. Before the ingested components reach the blood, they cross many barriers, such as enzymatic degradation and affinity for membrane transporters[18]. During digestion, several proteases existing in the small intestine, such as the pancreatic protease, and peptidases are involved in the degradation of the polymeric structure of proteins[10]. Possibly, the presence of proline and hydroxyproline in its structure is responsible for the formation of bioactive peptides, since both provide resistance against the action of proteases, limiting hydrolysis[19]. The bioaccessibility of amino acids and peptides in the intestine, their absorption rate and availability in the bloodstream define their bioavailability for the regulation of metabolic processes in target tissues[20].

According to Daniel[21], protein digestion results in a huge variety and quantity of short-chain peptides (di- and tripeptides), which are absorbed intact by the PEPT1 peptidyl carrier protein. Peptide transport is enantioselective, involving variable proton-substrate stoichiometry for peptides with neutral, mono-, or polyvalent charge[21]. For many years, only amino acids, di-, and tripeptides were believed to be absorbed in the intestine. However, as Urao[22] showed in his study a different pattern of intestinal permeability for particles with different molecular weights, the literature currently presents different absorption mechanisms, showing that oligopeptides can also be absorbed by passive diffusion across cell junctions[23]. According to Sibilla et al.[10], considerable evidence shows that peptides can be absorbed, since Pro-Hyp is the main dipeptide found in human plasma after ingestion of hydrolyzed collagen.

Yazaki et al.[24] identified by chromatography 17 collagen-derived peptides in the serum of adults (31.5 ± 6.5 years), especially high levels of the Gly-Pro-Hyp tripeptide after seven days of daily consumption of 300 mg/kg of hydrolyzed collagen. A similar study by Shigemura et al.[25] identified by chromatography peptides with hydroxyproline (Pro-Hyp) in blood after consumption of hydrolyzed collagen. Moreover, the authors showed the maximum concentration of collagen peptides in blood two hours after oral ingestion, with a subsequent decrease in serum concentration after this period. The maximum absorption data obtained by Shigemura et al.[25] corroborate the study by Iwaia et al.[26], who found the maximum concentration of peptides one to two hours after oral ingestion of hydrolyzed collagen, with the concentration decreasing by half after four hours. These results confirm the resistance of proline and hydroxyproline to the action of proteases in the intestine.

ORAL SUPPLEMENTATION OF HYDROLYZED COLLAGEN IN THE TREATMENT OF SKIN CHANGES

The skin is the largest organ in the human body and represents the main barrier to the external environment. Collagen, elastin, and hyaluronic acid are the main components of the skin and play an important role in maintaining its structure and hydration. Skin collagen is mainly produced by fibroblasts[10], which produce three components of the extracellular matrix of the dermis: collagen fibers, elastic fibers, and proteoglycans. The collagen-rich extracellular matrix builds and repairs the structure of skin components and collagen is the most abundant connective tissue in the dermis, besides being responsible for its strength and resilience[27-28].

However, individuals live under the constant influence of internal and external factors, which affect their aging process and some factors contribute to damage or loss of skin functionality (**Figure 2**). Solar and ultraviolet radiation, air pollution, tobacco smoke, poor nutrition, and the use of cosmetic products are examples of external or environmental factors[29]. In turn, intrinsic changes occur due to genetic determinants that differ between groups and different anatomical sites in the same individual.

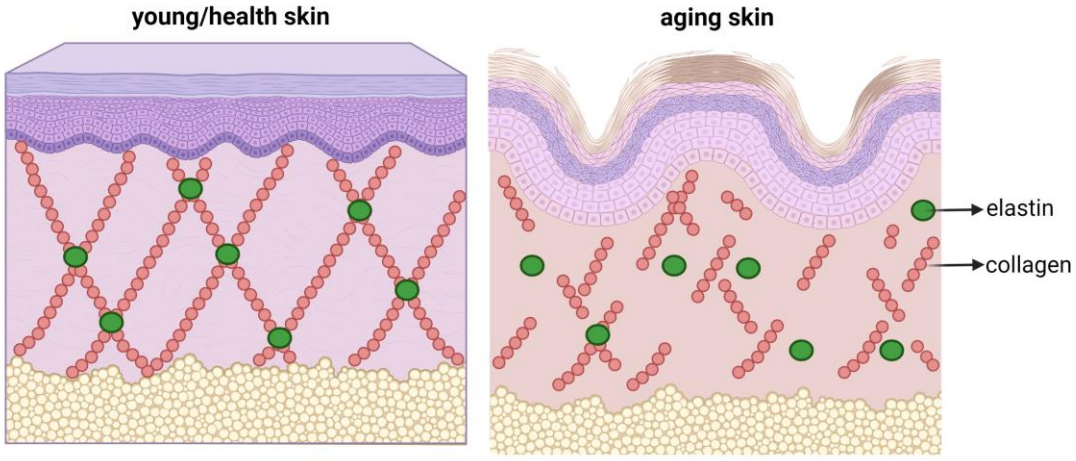

Figure 2. Skin structure and the effect of aging. The interaction between collagen and elastin guarantees skin strength and elasticity, however, with aging or due to exposure to other extrinsic factors (nutrition, sun exposure, infrared radiation, visible light, air pollution, for example), collagen production decreases, destabilizing this interaction and, consequently, reducing strength and skin elasticity. Created by the authors using BioRender.com.

According to Fensk[30], in the different layers of the skin, intrinsic aging causes structural and functional changes, making the skin thinner and, thus, reducing its protective barrier function. Moreover, Rittié and Fisher[31] state that changes in the structure of type I collagen (the most abundant structural protein in the skin) is a sign of a chronologically aged and photo-aged human skin and contributes to a decrease in its resistance and, consequently, wrinkle formation. Aging leads to a decrease in both the number of collagen bundles in the skin and their synthesis [32]. Lupu et al.[8] also suggest that these changes may contribute to increased skin flaccidity, fragility, and dryness. Aging can also interfere with wound healing, skin pigmentation, vasculature, and immunity[31].

As aforementioned, several situations can lead to loss of collagen in the skin. **Table 1** shows the beneficial effects of consuming oral hydrolyzed collagen supplements on skin changes based on scientific research. According to Sibilla et al. [10], in the dermis, hydrolyzed collagen has a dual-action mechanism, either providing amino acids for the synthesis of endogenous collagen and elastin fibers or stimulating the production of new collagen, elastin, and hyaluronic acid by bioactive peptides binding to fibroblast membrane

receptors. These data can be explained by histological evidence. Czakja et al.[33], in their study on hydrolyzed fish collagen supplementation, showed by histological analysis changes in the skin structure with reduced solar elastosis and improved organization of collagen fibers. Using another source of collagen extracted from fish (*Pangasius hypophthalmus*), Evans et al.[34] evaluated 85 women aged 45 to 60 years in a 12-week randomized clinical trial. By administering 10g of hydrolyzed collagen (Vinh Wellness Collagen, Vinh Hoan Corporation), the authors observed improvement in skin elasticity, hydration, brightness, firmness, and the presence of wrinkles.

Choi et al.[35], after evaluating 11 randomized clinical trials in their systematic review, showed that the consumption of oral hydrolyzed collagen supplement increases skin elasticity, hydration, and collagen density, improves wound healing, and protects the skin against aging. Barati et al.[36], in their systematic review, analyzed 10 randomized clinical trials and concluded that the consumption of both intact and hydrolyzed collagen improves clinical manifestations of skin health by either increasing the synthesis of extracellular matrix or the interaction of regulatory T-cells and type 2 macrophages in maintaining the skin immune response to endogenous collagen. De Miranda[37], in their systematic review and meta-analysis, corroborates the previous results, as the analysis of 19 studies (1,124 patients) showed that after 60 to 90 days of collagen consumption, skin elasticity and density increased and facial wrinkles reduced. However, the authors observed a great heterogeneity between studies, especially regarding the type of collagen used, treatment time, and dose.

Rustad et al.[38] highlights the importance of a critical evaluation of the literature, since the authors relate their results to studies with small samples and a great variation in administered doses, consumption time, and types of products (different hydrolysis processes generate different peptides). Moreover, conflict of interest is an essential issue, as many studies are funded by collagen-producing industries. Collagen, as well as other nutritional supplements, acts as an adjuvant in the treatment. Therefore, considering all the intrinsic and extrinsic factors that contribute to senescence, changes in lifestyle and environment are also important for the prevention and treatment of skin changes.

Among the studies presented in **Table 1 and 2**, the results regarding skin changes are associated with the consumption of bioactive collagen peptides, since all studies used hydrolyzed collagen or peptides in their clinical trials and experimental protocols. Although the interest of men in the field of aesthetics has increased in recent years, all studies were carried out only with women, mostly aged 30 to 60 years, with a variation in treatment time (8–12 weeks) and administered dose (1–10g/day). Thus, despite evidence that the consumption of hydrolyzed collagen can help minimize skin changes, especially those associated with aging, no study presented follow-up results, such as how long the changes last after 12 weeks of supplementation or the existence of any nutritional or physiological damage to the chronic collagen consumption. These and other questions remain open and unanswered.

Table 1: Studies that used collagen supplementation in the treatment of skin changes.

Collagen	Design	Population (n)	Period	Dose/day	Result	Reference
HC derived from fish (*Pangasius hypophthalmus*)	T-RCT	Women 45-60 years (45)	12 weeks	10 g	face wrinkles score; elasticity, hydration, shine, and firmness	[34]
HC containing dipeptides (Pro-Hyp and Hyp-Gly)	D-RCT	Chinese healthy women 37-48 years (56)	8 weeks	2.5 g	↑ skin hydration; ↑ facial skin elasticity; ↓ facial skin roughness	[68]
HC had a low ratio of dipeptide-to-product content (L-CP) and a high ratio of dipeptide-to-product content (H-CP)	D-RCT	Chinese women 35 to 55 years (85)	8 weeks	5 g	↑ skin moisture; ↓ wrinkles area; ↓ roughness H-CP intake additionally ↓ number of wrinkles; ↓ wrinkle depth	[69]
CP with 15% tripeptide form	S-RCT	Healthy Korean women and men 30 to 48 years (32)	12 weeks	3g	↑ stratum corneum hydration; ↔ TEWL; ↑ skin elasticity; ↔ skin erythema and pigmentation	[70]
CP of fish origin (PeptanF) and porcine origin (PeptanP)	D-RCT	Adult and middle-aged Japanese women 40–59 years (33)	8 weeks	10g	↑ skin hydration	[71]
HC with peptides of various sizes of swine-origin of the brand VERISOL@	D-RCT	Women 35-55 years (69)	8 weeks	2.5 to 5 g	↔ between the two collagen dosages; ↔ skin moisture and water evaporation; ↔ smoothness of the skin; ↑skin elasticity	[80]
HC containing more than 15% tripeptides, including 3% of Gly-Pro-Hyp.	D-RCT	Women 40–60 years (53)	12 weeks	1.0 g	↑ hydration after 6 and 8 weeks of treatment; visual wrinkle after 12 weeks; skin elasticity (general elasticity and liquid elasticity) after 12 weeks	[81]
CP derived from fish scales (NittaGelatin Inc., India)	D-RCT	Healthy women 40-51 years (71)	12 weeks	3.0 g	skin moisture; elasticity (crude, liquid, and biological elasticity); roughness.	[82]

HC: hydrolyzed collagen; CP: collagen peptide; T-RCT: randomized triple-blind placebo-controlled clinical trial; D-RCT: randomized double-blind placebo-controlled clinical trial; S-RCT: randomized single-blind controlled clinical trial; ↑: increase, ↓: decrease; ↔: no difference; TEWL: transepidermal water loss.

Table 2: Studies on the effect of the consumption of hydrolyzed collagen in animal models.

