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REVIEW ARTICLE

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Collagen supplementation for skin health: A mechanistic systematic review

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Abstract

Background: Over the last decade, many researchers tried to evaluate the effects of collagen supplements on skin aging and surprisingly revealed that the interventions improved skin aging parameters without any inconsistency.

Aim: This systematic review assesses the literature regarding the effects of collagen supplements on skin health parameters in healthy and patient subjects, focusing on mechanisms of action.

Methods: At the first step of search in the databases, 9057 items were obtained. After removal of duplicate items, 6531 publications remained. Further screening by title and/or abstract resulted in removal of 6500 items. Finally, full texts of the 31 remained items were assessed for eligibility and 10 publications were included in this review.

Results: The evidences obtained from these systematic reviews indicated that oral administration of intact or hydrolyzed collagen improves clinical manifestation of skin health. Almost all of the included studies reported the beneficial effects of collagen supplementation, and no inconsistencies have been seen in this regard between studies.

Conclusions: In this systematic review, three different mechanisms of action were clarified for the intervention. Direct effects of collagen peptides on fibroblasts, M2-like macrophages, and oral tolerance-related mechanisms are the possible mechanisms for the beneficial effects of collagen supplementation.

KEYWORDS
collagen, collagen hydrolysate, M2-like macrophage, oral tolerance, regulatory T cell, skin health

1 | INTRODUCTION

Collagen is the main structural protein in the various connective tissues such as skin and bone. It makes up about 25 percent of the body proteins in mammals. Although its tertiary structure is so complex and forms coiled coil structure, the amino acid sequence of collagen is simply formed by intermittent repetition of glycine, proline, and hydroxylproline-containing tri-peptides.[1] Over the last two decades, many experimental and randomized controlled trials have been done to evaluate the effects of intact or hydrolyzed collagen on skin health,[2-4] arthritis patients,[5-10] and even allograft rejection.[11] The collagen used in the studies is almost in hydrolyzed form and extracted from animal sources including porcine skin,[12] bovine bone,[13] and fish scales.[14]

When collagen molecules undergo different degradative processes including physical, chemical, and biological procedures, collagen hydrolysates (CH) are formed due to the hydrolysis of collagen strands' molecular bonds.[15] Compared to the intact form of collagen, hydrolyzed collagen has less antigenic trait.[16] Also, when interventional studies use intact collagen, the intervention dose is reduced by 2000 times.[10,13]

There are different environmental, hormonal, chronological, and photoaging factors which cause defect in appearance and integrity of skin with age.[17] Decrease in various metabolic activities related to changes in quantity and quality of dermal collagen and elastin, construction of skin changes, and typical aging symptoms can be seen. In cutaneous aging, the connective tissue is lost. This leads to decrease and loss in elasticity and skin tone. Also, in this process, development of facial creases' deeping and wrinkles—the major recognized skin aging signs—happens.[18]

Sufficiency of essential nutrients is fundamental factor related to the function of skin and its healthy appearance. In recent decades, researchers have great interest in investigating the potential association between skin health and nutrition. Results from intervention studies claimed that supplementation with dietary ingredients has potential role in modulation of skin aging or delaying it.[19]

Preclinical studies suggested the stimulatory effects of orally administered collagen peptides on extracellular matrix molecules production in human fibroblasts.[20] Also, findings of animal studies showed that oral collagen peptides treatment leads to increase in collagen fibrils, fibroblast diameter, and density. On the other hand, it has been shown that administration of CH attenuated reduction of type I collagen which was induced by UVB.[21] In this regard, a surprising tip is several reports of some researches on skin autoimmune defects about the immune response suppression against extracellular matrix after collagen oral administration.[13] Also, this finding is repeated in other studies on different immune system-related diseases.[11,22,23]

As mentioned above, the beneficial effects of intact or hydrolyzed form of collagen on skin health were reported by many recent studies. Although several mechanisms are reported for both effects and side effects of collagen intervention,[11,22] the exact mechanisms are unknown. In this systematic review, we evaluated the studies that used collagen supplementation for improving skin health parameters to find out if there are inconsistencies in this regard. Also, we discussed widely the cellular and molecular mechanisms of the collagen intervention effects.