Collagen	Animal Model	Period	Dose/day	Result	Reference
Type I - H	Male C57BL/6J mice (OA)	12 Weeks	Standard feed plus Type I-H bovine (200 Da) 3.8mg or 38mg	↑cartilage area; ↑chondrocytes; ↑proteoglycan matrix; ↓apoptosis; ↓MMP13 protein; ↓synovial hyperplasia and TnfmRNA; ↓inflammation	[47]
HC	Three months of age female Wistar rat (OVA)	8 Weeks	Standard diet formulated according to AIN 93-M plus 5 or 10 times the recommended human consumption of HC calculated according to rat weight, dietary protein content 13.15% and 14.30%	↑bone mass; ↑osteocalcin; ↑mechanical strength of the vertebrae; ↑vertebrae protein content	[62]
HFC	Five-week-old male Wistar rat in growth phase undergoing exercises	11 Weeks	Diet with 20% protein, 30% HC (1KDa) or diet with 40% protein, 30% HC (1KDa)	↑bone mass; ↔bone strength; ↑ exercise effect	[63]
CP	Eight-week-old maleSprague-Dawley rats (OA)	12 weeks	Gavage 0.8 g/kg.bw or 1.6 g/kg.bw Atlantic salmon (*Salmo salar*) CP	↓serum IL-6 and IL-17; ↓ cartilagem IL-1βand TNF-α; ↓cartilagedegeneration	[77]
HC	Nine-week-oldfemale Hos:HR-1 hairless mice exposed to UV-B irradiation	11 days 7 weeks	Gavage 2.0 g/kg.bw of fish scale HC Diet with 2 g of fish scale HC per 100 g of the AIN-93G diet	↓ TEWL on days 2, 3, and 4 ↓ TEWL at weeks 4 and 6; ↑ water content at weeks 2, 4, and 6; ↑ skin elasticity at week 6; ↑ dermal hyaluronic acid content	[78]
CTP	Five-week-old female hairless mice (SKH-1) exposed to UV-B irradiation	14 weeks	Gavage 167 mg/kg/day or 333 mg/kg/day	↓ wrinkle formation induced by UVB irradiation; ↓ collagenase (MMP3 and -13) and gelatinase (MMP-2 and -9); ↓ skinfold thickness; ↑ skin hydration; ↑ collagen fibers and hydroxyproline; ↑ skin elasticity; ↓ erythema formation	[79]

↑: increase; ↓: decrease; ↔: no difference; HC: hydrolyzed collagen; type I-H: hydrolyzed type 1 collagen; HFC: hydrolyzed fish collagen; CP: collagen peptides; CTP: collagen tripeptide; OA: osteoarthritis model; OVA: ovariectomy; BW: body weight; Tnf-α mRNA: tumor necrosis factor–messenger ribonucleic acid; MMP13 protein: matrix metallopeptidase 13; AIN-93-M: American Institute of Nutrition; TEWL: transepidermal water loss; IL-6: interleukin-6; IL-7: interleukin-7; IL-1β: interleukin-1β.

ORAL SUPPLEMENTATION OF HYDROLYZED COLLAGEN IN THE TREATMENT OF ORTHOPEDIC ALTERATIONS

The loss of collagen in osteoarticular tissues is a physiological phenomenon of multifactorial etiology and its intensification is related to senescence, hormonal profile, adiposity, inflammatory processes, immobility, mechanical overload, and joint damage[39-40]. Physical activity is regarded as a modifiable protective factor for the loss of collagen and many other comorbidities[41]. However, factors inherent to physical exercise, such as contact, impact, repetitive strain, and joint overload, increase the chance of joint injuries in active individuals[40].

Joints can be affected by several pathological conditions. Osteoarthritis is the most prevalent and can be characterized by slow and gradual cartilage degradation and joint space narrowing. This condition can evolve over decades and pain and progressive loss of joint function are the main symptoms[40, 42]. Joint discomfort, usually associated with pain, reduces mobility and the ability to perform routine tasks, directly affecting the individual's quality of life, especially when it occurs in the hips, knees, and lower back[43].

Joint diseases have no effective cure, so current resources focus mainly on reducing pain, inflammation, and joint stiffness[42]. In general, joint damage induces microlesions in connective tissue and reduce the ability of fibroblasts to synthesize new tissue (negative nitrogen balance), creating a deficit in the renewal rate (catabolic processes predominate over anabolic processes) and leading to degeneration of tissue matrix[40]. This deficit, along with joint biomechanical/functional stress, can induce an inflammatory response, which, in turn, can worsen, ultimately evolving into the irreversible loss of joint functional capacity [44].

Collagen is a low biological value protein, since its amino acid composition is poor in essential amino acids. However, it has a positive intrinsic value because its amino acid composition is equivalent to that of human connective tissue. Cartilage consists primarily of the extracellular matrix, a network of proteins, such as type II collagen, interacting with polysaccharides, such as hyaluronic acid and chondroitin sulfate—all synthesized and secreted by chondrocytes. During normal cartilage restoration (metabolism) in healthy

joints, the rate of extracellular matrix production balances with its degradation rate, ensuring homeostasis achieved by continued cartilage restoration[45].

C-terminal cross-linked telopeptides of type II collagen (CTX-II) are one of the main cartilage degradation biomarkers. CTX-II levels are high in patients with joint diseases, but also elevated by strenuous exercise, high-impact activities, high in postmenopausal women and individuals with overweight/obesity[44-46].

Ruff et al.[44] found that the treatment with 0.5g of hydrolyzed collagen from eggshell membrane significantly mitigated CTX-II levels. Moreover, the consumption of hydrolyzed collagen caused a reducing effect on biomarkers of muscle damage, inflammation, and apoptosis[47-48]. However, for Konig et al.[49] and Clifford et al. [50], CTX-I and B-CTX levels remained unchanged after treatment with hydrolyzed collagen.

Despite this, evidence supporting the idea of consuming hydrolyzed collagen to reduce joint pain has been increasing (**Table 3**). The popularization of studies on pain reduction is mainly related to the easy application and low cost use of the visual pain scale, making its implementation possible in a large number of studies. Furthermore, its self-applied results are similar to those obtained by experts[51].

Most interventional clinical studies show significant pain reduction compared with placebo/control groups[44, 50-56] and improved joint stiffness/mobility, both immediate [43-44, 53, 56] and for joint stability and recovery[57], except for the studies by Bruyère et al.[58], who observed no significant differences between groups, and Lopez, Ziegenfuss, and Park[48], who found an increase in pain in the intervention group and a reduction in the circulation of damage markers. Notably, the perception of pain can be hyperactivated by pro-inflammatory cytokines[44]. Furthermore, the reduction of muscle damage corroborates the findings of Clifford et al.[50], who found better muscle recovery resulting from the consumption of hydrolyzed collagen.

Table 3: Studies with functional and biochemical changes induced by the consumption of hydrolyzed collagen.

Collagen	Design	Population (n)	Period	Dose/day	Result	Reference
HC	D-RM	Young men 19-29 years (24)	1 week	20g	↓pain; ↑ muscle recovery (48 hours after exercise); ↔β-CTX; ↔P1NP; ↔bone collagen inflammation and synthesis	[50]
BioCP	D-RM	Young athletes 18–30 years with knee discomfort during sport, both gender (139)	12 weeks	5g	↓pain related to physical activity; ↔ pain at rest; ↔mobility; ↓ other medication options after BCP treatment	[51]
UC-II	D-RM	Adults 40–75 years with OA, both gender (186)	25 weeks + 5 days	0.4g	↓WOMAC; ↓pain; ↓stiffness; ↑mobility; ↓VAS score; ↓ LFI Score,↔ serum markers and knee flexibility	[53]
HC (Biocell Collagen®)	D-RCT	Adults 40–70 years with OA, both gender (68)	10 weeks	2g	↓pain (VAS score); ↓WOMAC; ↑PA	[55]
Type II	D-RCT	Adults 18-65 years with RA, both gender (454)	24 weeks	0.1 mg	↓pain; ↓joint stiffness; ↓ number of tender and swollen joints; ↓HAQ	[56]
SCP	D-RCT	Athletes 26.9 ± 9.1 years with ankle instability, both gender (50)	24 weeks	5g	↑ subjective ankle stability; ↓ joint injuries over time; ↔ankle stiffness; ↔feeding behavior	[57]
HC	D-RM	Caucasian adults 50 years or over with joint pain, both gender (144)	24 weeks	1.2g	↔pain; ↑clinical response (VAS score)	[58]
PCP and BCP	D-RCT	Adults and middle-aged individuals 30-65 years diagnosed with knee OA, both gender (30)	13 weeks	5g	↓ WOMAC, VAS and QOL	[72]
CP (Peptan B2000®)	D-RCT	Middle-aged to elderly individuals 50-75 years physically active, both gender (167)	12 weeks	10g	↔ knee joint pain and knee function	[73]
HC	D-RCT	Young adults 20.1 ± 1.47 years, physically active, both gender (72)	24 weeks	10g	↓ joint pain; ↓ use of alternative therapies	[74]
HC (Fortigel®)	D-RCT	Middle-aged to elderly individuals 49 years or older with mild to moderate severity knee OA (29)	48 weeks	10g	↑dGEMRIC score in medial and lateral tibial cartilage regions	[75]

HC (Colnatur®)	RCT	Middle-aged to elderly individuals 48-70 years with light symptomatology OA (207)	6 months	10g	↓ VAS for knee pain; ↓ WOMAC pain score	[76]

↑: increase; ↓: decrease; ↔: no difference; Type II: type II collagen; HC: hydrolyzed collagen; SCP: specific collagen peptides; UC-II: undenatured type II collagen; BioCP: bioactive collagen peptides; PCP: pork skin collagen peptide; BCP: bovine bone collagen peptide; RCT: randomized clinical trial; S-RCT: randomized single-blind clinical trial; D-RCT: randomized double-blind clinical trial; D-RM: randomized double-blind multicenter study; RA: rheumatoid arthritis; OA: osteoarthritis; HAQ: Health Assessment Questionnaire; VAS: Visual Analogical Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; LFI: Lequesne Functional Index, PA: physical activities; P1NP: terminal propeptide of type 1 procollage; β-CTX: C-terminal telopeptide of type 1 collagen; QOL: quality of life scores; dGEMRIC: delayed gadolinium-enhanced MRI of cartilage.

Traditionally, delayed onset muscle soreness is explained by myogenic factors, however, the interest in understanding the role of injury for other extramuscular connective tissue elements (such as extracellular matrix, basal lamina, types I, III, IV, and VI collagen, proteoglycans/glycosaminoglycans, muscular layers, and tendons) in delayed onset muscle soreness has been increasing[48]. The perception of musculoskeletal pain limits the performance of repetitive activities, reduces range of motion, and decreases strength production[44, 50].

Reduced pain and increased joint functional capacity improve functionality indices (**Table 3**). Several collagen intervention models showed a significant reduction in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC index) and other indices[52-55, 59]. However, Hewlings, Kalman, and Schneider[43]found no significant changes in functional tests.

Besides functional aspects, collagen consumption positively influences the entire osteoarticular structure (**Table 2**; **Table 4**). Collagen peptides have shown a positive effect on bone strength and mineral density, supporting the idea of effectiveness for diseases that debilitate these structures, such as osteoporosis. Human and animal studies have observed increased bone mineral density[49, 60-61], bone mass[62-63], and cartilage volume, besides a higher number of chondrocytes[47]. Collagen consumption in the growth phase can help bone formation [60] and increases muscle mass, strength, and motor control[64-67].

Table 4: Studies with changes in body composition induced by the consumption of hydrolyzed collagen.

Collagen	Design	Population (n)	Period	Dose/day	Result	Reference
SCP	D-RCT	Postmenopausal women 64.3 ± 7.2 years (102)	48 weeks	5g	↑BMD of the spine and femoral neck; ↑P1NP	[49]
SCP	D-RCT	Pre-menopausal women 29-48 years (77)	12 weeks	15g	↑muscle mass; ↑ hand pressure strength; ↓FM; ↑ leg strength gain	[64]
CP	D-RCT	Recreationally active young men 24 ± 3 years (57)	12 weeks	15g	↑muscle mass; ↑strength; ↔fCSA	[65]
CP	D-RCT	Young men 24.2 ± 2.6 years (25)	12 weeks	15g	↑muscle mass; ↑strength; ↑body mass; ↑ proteins related to contractile fibers	[66]
CP	D-RCT	Elderly people 72.2 ± 4.7 years with sarcopenia (53)	12 weeks	15g	↑muscle mass; ↑IQS; ↑muscle strength; ↑ loss of FM	[67]

↑: increase; ↓: decrease; ↔: no difference; D-RCT: randomized double-blind clinical trial; CP: collagen peptides; SCP: specific collagen peptides; BMD: bone mineral density; P1NP: procollagen type I N-terminal; PINP: amino-terminal propeptide of type I collagen; FM: fat mass; IQS: isokinetic quadriceps strength; fCSA: muscle fiber cross-sectional area.