2 | METHOD

2.1 | Information source and searching strategy

We searched PubMed, Scopus, Web of Science, the key journals (Journal of Biological Chemistry, Journal of Investigative Dermatology, and Journal of Biomaterials), conferences/congress research papers (as gray literature), and the reference list of the included primary studies until July 2019 (1997/01/01:2019/07/31) using the following syntaxes: ("Bioactive peptide"[ti] OR Collagen[ti] OR "Collagen hydrolysate"[ti] OR "Hydrolyzed collagen"[ti] OR (Collagen[ti] AND Hydrolyzed[ti]) OR (Hydrolyzed[ti] AND collagen[ti]) OR "Hydrolysed collagen"[ti] OR (Collagen[ti] AND Hydrolysed[ti]) OR (Peptide[ti] AND bioactive[ti]) OR Gelatin[ti] OR "Gelatin hydrolysate"[ti] OR (Hydrolysate[ti] AND gelatin[ti]) OR "Food-derived gelatin"[ti] OR Pro-Hyp[ti] OR Proline-hydroxyproline[ti] OR Proline[ti] OR Hydroxyproline[ti] OR Ala-Hyp[ti] OR Ala-Hyp-Gly[ti]) **AND (**Epidermis[ti] OR Dermis[ti] OR "Skin Wrinkle"[ti] OR (Skin[ti] AND wrinkle[ti]) OR Anti-ageing[ti] OR "ageing skin"[ti] OR (Skin[ti] AND aging[ti]) OR "skin thickening"[ti] OR (skin[ti] AND thickening[ti]) OR (Skin[ti] AND Elasticity[ti]) OR "Skin elasticity"[ti] OR "Skin Moisture"[ti] OR (Skin[ti] AND moisture[ti]) OR Eyelids[ti] OR "Eye Bag"[ti] OR (Eye[ti] AND bag[ti]) OR Dermal[ti] OR "Hyaluronic acid production"[ti] (Hyaluronic acid[ti] AND production[ti]) OR Cutaneous[ti] OR "Skin hydration"[ti] OR (Skin[ti] AND hydration[ti]) OR Keratinocytes[ti] OR (Proliferation[ti] AND fibroblast[ti]) OR "Fibroblast proliferation"[ti] OR Fibroblast[ti] OR "Extracellular matrix"[ti] OR "Skin damage"[ti] OR (damage[ti] AND skin[ti]) OR (health[ti] AND skin[ti]) OR "Skin health"[ti] OR "Aged skin"[ti] OR "Skin condition"[ti] OR "Skin moisture"[ti] OR (Skin[ti] AND moisture[ti]) OR "Skin evaporation"[ti] OR "skin dryness"[ti] OR (Dryness[ti] AND skin[ti]) OR "Skin scaling"[ti] OR (skin[ti] AND scaling[ti]) OR photo-ageing[ti] OR "skin surface"[ti] OR (skin[ti] AND line[ti]) OR "skin line"[ti] OR "sun-exposed skin"[ti] OR (sun-exposed[ti] AND skin[ti]) OR "skin appearance"[ti] OR "Skin properties"[ti] OR "transepidermal water"[ti]) AND 1997/01/01:2019/07/31[dp]. The complete search syntaxes were developed based on MeSH database, Emtree, and non-MeSH terms. We did not implement any language restriction.