However, the effects of hydrolyzed collagen depend on the concentration, experimental conditions, and characteristics of the hydrolysates tested[51, 61]. In the studies analyzed native collagen was used as an oral tolerance protocol, seeking to reduce the inflammatory response to collagen compounds in a scenario where consumption by itself leads to an inflammatory response. The doses of native collagen were small (0.01–0.0001g/day) but effectively generated positive results in functional and biomolecular aspects (**Table 3**). Studies with larger amounts of collagen hydrolysates (2–20g) aimed to induce an anabolic response of osteoarticular tissues (**Table 3**; **Table 4**). The anabolic effect can counteract the wear processes of cartilage tissue and, thus, the decreased degradation of the extracellular matrix could reduce pro-inflammatory and pain-stimulating processes. Moreover, a direct anti-inflammatory potential of collagen peptides can decrease joint pain intensity, since collagen peptide supplementation inhibits glycine-mediated cytokine release[51].

Despite the evident benefits of collagen consumption, studies present several relevant differences that deserve further discussion, such as the type of collagen used, dose, and the optimal time for consumption. These variations in experimental protocols (target population, sex, dose, duration of treatment, presence, or absence of orthopedic alterations) contribute to the lack of agreement on the observed results. Furthermore, a better understanding of the physiological mechanisms that promote these benefits is still required [20]. Therefore, considering the positive effect of collagen consumption on joint diseases and physiology and the wide variety of intervention protocols, future clinical studies should better address guidelines regarding the optimal dose for consumption, the type of collagen, and duration of intervention.

CONCLUSION

The loss of collagen can be influenced by intrinsic factors, such as genetics, or extrinsic factors, such as nutrition, sun exposure, infrared radiation, visible light, air pollution, and strenuous physical activity. The loss of collagen in osteoarticular tissues and skin is related to senescence, hormonal profile, adiposity, inflammatory processes, immobility, mechanical overload, and joint

damage. The literature shows that collagen supplementation can be beneficial in the treatment of skin changes, reducing wrinkles; increasing skin elasticity, hydration, firmness, and brightness; decreasing pores and solar elastosis; and increased collagen synthesis density and skin content. The use of collagen in the treatment of orthopedic alterations increases bone strength, density, and mineral mass; decreases extracellular matrix degradation; inhibits inflammatory cytokines; improves joint stability, functional capacity, and stiffness/mobility, and muscle recovery; reduces pain; and mitigates markers of joint cartilage degradation. These results show the economic and health-promoting potential of this product extracted from food industry by-products. We emphasize that future studies should address remaining gaps regarding signaling pathways and obtain bioactive peptides from intact collagen for health promotion.

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5. CAPÍTULO III

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THE COLLAGEN MARKET AND KNOWLEDGE, ATTITUDES, AND PRACTICES OF BRAZILIAN CONSUMERS REGARDING COLLAGEN INGESTION

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ABSTRACT

Collagen is considered a nutraceutical, and its consumption has been expanding due to the increased life expectancy, rising per capita income, and increased consumer awareness of health care. This study aimed to evaluate consumers' perceptions, knowledge, attitudes, and practices about the consumption of collagen-based products by using an online questionnaire and to correlate them with socio-economic data. A market survey (pharmacy stores and online) was also conducted to evaluate the available products. In total, 275 participants answered the survey, 73.3% from the Southeast region, mostly female (84.0%). Most participants reported three months as the period of collagen intake (31.6%), and the consumption period was associated with the perception of the health benefits ($p<0.001$). Furthermore, the participants' knowledge and perceptions regarding collagen intake are frequently associated with dermatological and orthopedic changes. Collagen-based products supplementation is a growing market with a broad target audience (genders, age groups, and socio-economic levels). The commercial presentation of collagen has been diversified over the years, and powder collagen is the most consumed (52.7%) and cheapest compared with capsules, pills, or gummies. The results of the present study demonstrate that most consumers of this type of supplement associate its benefits with aesthetic care such as skin, hair, and nails, although the scientific literature has shown its effects in treating osteoarticular diseases, for example. Undoubtedly, the correct dose prescription, treatment time, and choice of product presentation must be analyzed carefully, as they significantly impact treatment results.

Keywords: collagen production; consumer perception; nutrition supplement; dermatologic diseases; osteoarthritis.

INTRODUCTION

The collective term collagen refers to a family of glycoproteins that make up a quarter of the protein mass of humans and other vertebrates (Sorushanova et al., 2019). The structure and different types of collagens are essential to provide mechanical stability, elasticity, and resistance to organs and tissues, also acting on their organization and shape (Ricard-Blum, 2011).

Collagen is one of the main components of the skin and plays an important role in maintaining its structure and hydration, also acting on the structure of nails and hair (Sibilla, Godfrey, Brewer, Budh-Raja, & Genovese, 2015; Subhan, Hussain, Tauseef, Shehzad, & Wahid, 2021). In bones and teeth, type I collagen is responsible for most of the organic matrix, providing resistance and rigidity to fracture; in tendons and ligaments, it transmits force to the muscles and bones and stores elastic energy, among other actions. Type II collagen is a critical component of articular cartilage (Fratzl, 2008).

Some population groups are at greater risk of collagen tissue deterioration due to factors related to age (generally over 40 years), excessive use of cartilage (sports and intense physical activity), and other circumstances such as being overweight, menopause, trauma, burns, dermal or dental implants, aggressive cancer treatments, smoking, nutritional deficiencies, and hormonal imbalances (Figueres Juher & Basés Pérez, 2015; Souyoul, Saussy, & Lupo, 2018). Concerning the skin, we observed a decrease in collagen type I and III syntheses from the second decade of life at a rate of 1 to 1.5% per year, which would justify the greater concern and consumption of collagen supplements by a population with a higher life expectancy (Marcos-Garcés et al., 2014; Reilly & Lozano, 2021).

The susceptibility to degradation and changes in collagen structure is associated with loss of skin elasticity, deterioration of cartilage and bones, and cardiovascular and respiratory dysfunctions (Panwar et al., 2018). These factors are strongly associated with human aging. As a result, the modern world population has shown greater interest in health care, which contributed to the collagen market, expanding the offer of products with claims of benefits to the health for people who suffer from diseases related to collagen loss and especially for older people (Reilly & Lozano, 2021).

In Brazil (Brasil, 2020) as well as in other parts of the world, collagen is considered a food supplement and may also be considered a nutraceutical in the consumer market (Kwatra, 2020), or a bioactive ingredient for nutricosmetic products (Asserin, Lati, Shioya, & Prawitt, 2015), and is widely used in the food, pharmaceutical, and cosmetic industries (D. Liu, Nikoo, Boran, Zhou, & Regenstein, 2015). In 2022, a global financial movement around collagen was worth US$ 9.1 billion and had an estimated Compound Annual Growth Rate (CAGR) of 10.2% between 2023 and 2030 (Grand View Research, 2023).

Most of the collagen products produced in Brazil come from by-products of the beef industry due to its high production for export (Silva & Penna, 2012). The key source of collagen is bovine, but it is possible to use different sources like porcine, chicken, fish, and marine algae. In 2020, the global collagen market produced 34.9% of products of bovine origin, which can be explained due to the high number of available cattle byproducts (Grand View Research, 2023). Using these byproducts (tendons, hides, bones, skin) to produce collagen is an alternative to improve the circular economy of this sector.

Collagen is an economically renewable source (Ali, Bahri, & Aykut, 2020) since its extraction adds value to by-products from the slaughter of animals, and this reuse is considered of great importance in the pursuit of a clean, sustainable, and circular economy (Masilamani, Madhan, Shanmugam, Palanivel, & Narayan, 2016; Schmidt et al., 2016). In this context, leather processing by-products are valuable materials due to their composition, consisting of ideal substances for producing gelatin and collagen peptides (Ali et al., 2020).

Considering the potential and growth of collagen consumption by the population, this study aims to identify collagen products available in the digital market in Brazil and evaluate the perception, knowledge, attitudes, and consumption practices of collagen consumers with a questionnaire online, seeking to correlate this information with socioeconomic data. The initial hypothesis is that collagen consumption is more often based on the benefits associated with skin maintenance and elasticity than its benefits associated with bone loss and joint maintenance.

MATERIALS AND METHODS

This study is a cross-sectional survey using a non-probabilistic convenience sample. Individuals aged 18 years or older who have already used collagen were included in the study, and individuals who had never used collagen were excluded. The survey questionnaire was pre-tested by 15 individuals before being disseminated on social networks (Facebook and Instagram) in groups that potentially use this type of supplement, such as athletes, runners, people with osteoarticular diseases, people with skin problems, etc. In addition, the invitation to participate in the survey was communicated by email, focusing on the snowball methodology. An exploratory approach was used to collect the characteristics of consumers of collagen-based products using the KAP method (Knowledge, Attitudes, and Practices). The knowledge, attitude, and practice (KAP) survey is a quantitative method based on a structured questionnaire that collects information or opinions from respondents regarding how much they know, feel and behave about a given concept or problem. The research was approved by the Ethics and Research Committee of the Universidade Estadual de Campinas (UNICAMP, CAAE: 47819121.0.0000.5404), and its activities were conducted from September 2021 to November 2021.

The questionnaire was built in Google Forms (**Supplementary Material)** extension and was structured in two parts: the first refers to questions characterizing the population with socioeconomic data, and the second with questions regarding knowledge, attitudes, and practices about the consumption of collagen. The knowledge section included questions about the benefits of collagen consumption known to individuals. These questions were elaborated based on data collected in the literature and advertisements with collagen products in Brazil since this type of information is more accessible to the population. The questions about attitude were directed to questions regarding the reasons for consuming collagen and the time of use. Finally, the practice was investigated using questions about the participants' perceptions regarding the benefits or improvement of their health status due to consuming collagen. The questionnaire was structured with open and closed questions in which the participants indicated their opinions. The purpose of the questionnaire is to capture what the participants said to provide evidence about the use of collagen, so there was no intention to identify right or wrong answers.

A digital market survey was also carried out on collagen-based products available for purchase on pharmacy websites and stores (all major drugstore chains were included), as well as advertisements on Instagram, Facebook and linked to influencers from January 2021 to January 2022 **(Supplementary Material).** Data were collected regarding the description of the label, type of collagen, brand, product presentation, suggested consumption portion, and price.

For research data analysis, Microsoft Excel 2013 and SPSS version 29 (IMB SPSS Statistics) software were used, and the qualitative statistical methods used were chi-square, and descriptive statistics. Descriptive statistics were used to present the data as frequencies, percentages, and means. To verify the association between KAP and sociodemographic variables, the Chi-square (χ^2) test was used.

RESULTS AND DISCUSSION

A total of 331 individuals answered the questionnaire, but only 275 were collagen consumers, with 56 questionnaires being excluded from the study (do not use collagen, respondents from other countries). The study showed a greater adherence of the female public 236 (84.1%). It is worth noting that Brazil ranks second in the world regarding plastic surgeries, many related to aesthetic issues (Michas, 2022). Although men's interest in appearance has grown in recent years, women are leaders in aesthetic and surgical procedures (Haag, 2011), which may be one of the reasons why this study attracted more female respondents. In addition, it is important to remember that collagen supplements are strongly associated with aesthetic treatment on social media. Despite being an online study with wide dissemination on social networks, since it is a survey conducted by researchers from the state of São Paulo, 73.3% of the participants claimed to live in the southeast region (**Table 1**).

Table 1. Sociodemographic characteristics of the participants (n = 275).

Variable		Number	Percentage
Gender	Female	231	84.0
	Male	44	16.0
Age	18-24 years	28	10.2
	25-30 years	40	14.5
	31-35 years	55	20.0
	36-40 years	41	14.9
	41-50 years	66	24.0
	> 50 years	45	16.4
Educational level	High School	48	17.5
	Undergraduate	90	32.7
	Postgraduate	137	49.8
Region	North	5	1.8
	Northeast	13	4.7
	Midwest	6	2.2
	South	50	18.1
	Southeast	203	73.3
Income	Up to 1 minimum wage	11	4.0
	1-3 minimum wage	73	26.5
	3-6 minimum wage	83	30.2
	6-9 minimum wage	43	15.6
	9-12 minimum wage	33	12.0
	> 12 minimum wage	32	11.6

*Value of 1 minimum wage in 2021 - R$1,100 (equivalent to U$$215.82).

The literature consistently provides information about the influence of age, gender, and educational level on food choices and behavior (Ares & Gámbaro, 2007). For women, nutrition plays a central role in the conception of health and, therefore, in the interpretation of product healthiness (Missagia, Oliveira, & Rezende, 2013). For the National Health Surveillance Agency of Brazil (ANVISA), food supplements are not considered medicines, and are intended for healthy people to provide the body with nutrients, bioactive substances, enzymes, or probiotics to

complement food (Brasil, 2020). However, for some consumers, taking supplements means doing something proactive, such as fighting aging consequences, maintaining/improving overall health, and replacing nutrients lost due to a health condition, diet, or aging (Food Standards Agency, 2018).

Although most of the respondents were female, the chi-square analysis showed no association between gender and age ($\chi^2(5) = 3.627$, $p < 0.604$), as well as gender and educational level ($\chi^2(2) = 4.512$, $p < 0.105$), which means that the samples have a homogeneous distribution.

This study did not observe a statistical difference between age groups regarding collagen consumption and reported consumption in adults aged 18 or older, including older adults. Candido et al. (2020), in their study on the consumption of nutricosmetics, including collagen, observed that the public that uses this type of product is mostly of women over 40 years old. Shahrin et al. (2020) also observed greater female participation (63.2%) analyzing the behavior of consumers of nutricosmetics aged between 31 and 40 years (35.3%), with 62.7% being bachelors with income mostly between 3001-4000 Malaysian Ringgit (Malaysian currency) equivalent to 2.5-3.4 minimum wages in Brazil (middle social class or C).

Reasons for the higher consumption of supplements by women around 40 years of age may be related to collagen reduction that occurs linearly at about 1% per year in adult life (Shuster, Black, & McVitie, 1975) and changes in skin components that are strongly related to skin modifications that occur during menopause. During this period, cellular components suffer from changes resulting from the decrease of hormones estrogen, estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), anti-Mullerian hormone (AMH), Inhibin B, and gonadotropin-releasing hormone (GnRH). Such changes result in a decrease in the water content, glycosaminoglycans, collagen, thickness, and elasticity of the skin, impacting all its layers (Reus, Brohem, Schuck, & Lorencini, 2020).

In their systematic review, Teoh et al. (2019) identified some factors that may influence the purchase decision of nutraceutical consumers, with the perception of health benefits, product safety, and advice from health professionals, friends and family as the most cited. In the study by Nathan et al. (2020), when interviewing consumers of dietary supplements in pharmacies, they observed self-medication in 75% of individuals, with only 13% using supplements recommended by physicians or

nutritionists. In our study, 47.3% of the individuals reported using collagen as recommended by a health professional, and 52.7% reported self-medication.

Despite being quite dangerous, many consumers of dietary supplements believe the practice of self-medication does not pose a health risk and consider it safe (Lopes, Coimbra, Costa, & Ramos, 2021). However, many should be more knowledgeable regarding drug-nutrient interaction, cost-benefit, or dietary supplement regulations (Tarn et al., 2014).

Vulnerabilities regarding the safety of dietary supplements, stricter regulations, and the increased awareness of the need for individual risk-benefit assessment and prescription by a health professional are aspects that must be evaluated and discussed, especially in the current scenario, in which food supplements have become routinely consumed. Therefore, health professionals must know how dietary supplements are available and how they can affect their patients' health and general well-being (Pence, Martin, & Bloomer, 2021).

Nutrivigilance systems linked to pharmacovigilance systems, such as those used in Europe, allow specialist health professionals to access risk analysis/management information and increase their attention to signs/symptoms of drug interactions with dietary supplements (Lopes et al., 2021). However, not all countries have this type of tool. In the present study, we observed a great variation regarding the time of consumption, types, and forms of collagen supplements available on the market, as well as a variety of results, which in a previous review of the literature showed only sometimes to be positive (Campos, Santos Junior, Pimentel, Carregã, & Cazarin, 2023). Therefore, even if there is no scientific evidence of adverse effects, a health professional should always guide the consumption of these supplements to obtain health benefits.

When evaluating the degree of knowledge regarding the health benefits associated with the consumption of collagen, most responses were related to dermatological and orthopedic benefits (41.9% associated with improvement in the skin, hair, and nails and 30.5% with a reduction in joint pain). On the other hand, 16.8% of the responses were associated with preventing bone loss and 10.8% with improving protein intake (**Figure 1**).

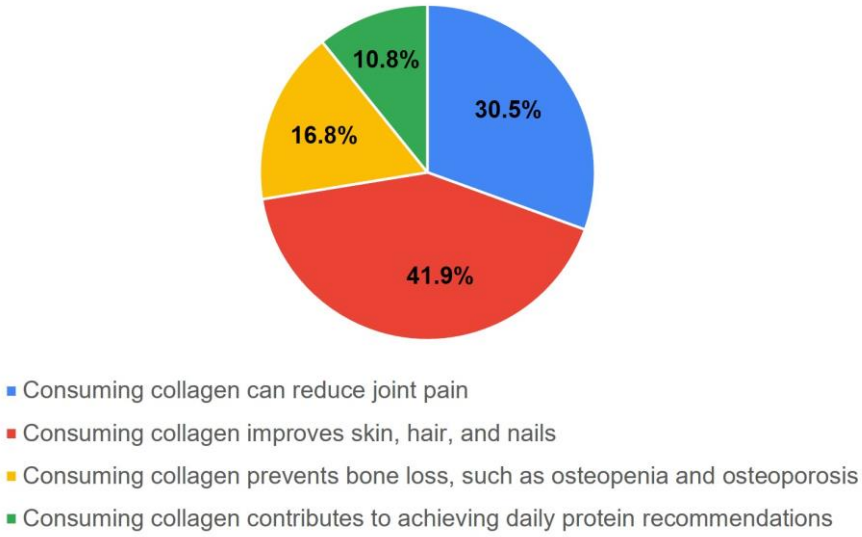

Figure 1. Knowledge reported by consumers regarding the benefits associated with consuming collagen products.

The perception of health benefits associated with consuming collagen-based products in our study is relatively high and positive (69.1%), with a statistical association between the period of consumption and the perception of benefit ($\chi^2(4) = 25.745$, $p < 0.001$ – **Table 2**). In this research, the time of collagen consumption was not associated with gender ($\chi^2(4) = 2.211$, $p < 0.697$), nor was the period of use associated with the indication of supplementation by a health professional ($\chi^2(4) = 7.610$, $p < 0.107$). A chi-square test of adherence was performed to investigate if the consumption period reported by the 275 participants showed a difference. The result demonstrates that the period of collagen consumption ($\chi^2(4) = 51.345$, $p < 0.001$), showed statistically significant differences, with three months being the period with the highest number of reports (**Table 3**). This result corroborates data from the literature that demonstrate the benefits of collagen after three months or more of consumption (Czajka et al., 2018; Evans, Lewis, Zakaria, Pelipyagina, & Guthrie, 2021; Kim, Chung, Choi, Sakai, & Lee, 2018; Koizumi et al., 2018). In a meta-analysis with 19 studies, Miranda et al. (de Miranda, Weimer, & Rossi, 2021) highlighted that 90 days of consumption was the time used by most studies to observe significant results on the skin, corroborating Honvo et al. (2020) that describe the period of three and six months as treatment time in most of the studies

included in their systematic review. Likewise, Khatri et al. (2021) observed in their systematic review that three months of adherence to collagen peptide supplementation are essential for the effect on joint function and recovery from joint injuries, especially in athletes.

Table 2. Evaluation of the association between the time of collagen consumption and the perception of benefit.

	Period of collagen consumption (months)				
Benefits perception	*Less than 1*	*For 1*	*For 3*	*For 12*	*> 12*
Yes (*n*)	9*	18*	64	37	62*
Adjusted residuals	-3.2	-3.3	1.1	1.1	2.6
Not (*n*)	14*	21*	23	12	15*
Adjusted residuals	3.2	3.3	-1.1	-1.1	-2.6

*p<0,001

Table 3. Report of the participants regarding the period of collagen consumption.

Period of collagen consumption	*N*	c^2 *(df)*
Less than 1 month	23	
During 1 month	39	51.345 (4)*
During 3 months	87	
During 12 months	49	
More than 12 months	77	

* p < 0,001; χ^2 *=chi-square; df = degrees of freedom*

Collagen mechanisms of action are still being researched. Some authors, such as Liu et al. (2019), describe the activity of hydrolyzed collagen in inhibiting reactive oxygen species, improving protein folding and DNA repair, and facilitating the synthesis of extracellular matrix proteins. Other literature data describe the reduction of cytokines and inflammatory markers (Song, Zhang, Luo, Zhang, & Li, 2018), the induction of regulatory T-cells with improved macrophage infiltration (Barati et al., 2020), and the motility and proliferation of fibroblasts (Sibilla et al., 2015), tyrosinase inhibition and antioxidant activity (Li et al., 2022) in addition to

mechanisms of competition for receptors and regulation of pathways by phosphorylation of kinases (Lian et al., 2019).

Thus, we can suggest that the functional mechanisms of collagen peptides improve cell function and extracellular tissues by direct and indirect mechanisms and that they may have cumulative chain and possibly simultaneous effects so that a more extended period of supplement intake appears to be essential for its effectiveness.

Among the benefits associated with consuming collagen-based products, the most cited were improvement in skin health 57.4% (increased firmness, elasticity, brightness, skin hydration; reduction of expression marks; nail strengthening; decrease in hair loss) and improvement in joint health 36.8% (decreased in joint pain including knee and spine, greater comfort in joint movements, among others). Also, some reports (5.9%), scarce in the literature, were observed regarding the perception of benefits after consuming collagen, such as weight loss, increase in lean mass, improvement in swelling, and improvement in sports practice. This result corroborates the data related to the participants' knowledge of the benefits of consuming collagen or collagen-based products. The knowledge reported by the participants may be closely associated with the benefits perceived after consuming the supplement. Also, evidence shows that consumers' knowledge is restricted to the benefits most explored by the media, that is, benefits to the health of the skin, nails, and hair, as well as joint health.

Furthermore, the description of skin health benefits corroborates the findings described in the systematic review by Barati et al. (2020), where the authors described that the administration of intact or hydrolyzed collagen could improve clinical manifestations in skin health. The meta-analysis by Miranda et al. (2021) also states that hydrolyzed collagen supplementation promotes favorable results regarding skin hydration, elasticity, and wrinkle reduction. Corroborating the results mentioned above, Miyashiro et al. (2022), in their systematic review, also point out that consuming collagen peptides can help reduce wrinkles and expression lines and improve skin hydration.

Improved joint health was the second benefit most reported by participants, as observed by Garcia-Coronado et al. (2019) in their meta-analysis, which observed a decrease in the Western Ontario Mc Master Universities (WOMAC) index and in the visual analog scale (VAS) parameters that assess the three-dimensional quality of

life (pain, joint stiffness, and physical activity) in patients with osteoarthritis, and pain intensity (Nascimento, 2017). Other systematic reviews describe different benefits such as improvement in joint pain (Khatri et al., 2021; X. Liu, Machado, Eyles, Ravi, & Hunter, 2018; Porfírio & Fanaro, 2016), improvement in joint functionality (Khatri et al., 2021), and articular cartilage protective effect (Porfírio & Fanaro, 2016).

Benefits for nails and hair after collagen supplementation have also been described in the literature, such as increased nail growth, decreased frequency of breakages (Hexsel et al., 2017; Yousif, Farshchian, & Potts, 2022), and improved appearance (Hexsel et al., 2017; Tyson, 1950; Yousif et al., 2022). Regarding the hair, some characteristics were observed after collagen supplementation, such as an increase in the proliferation of hair follicle cells, increased hair thickness (S. Oesser, 2020), and improvement in hair properties (Czajka et al., 2018).

After crossing the intestinal barrier and entering the circulation, peptides and amino acids from collagen digestion are available for metabolic processes in target tissues (Daneault, Prawitt, Fabien Soulé, Coxam, & Wittrant, 2017) such as skin, cartilage (Kawaguchi, Nanbu, & Kurokawa, 2012; Steffen Oesser, Adam, Babel, & Seifert, 1999), and bone tissue (Daneault et al., 2017). As previously stated, elucidating this trajectory and the possible implications is still necessary. However, we can suggest the action of collagen peptides in more than one tissue, providing simultaneous benefits or even possibly chain benefits in the same tissue as previously described. We emphasize that, among the 200 products found on the market, 73.5% had hydrolyzed collagen in their composition and the addition of other nutrients associated with collagen (vitamins, minerals, hyaluronic acid, β-carotene, lycopene, omega-3, for example).

Using supplemental collagen-based products can cover a new line of treatment for various diseases and for combating aging, in addition to osteoarticular and dermatological diseases. Therefore, new studies are needed to identify peptides, their metabolic functionalities, and specific large-scale production processes. Other aspects still being studied are the alteration of such products by digestive processes and possible interactions with nutrients and medications. However, the benefits of collagen-based products for health and for combating aging are undeniable.