2.2 | Eligibility criteria and selection process

Studies were included in this systematic review if they had the following criteria: (a) full-text article in any language, (b) all placebo-controlled trials (either parallel or cross-over designs), and (c) carried out on adults (age ≥ 18). We excluded studies which assessed the combined effect of collagen supplement with another supplement. Also, we excluded books, reviews, editorial, letters, and articles which did not intend to assess the effect of collagen supplements on skin parameters. Included studies contain nine studies on healthy adults and one study on diffuse cutaneous systemic sclerosis (DCSS) patients compared to control group. We performed search in the different mentioned sources and exported the search outputs into the EndNote software. The duplicated primary studies were deleted (only one version of the duplicated documents was kept). The screening phase (selecting included/probable included versus excluded primary studies using the title or/and the abstract) was performed. The selection or verification process (selecting included versus excluded primary studies) was performed based on the eligibility criteria. All steps for preparing this systematic review such as searching, screening based on titles of papers and abstracts, and

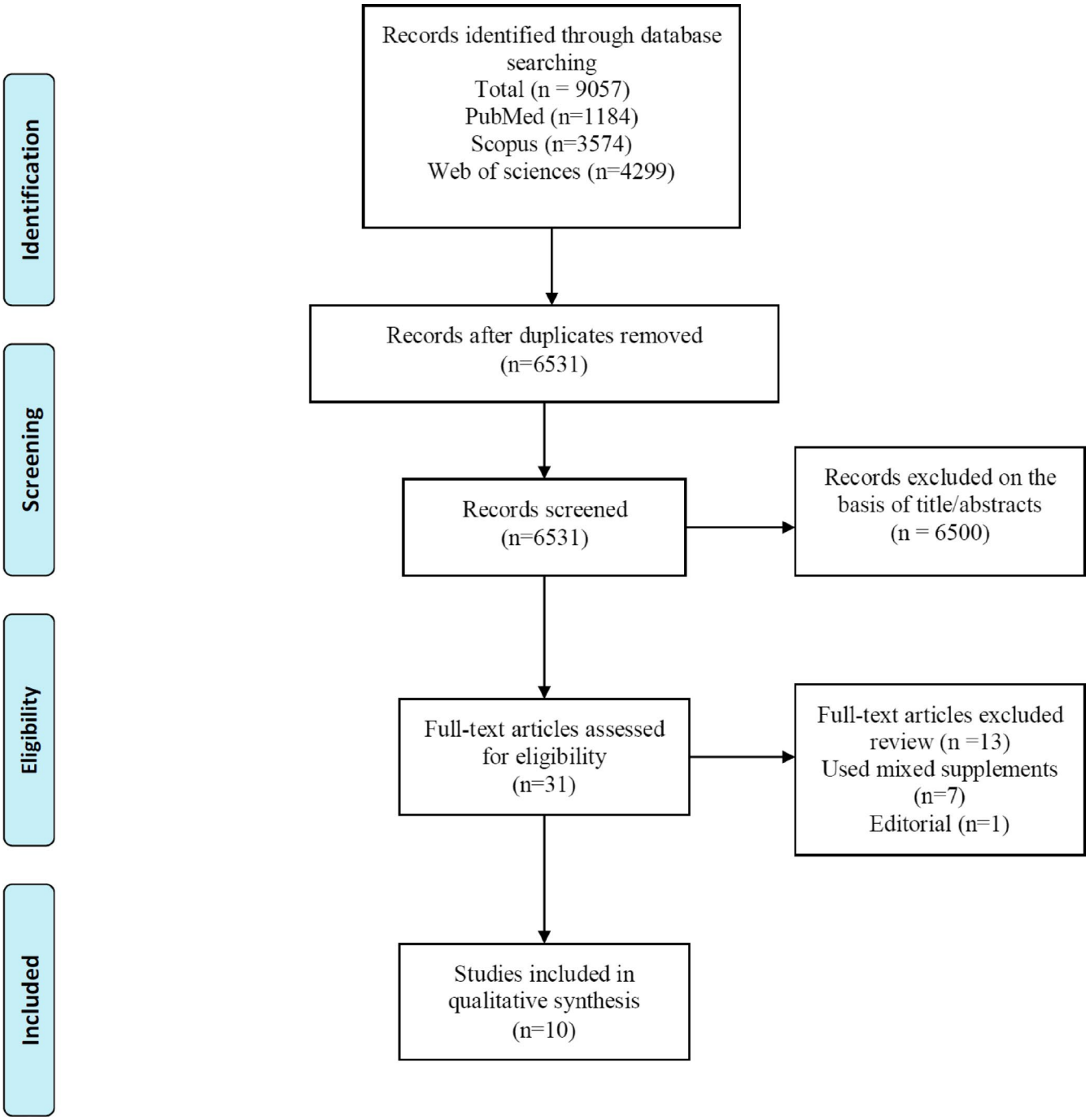

FIGURE 1 The study selection process

TABLE 1 The RCTs used intact of hydrolysate collagen of skin aging parameters

Author (s)/funding source	The study groups	Subjects (n)/study duration	Collagen origin/form/dose
Postlethwaite et al; 2008; USA[13]/noncommercial	Intervention: type I collagen (n = 83) Placebo: acetic acid (n = 83)	DCSS patients (n = 168)/12 mo	Bovine/intact/500 μg per day
Choi et al; 2014; South Korea[25]/not reported	Group A: no supplement (n = 8) Group B: CH (n = 8) Group C: CH + vitamin C (n = 8) Group D: vitamin C (n = 8)	Healthy subjects/12 wk	NR/hydrolysate/CP = 3 g and vitamin C = 500 μg
Kuwaba et al; 2014; Japan [26]/not reported	Intervention: CH Placebo: -	Women with dry and saggy face/8 wk	Fish/hydrolysate/5 g
Proksch et al; 2014; Brazil[2]/ not reported	Intervention: BCP (VERISOL®) Placebo: maltodextrin	Healthy females (n = 57)/8 wk	NR/hydrolysate/2.5 g per day