For industries, investments in collagen-based products and process patents are extremely promising. Categorizing peptides and means of action makes products more specific, so that unique formulations can be created and targeted to certain clinical/individual conditions.

Collagen-based products supplementation is a growing market, which has a broad target audience (genders, age groups, and socioeconomic level), and the commercial presentation of collagen has diversified over the years with new patents on methods of production of collagen peptides, expansion of the national and international market, use of new sources of raw materials, and circular economy processes (Grand View Research, 2023).

The growing demand for collagen has driven the market by expanding its offer and diversifying its presentation form (powder, liquid, capsule, and gum). Powdered collagen is the product with the highest consumption (52.7%), followed by capsules (43.6%) and gummies (3.6%) (**Figure 2A**). According to Mukattash et al. (2022) ease of swallowing is the main concern of consumers when deciding on the type of food supplement to be consumed, followed by price and flavor. Therefore, diversifying the product presentation can be a strategy for companies to increase collagen consumption since consumers can choose the best way to include the supplement in their daily lives, increasing practicality and versatility at the same time. In the market analysis carried out in our study, we observed the offer of 200 collagen-based products available in Brazil (physical pharmacies and online purchases). Most products were in capsules or powder form (pots or sachets) (**Figure 2B**), which corroborates the data collected in the questionnaire in which we observed a higher consumption of collagen in capsule or powder presentation (**Figure 2A**). However, the cost of the capsules is 2.8 times higher than the products in the powder version. In agreement with our data, Domingues Junior et al. (2019) found that in the city of Jundiaí, in the state of São Paulo, 71.4% of the collagen products are sold in powder form. The offer of this type of product is very dynamic and new products can be constantly found on the market. We did not observe a correlation between forms of presentation/consumption (powder, capsules, and pills) and the gender of respondents in our study.

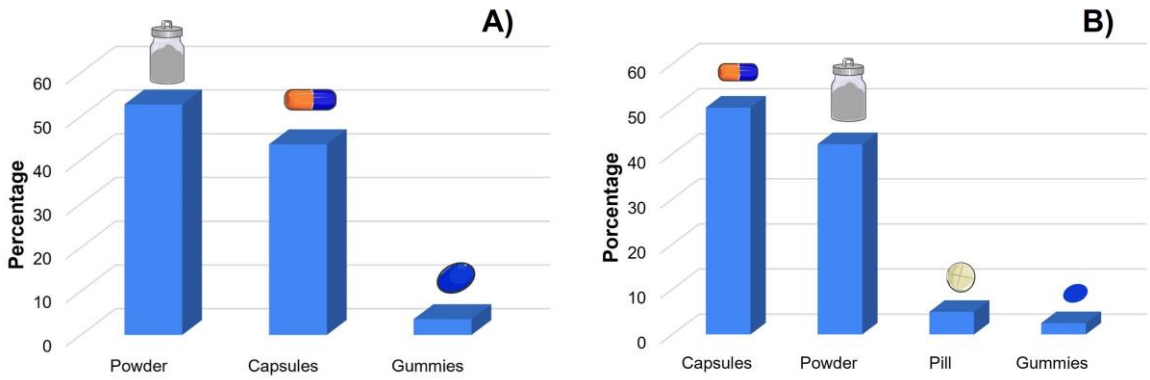

Figure 2. Different forms of collagen consumption reported by the individuals in the questionnaires (A) and available in pharmacy stores and online (B). The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under aCreative Commons Attribution 3.0 unported license (https://creativecommons.org/licenses/by/3.0/).

The greater supply of products in powder form may be correlated with greater ease of production and time savings compared with the manufacture of tablets, less addition of excipients, and fewer processing steps (Shanmugam, 2015). Powdered supplements can also be added to food or easily dissolved in hot or cold liquids, expanding the possibility of their use.

It is important to point out that 75% of the products observed on the market survey (**Supplementary Material**) had collagen in their composition associated with other elements, such as vitamins and minerals, among other substances. In this way, the results obtained from consuming this supplement cannot be directly associated with collagen since combining these substances can influence the final response.

We also investigate a homemade way to insert collagen into the diet by consuming bone soup/broth, which is widespread on social media but is also available for purchase (the last two questions in the questionnaire). Among the research participants, 39.6% reported having already consumed bone soup, and 78.9% believed that this soup could contribute to the collagen intake in the body. Recently, bone soup has stood out in the media and social networks, especially from bloggers and influencers, who have been associating its consumption with collagen intake. However, Alcock et al. (2019), using high-performance liquid

chromatography, compared the amino acid profile of standard bone broth and the therapeutic dose of reference collagen supplement, observing a significantly lower concentration of hydroxyproline, glycine, and proline ($p = 0.003$) and hydroxylysine, leucine, and lysine ($p = 0.004$) in the bone broth compared with a reference collagen supplement. Also, the authors conclude that the consumption of bone broth can scarcely influence the endogenous synthesis of collagen since the concentration of precursor amino acids for synthesizing new collagen is low. In addition, they reinforce that the variability in the concentration of amino acids in the broth can occur according to the preparation method, ingredients used, and the animal tissue source.

It is important to highlight that the present study brings interesting data regarding the consumption of collagen supplements in Brazil. This study was conducted during the COVID pandemic. Because of the restrictions imposed to counteract the disease dissemination, the KAP questionnaire was applied virtually, which is one of the weaknesses of the study. We believe that face-to-face interviews could have added a more detailed analysis of consumer behavior, a greater balance between genders, and access to lower-income individuals in the selection of participants. However, using digital resources allowed the inclusion of other regions in the study, which would demand a considerable investment for the research.

Finally, we can observe that expanding scientific knowledge about collagen products' potential seems promising and necessary. The consolidation of benefits concerning the supplementation of collagen-based products increases every day. Studies with greater population coverage and of longitudinal coverage become necessary in conjunction with meta-analyses so that its use is provisioned as a method that is not only curative but preventive. The results of the present study demonstrate that most consumers of this type of supplement associate its benefits with aesthetic care such as skin, hair, and nails, although the scientific literature has shown its effects in treating osteoarticular diseases, for example. The high consumption of collagen supplements through self-medication may be associated with the growing number of products on the market and advertisements and disclosures by influencers on social media. However, it should be noted that the practice of self-medication is not safe or even viable, as we observed in the market survey a considerable variation in the concentration of collagen or peptides in the products, as well as the type and presentation (native or hydrolyzed protein). Undoubtedly, the correct dose prescription, treatment time, and choice of product

presentation must be analyzed carefully, as they significantly impact treatment results.

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SUPPLEMENTARY MATERIAL

	Educational level		
Gender	*High School*	*Undergraduate*	*Postgraduate*
Female (*n*)	40	70	121
Adjusted residuals	-0.1	-2.0	1.9
Male (*n*)	8	20	16
Adjusted residuals	0.1	2.0	-1.9

	Income (Brazilian Minimum Wage)					
Gender	*Up to 1*	*1 to 3*	*3 to 6*	*6 to 9*	*9 to 12*	*> 12*
Female (*n*)	22	32	45	38	56	38
Adjusted residuals	-0.8	-0.7	-0.5	1.6	0.2	0.1
Male (*n*)	6	8	10	3	10	7
Adjusted residuals	0.8	0.7	0.5	-1.6	-0.2	-0.1

6. CAPÍTULO IV

DISCUSSÃO GERAL

O suplemento alimentar à base de colágeno vem passando por processos de reconhecimento científico, em relação a seus benefícios, dose, período de utilização, digestão, metabolismo, efeitos do produto em diferentes públicos, entre outros. O escopo desta pesquisa se baseou na análise do uso e conhecimento deste suplemento em diferentes públicos, analisados através de questionário de autopreenchimento fundamentado na metodologia KAP (knowledge, attitude, and practice - traduzido para conhecimentos, atitudes e práticas).

No início deste trabalho foi desenvolvido um levantamento bibliográfico com relação ao uso do colágeno no tratamento de alterações dermatológicas e ortopédicas. Deste levantamento foi elaborado o capítulo 2 “Suplementação de colágeno em doenças dermatológicas e ortopédicas” desta dissertação. Foram incluídos nesta revisão bibliográfica: revisões sistemáticas e metanálises, estudos desenvolvidos com modelos animais, estudos clínicos randomizados e controlados, entre outras fontes científicas. Foi possível observar nesta revisão bibliográfica o grande potencial econômico e de promoção de saúde deste suplemento ao detalhar uma variedade de benefícios ocasionada por sua suplementação, especialmente em relação às alterações dermatológicas e ortopédicas.

Sequencialmente, foi desenvolvida a pesquisa que deu origem ao capítulo 3, com objetivo de avaliar a percepção, conhecimento, atitudes e práticas dos consumidores em relação ao consumo do colágeno, produzindo desta maneira dados científicos sobre um público com estimativa de ascensão, sob consumo de um suplemento em processo de consolidação científica. A associação da metodologia KAP com características sociodemográficas, e dados sobre a percepção dos consumidores de suplementos alimentares à base de colágeno, possibilitou estudar os benefícios deste produto fora de um enquadramento pré-determinado em relação ao tempo ou outras características de estudos controlados.

Os resultados deste estudo geraram associações estatísticas sobre a percepção de benefícios dos consumidores de acordo com período de consumo de menos de 1 mês a mais de 1 ano, em conjunto com renda, escolaridade, prescrição de profissional habilitado entre outras variáveis. As análises estatísticas aplicadas nos dados obtidos sobre o consumo em relação ao tempo com uma amostra populacional significativa, nos possibilitou observar dados sobre o consumo de suplementos alimentares à base de colágeno em período superior a seis meses de duração, dados não comumente encontrados.

Embora a maior porcentagem de indivíduos do presente estudo seja do gênero feminino (84,1%), não houve associação estatística entre gênero e idade, assim como gênero e escolaridade, demonstrando uma amostra de distribuição homogênea. Esses dados contrastam os estudos sobre nutricosméticos de Candido et al. (2020) e Shahrin et al. (2020) que embora apresentem um maior público de gênero feminino, se diferenciam desta análise na variável idade dos participantes com maior incidência de indivíduos acima de 40 anos. A metanálise de Miranda et al. (2021) analisou 19 estudos com 1125 participantes entre 20 e 70 anos, sobre a suplementação de colágeno hidrolisado apontando 95% do gênero feminino com média de idade de 49,8 ± 5,68 anos no grupo intervenção.

A percepção de benefícios foi sentida por 69,1% dos participantes desta pesquisa e foi associada estatisticamente ao tempo de consumo ($p<0,01$) com maior apontamento a utilização do suplemento por 3 meses (31,6%), seguido daqueles que fizeram uso por mais de um ano (28%). O tempo de 3 a 6 meses parece ser um fator essencial para a funcionalidade do suplemento, sendo considerado essencial (Khatri et al., 2021). A partir de tal observação propomos no capítulo 3, utilizando como base os estudos sobre a síntese/funcionalidade do colágeno de Liu et al. (2019) , Song et al. (2018), Barati et al. (2020), Sibilla et al.(2015), Li et al. (2022), Lian et al. (2019) que a funcionalidade de peptídeos de colágeno está relacionada a sua atuação na função celular e nos tecidos extracelulares por mecanismos diretos e indiretos, possivelmente cumulativos, em cadeia e simultâneos o que justificaria o tempo necessário para a eficácia do suplemento.

Os benefícios mais descritos pelos participantes da pesquisa foram em relação a melhora da saúde da pele (57,4%) e melhora na saúde das articulações (36,8%). Os mesmos observaram na pele melhora da hidratação, elasticidade, firmeza, efeito antienvelhecimento e aparência em geral. Estes efeitos também foram descritos na metanálise de Miranda et al. (2021) e nas revisões sistemáticas de Miyashiro et al. (2022), Shenoy et al. (2022), e Choi et al. (2019). Já nas articulações observaram maior conforto nos movimentos articulares, melhora na mobilidade das articulações e diminuição das dores articulares incluindo joelho e coluna. Estes resultados estão de acordo com os estudos de Czajka et al., (2018), Khatri et al. (2021) e Lugo et al., (2013). A diminuição da dor parece ser o aspecto mais estudado, descrito pela metanálise de Garcia-Coronado et al. (2019), e pelas revisões sistemáticas de Khatri et al. (2021); Porfírio e Fanaro, (2016); Liu et al. (2018).

Embora benefícios em relação ao consumo de colágeno em alterações ortopédicas sejam a mais tempo reconhecidos pelo principal órgão regulamentador do país e este aspecto possua diversas pesquisas indicando sua eficácia, os resultados do presente estudo apontam que houve maior menção a percepção de benefícios em alterações dermatológicas entre os consumidores de colágeno como apontado na hipótese inicial desta pesquisa.

Neste contexto, muitas variáveis podem alterar a percepção do consumidor sobre o produto tanto em relação ao conhecimento, quanto aos seus benefícios, muitas vezes superestimados como: alegações não cientificamente formuladas, a influência das mídias sociais, erros e usos incorretos em relação ao conhecimento científico, a busca por opiniões (grupos, influencers, familiares, entre outros) o contexto informacional e do país, o marketing da beleza, crenças, a utilização de mídias sociais e tradicionais, a publicidade, entre outros vieses circunstanciais, (Cândido et al.,2020; Pereira-Filho et al.,2021;Arauzo et al., 2020; Rustad et al., 2021; Aschemann-Witzel e Grunert ,2015; Wongsuphasawat e Buatama, 2019; Saeed 2018; France et al., 2005; Sfodera et al.,2019). Segundo Lemos et al. (2022) a publicidade de alimentos permite a incorporação de valores que passam a ser indissociáveis do produto, o que pode representar um atributo de peso no consumo alimentar.

Os veículos informacionais podem expressar informações através de mídias sociais, as quais alcançam uma grande parcela da população. Deste modo à promessa de uma variedade de benefícios, divulgada amplamente, sobre os suplementos alimentares à base de colágeno para aumento da saúde da pele, possivelmente influenciaram a maior menção deste benefício no presente estudo.

Outras descrições relatadas pelos participantes da pesquisa incluíram benefícios sobre à saúde das unhas, como firmeza, resistência e aparência geral. Esses dados também foram descritos por Hexsel et al. (2017), Yousif et al. (2021), Farshchian, & Potts (2022). Quanto à percepção em relação aos cabelos (20,3%) os participantes descreveram, fortalecimento dos cabelos, diminuição da queda, aumento da velocidade de crescimento, entre outras, as quais faltam pesquisas para consolidação/corroboração destes dados. No entanto, podemos notar similaridade com os benefícios descritos por Oesser (2020) e Czajka et al. (2018) como aumento da espessura e a melhora nas propriedades do cabelo.

Na contextualização realizada acima foi possível a constatação de que os benefícios adquiridos com a suplementação de produtos à base de colágeno em

relação à saúde articular e da pele são mais estudados na literatura científica do que benefícios em relação à saúde de cabelos e unhas. A utilização de suplemento alimentar à base de colágeno para tratamento com objetivo de melhora das características de cabelos e unhas necessita de mais pesquisas e desenvolvimento da literatura científica.

O levantamento no mercado digital (farmácias físicas e compras online) realizado nesta pesquisa registrou 200 produtos disponíveis para os consumidores. Os produtos foram considerados de fácil disponibilidade de aquisição e apresentaram variedade comercial de marcas e formas de apresentação como gomas, comprimidos, pós e cápsulas. O maior percentual dos produtos disponíveis estava na forma de cápsulas 50,5%, seguido de pós 42%. Algumas marcas apresentaram diferentes formas de apresentação do produto com variação monetária. O cálculo estatístico da variedade monetária em relação a forma de apresentação resultou em diferença no perfil de custo de cápsulas, considerado 2,8 vezes superior ao custo dos produtos na forma de pó. A constante variedade de preços e sua flutuação, aliada a introdução de novos produtos no mercado podem promover alteração nas variáveis utilizadas no cálculo, porém, estes dados possivelmente sugerem uma tendência de mercado ou estratégia de marketing em relação a variação da forma de consumo. Futuros estudos da recomendação diária descrita pelos órgãos regulamentadores em relação a porção descrita no rótulo destes produtos associada ao seu custo, poderia esclarecer aspectos em relação a diferença monetária aliada a dose/eficácia, aspectos ainda não abordados na literatura científica sobre suplementos à base de colágeno.

A facilidade de deglutição do suplemento à base de colágeno em pó (Miranda et al., 2021), a possibilidade de diversificação de seu preparo em líquidos quentes e frios, e o melhor custo-benefício em relação ao preço, apontado neste estudo, podem ser fatores que contribuíram para que a forma de apresentação pó fosse a mais consumida pelos participantes do presente estudo com cerca de 52,7%.

A maioria dos participantes do presente estudo declararam possuir nível educacional de pós-graduação completa (49,8%). Este percentual está bem acima do que o Instituto Brasileiro de Geografia e Estatística, em 2020, informou sobre nível de escolaridade superior completo para a população brasileira com mais de 25 anos (17,4%). Apesar de o presente estudo possuir uma porcentagem maior de consumidores com pós-graduação, os benefícios conhecidos pelos mesmos se

restringem em sua maioria aos benefícios explorados pela mídia em relação a saúde de pele, unhas, cabelos e articulações (41,9% e 30,5%). Os benefícios em relação a diminuição da perda de massa óssea/prevenção de osteopenia e osteoporose e contribuição do colágeno para as necessidades diárias de proteínas foram citados por apenas 10,8% e 16,8%.

O estudo de Morais et al. (2020) utilizou um questionário para avaliar conhecimentos e o uso de informações de rótulos nutricionais com 415 consumidores com mais de 18 anos. Os autores observaram que muitos dos participantes apresentaram dificuldade para compreender informações e conceitos básicos, sendo que esses parâmetros podem ser influenciados por idade e renda.

Segundo a pesquisa Cowan et al. (2018) que analisou o uso de suplementos dietéticos e características socioeconômicas relacionadas a saúde de cidadãos americanos entre 2011 e 2014, o uso de suplementos dietéticos foi maior entre aqueles com renda familiar considerada acima do nível de pobreza (≥ 350%) e entre aqueles que encontravam-se em situação de segurança alimentar e não eram elegíveis para programas de suplementação nutricional.

As rendas mais assinaladas no presente estudo foram 3 e 6 salários-mínimos (29,79%) e 1 a 3 salários-mínimos (26,95%). Segundo Bueno et al. (2022), a utilização de uma linguagem acessível a diferentes classes sociais é uma alteração que necessita ser amplamente adotada para benefício de todos os consumidores. Isso significa que as estratégias de marketing e comunicação devem ser acessíveis a todas as classes sociais e nível educacional.

No presente estudo, 52,7% dos indivíduos relataram automedicação. O delineamento de Cândido et al. (2020) sobre nutricosméticos indicou que os indivíduos que não compraram os produtos por prescrição médica obtiveram informações de familiares, amigos e propagandas. Segundo Bjelica et al. (2020) a expansão do uso de marketing digital e a indisponibilidade ao acesso a informações médicas relevantes sobre suplementos alimentares em sites de venda, apontam uma clara necessidade de melhoria no controle de qualidade dos sites de venda de suplementos alimentares e maior conscientização do público sobre suplementos alimentares.

Ao buscar por informações em fontes confiáveis, como por exemplo os sites de sociedades médicas, notamos divergências em relação às recomendações. A Associação Brasileira de Nutrologia (ABRAN), utiliza o estudo Choi et al. (2019) como base informar os benefícios da suplementação de colágeno e a Sociedade

Brasileira de Dermatologia atesta a funcionalidade das patentes de produtos à base de colágeno Verisol® e Peptan®. Já a Sociedade Brasileira de Reumatologia afirma que não há comprovação científica de que o colágeno tenha atuação benéfica nas articulações, apesar de tal alegação ser reconhecida pela ANVISA (2018 /2021).

Embora ainda não sejam reconhecidos pela Sociedade Brasileira de Reumatologia, os estudos sobre os efeitos do consumo do colágeno e seus derivados aumentaram na última década. Em uma busca rápida na base de dados Pubmed utilizando a palavra colágeno, até o ano de 2013 encontramos 17117 artigos. Ao ampliar o período até 2023 encontramos 26119 artigos, demonstrando um aumento de 52,1% na última década. Além disso, os peptídeos de colágeno possuem muitas atividades biológicas, sendo seus benefícios demonstrados por inúmeros estudos científicos (Nasri, 2019). Contudo Honvo et al. (2020) ressaltam em sua revisão sistemática que antes da recomendação dos derivados de colágeno pelas sociedades científica, a harmonização dos resultados deve ser realizada por meio de estudos randomizados controlados por placebo e pré-clínicos, executados por períodos mais longos, com populações maiores e parâmetros recomendados e validados.

Para Cao et al., (2022) ainda é necessário descrever a dose, o ciclo e a interação dos peptídeos de colágeno com outros nutrientes no sistema digestivo. Neste sentido, Chang et al. (2020) relataram em seu estudo um ciclo circadiano de homeostase de colágeno, assim como Liao et al. (2020) afirmam que peptídeos de colágeno derivados do osso de tilápia podem ser utilizados como suplemento alimentar para aumentar a absorção de cálcio.

Peptídeos bioativos, suplementos alimentares e nutracêuticos parecem ser produtos promissores no tratamento de doenças crônicas não transmissíveis e possíveis produtos a serem utilizados no combate a epidemia mundial destas doenças (Chew et al., 2019; Domínguez Díaz et al., 2022). Diversas funcionalidades associadas aos peptídeos bioativos de colágeno foram descritas em estudos recentes como: ação antiplaquetária (Ye et al., 2020), capacidade de redução de colesterol, hipoglicemiante, anti-hipertensivo, anticancerígeno (Nasri, 2019), entre outras.

Segundo Domínguez Díaz et al. (2022) um potencial que pode ser considerado ainda é a combinação de suplementos alimentares e nutracêuticos a medicamentos e a realização de pesquisas para estabelecimento de combinações nutri-farmacêuticas favoráveis. Além destes aspectos a serem explorados, é

necessária a realização de estudos em relação à estabilidade de peptídeos *in vivo*, abordando sua relação com enzimas gastrointestinais e absorção (Chew et al., 2019).

Por fim, podemos observar que as pesquisas sobre suplementos alimentares à base de colágeno/ peptídeos de colágeno são promissoras e apresentam benefícios que atuam em diversas áreas do corpo humano. O desenvolvimento do mercado de colágeno nos próximos anos, assim como, descobertas científicas recentes, impulsionam as pesquisas e o desenvolvimento industrial deste produto. Desta forma, entender aspectos que envolvem os conhecimentos, atitudes e práticas dos consumidores destes produtos pode ser uma ferramenta importante para a indústria, proporcionando acesso à informações relativas ao uso e expectativas em relação ao produto que beneficiará sua formulação e comercialização.

7. CAPÍTULO V

CONCLUSÃO GERAL

A suplementação de colágeno hidrolisado e colágeno tipo II são utilizados em diversos estudos da literatura com público em geral do gênero feminino com idade entre 30 a 50 anos. Estes estudos apresentam uma variedade de benefícios para a saúde da pele e articulações citados no capítulo 1. Embora a diversidade de estudos existentes, alguns aspectos necessitam de consolidação como dose ideal, tempo de consumo/ eficácia, metabolismo dos peptídeos de colágeno no corpo humano e utilização de colágeno por outros públicos, entre outros. Estudos com maior número populacional e com análises histológicas, laboratoriais e exames de imagem aumentariam o grau de evidência das análises.

No levantamento dos produtos disponíveis no mercado digital podemos constatar que o suplemento alimentar à base de colágeno possui fácil aquisição e comercialização nas formas de pó, sachê, gomas, comprimidos e cápsulas. A cápsula foi a forma de apresentação mais encontrada no levantamento de mercado realizado no presente estudo, possivelmente justificada pela produção industrial em ampla escala. Entretanto, o custo de produção das cápsulas torna o consumo dos produtos em pó um pouco mais atrativo para os consumidores, uma vez que os mesmos acabam apresentando um custo mais acessível.

O método KAP aplicado aos consumidores de suplementos alimentares à base de colágeno, associado ao perfil socioeconômico, permitiu concluir que:

- A prática de automedicação é frequente entre os consumidores de suplemento à base de colágeno.
- As percepções dos benefícios citados pelos participantes da pesquisa corroboram os dados observados na revisão bibliográfica apresentada no capítulo 1 desta dissertação.
- O conhecimento dos participantes pode estar relacionado aos benefícios mais explorados pelas mídias (visual, impressa e digital), utilizados como estratégia de marketing para aumento das vendas.
- O maior consumo dos produtos na forma de pó pode estar relacionado ao seu menor custo em relação a capsulas e a sua facilidade de deglutição/consumo.
- A associação da percepção de benefício e período de consumo de suplementos alimentar à base de colágeno (superior a três meses), permitiu identificar que o tempo é um fator essencial para eficácia do suplemento.

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8. ANEXOS

ANEXO 1 - APROVAÇÃO DO COMITÊ DE ÉTICA E PESQUISA

UNICAMP - CAMPUS CAMPINAS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Estudo das características e percepções dos consumidores em relação aos produtos à base de colágeno.

Pesquisador: LUANA DIAS CAMPOS

Área Temática:

Versão: 2

CAAE: 47819121.0.0000.5404

Instituição Proponente: Faculdade de Engenharia de Alimentos

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.895.802

Apresentação do Projeto:

As informações contidas nos campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram obtidas dos documentos apresentados para apreciação ética e das informações inseridas pelo Pesquisador Responsável do estudo na Plataforma Brasil.

Introdução:

Onipresente em animais vertebrados o colágeno é um biomaterial (Bielajew, Hu & Athanasiou, 2020) que corresponde a um quarto da massa proteica total de humanos e outros vertebrados, sendo constituído por proteínas fibrosas insolúveis (Arseni, Lombardi & Orioli, 2018) que formam redes que reforçam os tecidos e fornecem matriz extracelular para as células. Essas estruturas possuem funcionalidades de enrijecimento de tensões que ajustam funções mecânicas dos tecidos e regulam o comportamento celular (Jansen, Licup, Sharma, Rens, MacKintosh & Koenderink, 2018), sendo ainda fundamentais para proporcionar elasticidade e resistência aos órgãos e tecidos (Arseni et al., 2018) e contribuem para as propriedades de organização e forma dos tecidos (Ricard-Blum, 2011), provendo rigidez e resiliência (Panwar, Butler, Jamroz, Azizi, Overall &römme, 2018).

Os colágenos são capazes de interagir com células por meio de várias famílias de receptores, regulando a proliferação, migração e diferenciação celular. Alguns colágenos possuem distribuição restrita nos tecidos e assim funções biológicas específicas (Ricard-Blum, 2011). Alterações na

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Bairro: Barão Geraldo **CEP:** 13.083-887
UF: SP **Município:** CAMPINAS
Telefone: (19)3521-8936 **Fax:** (19)3521-7187 **E-mail:** cep@unicamp.br

-O pesquisador deve manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda e responsabilidade, por um período de 5 anos após o término da pesquisa.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1768143.pdf	28/07/2021 18:06:25		Aceito
Parecer Anterior	PB_PARECER_CONSUBSTANCIADO_CEP_4815185.pdf	28/07/2021 18:05:47	LUANA DIAS CAMPOS	Aceito
Outros	Curriculo_Lattes_Cinthia_Bau_Betim_Cazarin.pdf	28/07/2021 18:03:57	LUANA DIAS CAMPOS	Aceito
Declaração de Pesquisadores	CARTA_RESPOSTA_CEP_Luana_Dias_Campos.pdf	28/07/2021 17:56:11	LUANA DIAS CAMPOS	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TERMO_DE_CONSENTIMENTO_LIVRE_E_ESCLARECIDO_Luana_Dias_Campos.pdf	28/07/2021 17:55:12	LUANA DIAS CAMPOS	Aceito
Outros	Comprovante_de_vinculo_Cinthia_Bau_Betim_Cazarin.jpg	26/07/2021 13:45:59	LUANA DIAS CAMPOS	Aceito
Declaração de Instituição e Infraestrutura	AtestadoMatricula_Luana_Dias_Campos.pdf	08/06/2021 15:17:03	LUANA DIAS CAMPOS	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_de_Pesquisa_Luana_Dias_Campos_Estudo_das_caracteristicas_e_percepcoes_dos_consumidores_em_relacao_aos_produtos_a_base_de_colageno.pdf	07/06/2021 13:43:02	LUANA DIAS CAMPOS	Aceito
Folha de Rosto	Folha_de_Rosto_CEP_Luana_Dias_Campos.pdf	07/06/2021 13:35:55	LUANA DIAS CAMPOS	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CAMPINAS, 10 de Agosto de 2021

Assinado por:
Renata Maria dos Santos Celeghini
(Coordenador(a))

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ANEXO 2 - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Estudo das características e percepções dos consumidores em relação aos produtos à base de colágeno

Certificado de Apresentação de Apreciação Ética (CAAE), número: 47819121.0.0000.5404

Pesquisadora Responsável: Luana Dias Campos (Mestranda do programa de Pós-Graduação em Alimentos e Nutrição da Faculdade de Engenharia de Alimentos/UNICAMP); luana.diasc81@gmail.com

Pesquisadora Colaboradora: Profª. Drª. Cinthia Baú Betim Cazarin (Professora Assistente do Depto. de Ciência de Alimentos e Nutrição da Faculdade de Engenharia de Alimentos/UNICAMP); cbetim@unicamp.br.

Você está sendo convidado a participar como voluntário de uma pesquisa online. Este documento, chamado Termo de consentimento Livre e Esclarecido, visa assegurar seus direitos como participante da pesquisa. Você receberá uma cópia assinada deste documento em seu e-mail. Dada à importância deste documento recomendamos o arquivamento da cópia recebida. Leia o documento com atenção e calma e caso você possua alguma dúvida antes ou após início/ termino da pesquisa, entre em contato com as pesquisadoras para esclarecimento

O consumo de suplementos tem crescido nos últimos anos, entre eles podemos citar o colágeno. Gostaríamos de conhecer sua opinião, conhecimento e práticas em relação ao colágeno. Essas informações poderão ser uteis para o desenvolvimento de novos produtos e para o desenvolvimento de meios de comunicação com os consumidores. Para participar desta pesquisa você deve ter mais de 18 anos, ter consumido ou consumir produtos à base de colágeno e ler este documento e clicar nas opções “aceito participar da pesquisa” ou “não aceito participar da pesquisa”.

Esta pesquisa é composta por o preenchimento um questionário on-line com duração aproximada de 5 minutos, abrangendo questões sobre seu conhecimento sobre o colágeno e um questionário socioeconômico.

A participação nessa pesquisa não apresenta riscos previsíveis, no entanto, caso você sinta-se desconfortável em responder as questões, você poderá não responder ou poderá finalizar a pesquisa a qualquer momento, sem nenhum prejuízo para você.

Não há benefícios diretos e nem financeiros para a participação nesta pesquisa. Os participantes terão benefícios indiretos ao contribuir com uma pesquisa que investiga a percepção do consumidor sobre produtos à base de colágeno. Os resultados da pesquisa poderão ser utilizados como embasamento para melhorar a qualidade dos produtos e a comunicação das empresas produtoras de colágeno com os consumidores.

Essa é uma pesquisa on-line, e que não gera despensa para o participante, por isso, o participante não receberá nenhum ressarcimento por sua participação. Caso ocorra alguma despesa extra não citada neste termo ou algum dano decorrente da participação nesta pesquisa, os participantes terão garantia ao direito a ressarcimento integral da despesa ou indenização em virtude do dano.

Caso o participante sofra algum dano decorrente da pesquisa, de forma direta, indireta, em imediato ou após a pesquisa (dano tardio) ele será assistido de forma integral e gratuita pelo tempo que for necessário.

Você tem a garantia de que sua identidade será mantida em sigilo. Nenhum dado será fornecido para pessoas que não façam parte da equipe de pesquisa e na divulgação do estudo não haverá identificação dos participantes. As respostas deste questionário serão salvas e mantidas em uma base de dados por 5 anos pelas pesquisadoras, após o término do desta pesquisa.

Esta pesquisa não apresenta riscos diretos/ iminentes, porém destaca-se se o risco de ambientes virtuais quanto à violação e exposição de dados de forma não desejada e fora do controle das pesquisadoras, mesmo que haja apenas acesso exclusivo das pesquisadoras.

Você poderá suspender a sua participação da pesquisa a qualquer momento, mesmo após o término do preenchimento do questionário, ficando seus dados sob sigilo. Para suspender sua participação e solicitar a exclusão de seus dados, basta entrar em contato com a pesquisadora Luana Dias Campos por e-mail (luana.diasc81@gmail.com) e fazer a solicitação. A pesquisadora lhe enviará um documento assinado e escaneado confirmando a exclusão de seus dados.

Caso deseje você poderá receber informações sobre os resultados da pesquisa em seu e-mail ou informações referentes a publicações sobre os resultados da pesquisa. Esta opção constará para preenchimento após a autorização de participação deste documento.

Em caso de dúvidas sobre a pesquisa, você poderá entrar em contato com as pesquisadoras Cinthia Baú Betim Cazarin e Luana Dias Campos, pelos seguintes meios:

- Telefone: (11) 99803-4291
- E-mails: cbetim@unicamp.br, luana.diasc81@gmail.com.
- Endereço: Universidade Estadual de Campinas - Faculdade de Engenharia de Alimentos/DECAN - R: Monteiro Lobato, 80- Cidade Universitária, Campinas-SP.

Em caso de denúncias ou reclamações sobre sua participação e sobre questões éticas do estudo, você poderá entrar em contato com a secretaria do Comitê de Ética em Pesquisa (CEP) da UNICAMP das 08:00hs às 11:30hs e das 13:00hs as 17:30hs na Rua: Tessália Vieira de Camargo, 126; CEP 13083-887 Campinas – SP; telefone (19) 3521-8936 ou (19) 3521-7187; e-mail: cep@unicamp.br

O Comitê de Ética em Pesquisa (CEP):

O papel do CEP é avaliar e acompanhar os aspectos éticos de todas as pesquisas envolvendo seres humanos. A Comissão Nacional de Ética em Pesquisa (CONEP) tem por objetivo desenvolver a regulamentação sobre proteção dos seres humanos envolvidos nas pesquisas. Desempenha um papel coordenador da rede de Comitês de Ética em Pesquisa (CEPs) das instituições, além de assumir a função de órgão consultor na área de ética em pesquisas.

Responsabilidade do Pesquisador:

Asseguro ter cumprido as exigências da resolução 466/2012 CNS/MS e complementares na elaboração do protocolo e na obtenção deste Termo de Consentimento Livre e Esclarecido. Asseguro, também, fornecer uma via deste documento ao participante da pesquisa. Informo que o estudo foi aprovado pelo CEP perante o qual o projeto foi apresentado e pela CONEP, quando pertinente. Comprometo-me a utilizar o material e os dados obtidos nesta pesquisa exclusivamente para as finalidades previstas neste documento ou conforme o consentimento dado pelo participante da pesquisa.

Consentimento livre e esclarecido:

Após ter recebido esclarecimentos sobre a natureza da pesquisa, seus objetivos, métodos, benefícios previstos, potenciais riscos e o incômodo que esta possa acarretar, aceito participar:

( ) Aceito participar da pesquisa ( ) Não aceito participar da pesquisa

ANEXO 3 – QUESTIONÁRIO PERCEPÇÃO, CONHECIMENTOS, ATITUDES E PRÁTICAS EM RELAÇÃO AO COLÁGENO.

Estudo das características e percepções dos consumidores em relação aos produtos à base de colágeno

Você está sendo convidado a contribuir com esta pesquisa com seus dados. Você deve autorizar a sua participação lendo o termo abaixo e assinalando uma das alternativas. Informe seu e-mail abaixo.

*Obrigatório

Termo de Consentimento Livre e Esclarecido

Gostaríamos de conhecer sua opinião, conhecimento e práticas em relação ao colágeno. Para participar desta pesquisa você deve ter mais de 18 anos, ter consumido ou consumir produtos à base de colágeno e clicar nas opções “aceito participar da pesquisa” ou “não aceito participar da pesquisa”.

Abaixo está o link para acesso ao Termo de Consentimento Livre e Esclarecido, um documento que resguarda seus direitos ao participar desta pesquisa. Recomendamos a sua leitura.

Link de acesso para o Termo de Consentimento Livre e Esclarecido:

https://drive.google.com/file/d/1I5OlmjZbdbBaTrBe_lw6–4vdfaZC9zE/view?usp=sharing

1. Após ter recebido esclarecimentos sobre a natureza da pesquisa, seus objetivos, métodos, benefícios previstos, potenciais riscos e o incômodo que esta possa acarretar. Você aceita participar da pesquisa? *

Marcar apenas uma oval.

- ◯ Aceito participar da pesquisa
- ◯ Não aceito participar da pesquisa

Questionário Socioeconômico

2. Qual é o seu sexo? *

Marcar apenas uma oval.

- ◯ Feminino
- ◯ Masculino
- ◯ Outro: _____

3. Qual sua faixa etária? *

Marcar apenas uma oval.

- ◯ 18 a 24 anos
- ◯ 25 a 30 anos
- ◯ 31 a 35 anos
- ◯ 36 a 40 anos
- ◯ 41 a 50 anos
- ◯ Acima de 50 anos

4. Qual é o seu grau de escolaridade *

Marcar apenas uma oval.

- ◯ Não alfabetizado/ Fundamental incompleto
- ◯ Fundamental completo
- ◯ Médio completo
- ◯ Superior completo
- ◯ Pós graduação completa

5. Qual a sua renda familiar? *

Marcar apenas uma oval.

- ◯ Até 1 salário mínimo
- ◯ De 1 a 3 salários mínimos
- ◯ De 3 a 6 salários mínimos
- ◯ De 6 a 9 salários mínimos
- ◯ De 9 a 12 salários mínimos
- ◯ Mais de 12 salários mínimos

6. Quantas pessoas residem na sua casa? (Contando com você) *

Marcar apenas uma oval.

- ◯ Moro sozinho
- ◯ 02 pessoas
- ◯ 03 pessoas
- ◯ 04 pessoas
- ◯ 05 pessoas ou mais

7. Em qual estado você reside atualmente? *

Questionário percepção, conhecimento, atitude e práticas em relação ao colágeno.

8. 1. Você já consumiu algum tipo de colágeno? *

Marcar apenas uma oval.

- ◯ Sim
- ◯ Não

Questionário percepção, conhecimento, atitude e práticas em relação ao colágeno.

9. Se sua resposta foi sim na pergunta anterior, qual a marca do colágeno que você consumiu ou consome?

10. O consumo foi recomendado por um profissional da área da saúde (por exemplo: médico, nutricionista)? *

Marcar apenas uma oval.

- ◯ Sim
- ◯ Não

11. Em que forma você consome ou consumiu o colágeno? *

Marcar apenas uma oval.

- ◯ Pó
- ◯ Cápsula
- ◯ Goma (bala)

12. Por quanto tempo você fez ou faz uso do colágeno? *

Marcar apenas uma oval.

- ◯ Menos de 1 mês
- ◯ Durante 1 mês
- ◯ Durante 3 meses
- ◯ Durante 1 ano
- ◯ Mais de 1 ano

13. 6. Assinale uma ou mais alternativas que você acha estar correlacionada ao consumo do colágeno? Você pode assinalar mais de 1 opção. *

Marque todas que se aplicam.

- ☐ Consumir o colágeno pode diminuir dores articulares
- ☐ Consumir o colágeno melhora a pele, o cabelo e as unhas.
- ☐ Consumir o colágeno previne perdas ósseas como, por exemplo: osteopenia e osteoporose
- ☐ Consumir o colágeno contribui para alcançar as recomendações de proteínas diárias
- ☐ Outro: _____

14. 7. Você percebeu algum benefício ou melhora dos seus sintomas após consumir o colágeno? *

Marcar apenas uma oval.

- ◯ Sim
- ◯ Não

15. Se sua resposta na pergunta anterior foi sim, descreva qual foi à melhora observada após o consumo do colágeno.

16. Você já consumiu sopa ou caldo preparado com ossos de boi ou frango? *

Marcar apenas uma oval.

- ◯ Sim
- ◯ Não

17. Você acha que o consumo da sopa de ossos poderia contribuir com o consumo de colágeno no organismo? *

Marcar apenas uma oval.

- ◯ Sim
- ◯ Não

ANEXO 4 – LICENÇA USO DA FIGURA1 - CAPÍTULO I

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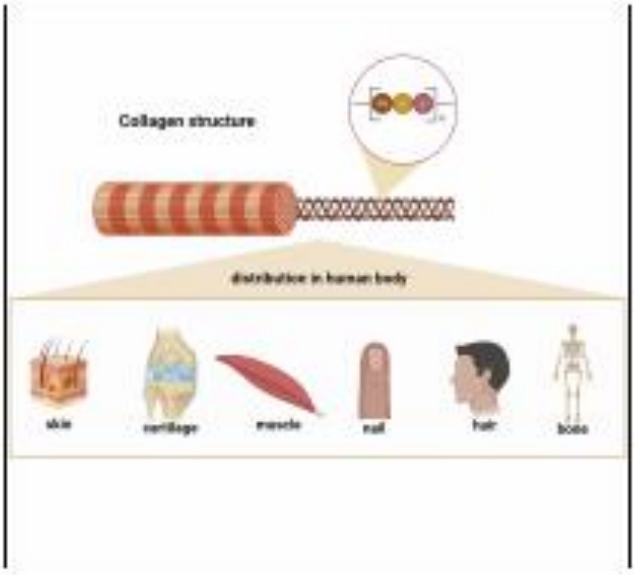

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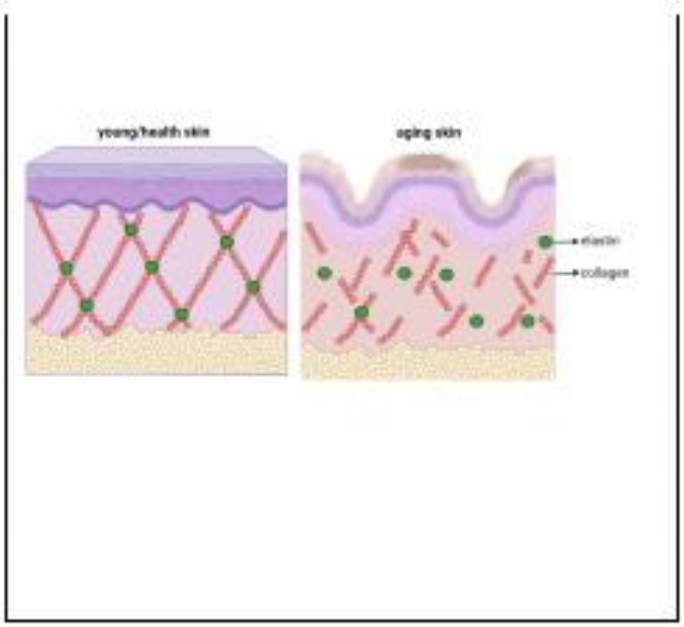

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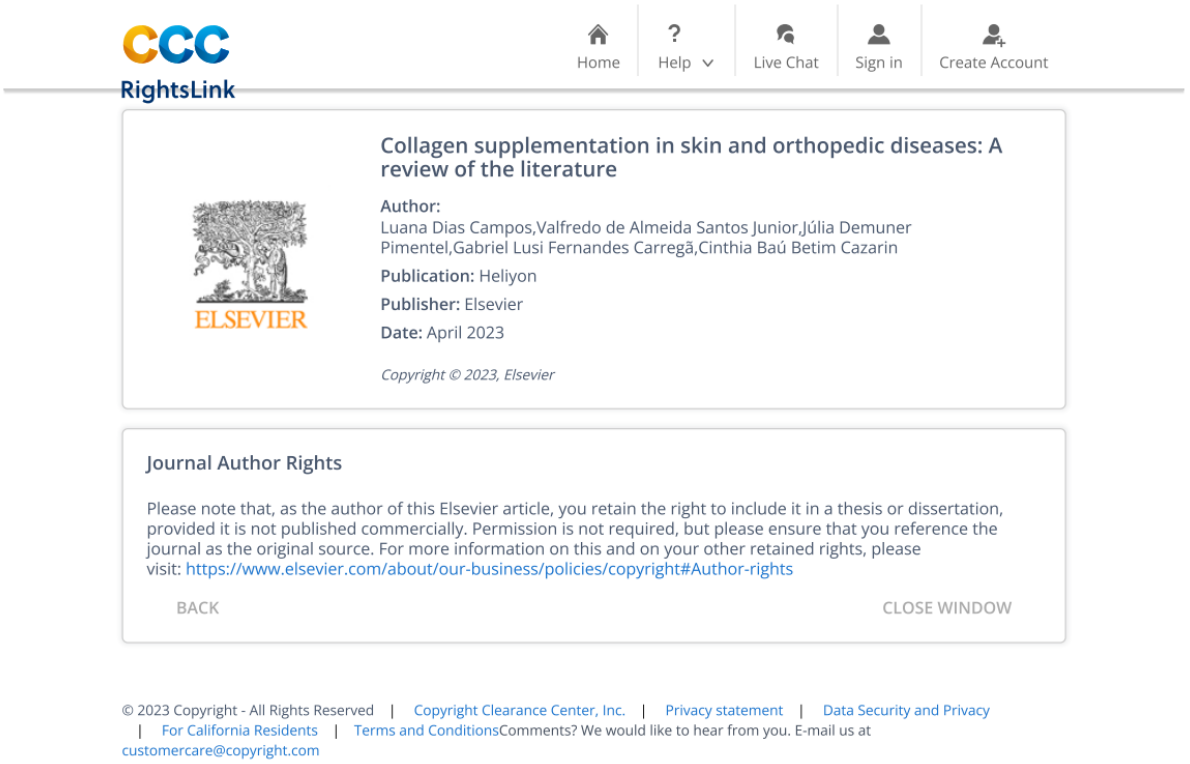

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Collagen supplementation in skin and orthopedic diseases: A review of the literature

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Luana Dias Campos,Valfredo de Almeida Santos Junior,Júlia Demuner Pimentel,Gabriel Lusi Fernandes Carregã,Cinthia Baú Betim Cazarin

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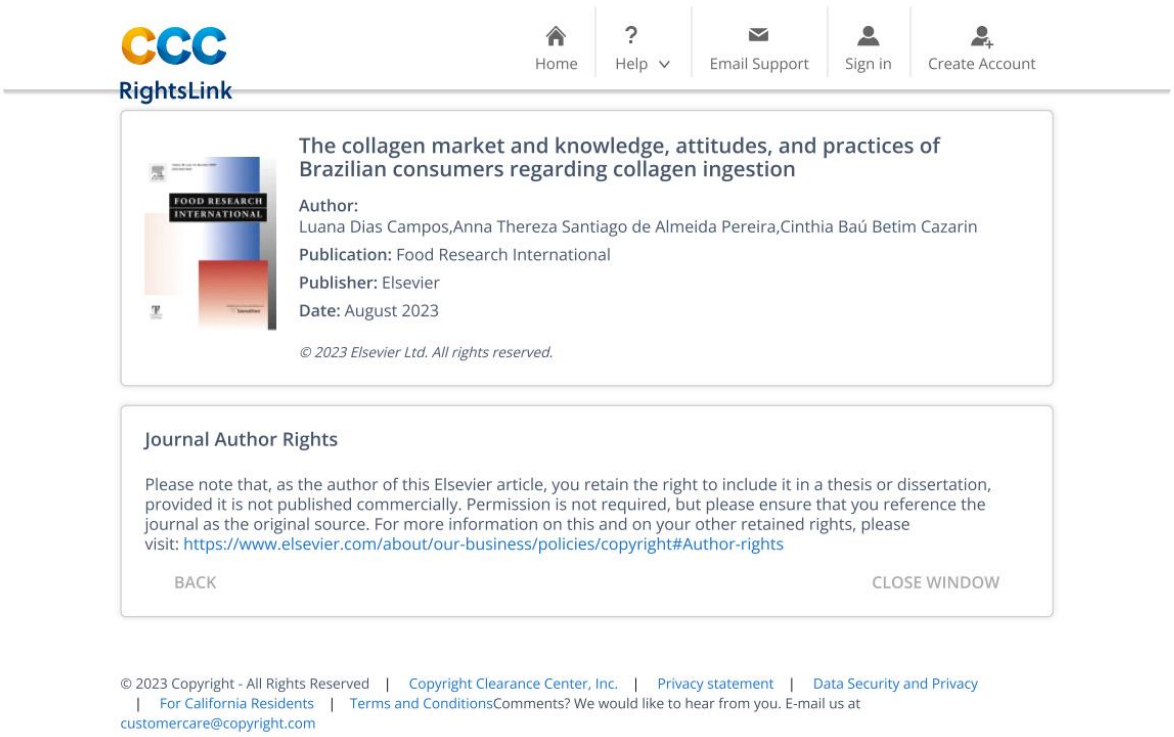

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The collagen market and knowledge, attitudes, and practices of Brazilian consumers regarding collagen ingestion

Author:
Luana Dias Campos,Anna Thereza Santiago de Almeida Pereira,Cinthia Baú Betim Cazarin

Publication: Food Research International

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Date: August 2023

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