Inoue et al; 2015; China[14]/ not reported	Intervention 1: H-CH (n = 28) Intervention 2: L-CH (n = 29) Placebo: maltodextrin (n = 28)	Healthy females/8 wk	Fish gelatin/hydrolysate/5 g
Sugihara et al; 2015; China[27]/not reported	Intervention: CH (n = 28) Placebo: maltodextrin (n = 28)	Healthy females/8 wk	NR/hydrolysate/2.5 g
Mori et al; 2017; Japan[12]/not reported	Intervention: CH (n = 10) Placebo: dextrin (n = 10)	Healthy females with nail fragile and/or thinly peeled off/12 wk	Porcine skin/hydrolysate/5 g
Kim et al; 2018; Korea[3]/ noncommercial	Intervention: LMWCH (n = 32) Placebo: same formula except CH	Healthy females/12 wk	Fish/hydrolysate/1 g
Koizumi et al; 2018; Japan[15]/ commercial	Intervention: beverage containing CH (n = 38) Placebo: beverage	Healthy females/12 wk	Fish/hydrolysate/3 g
Yamamoto et al; 2018; Japan[28]/not reported	Intervention: drink containing CH (n = 18) Placebo: drink (n = 18)	Healthy subjects with dry skin/8 wk	Porcine skin/hydrolysate/10 g

Abbreviations: BCP, bioactive collagen peptides; CH, collagen hydrolysate; DCSS, diffuse cutaneous systemic sclerosis; H-CH, collagen hydrolysate containing high amount of low molecular weight peptides; L-CH, collagen hydrolysate containing low amount of low molecular weight peptides; LMWCH, low molecular weight collagen hydrolysate; MRSS, modified Rodnan skin score; NSC, not significant change; TEWL, transepidermal water loss.

selection according to examination of full text of articles were done independently by two authors (MJ and RN). Also, quality assessment and data extraction were done by two authors (MJ and MB) independently. Any disagreements regarding the inclusion/exclusion criteria and data extraction were resolved by a third reviewer (MB).

2.3 | Data extraction

Data extraction was done by two independent reviewers (MB and MJ). Our data extraction sheet included the following information: the general description of the studies and populations (including first author, study location, publication year, study design, type of participants,

The variables	Results	Conclusion/side effects
MRSS	↓ in late-phase DCSS compared with placebo	Intact type I collagen improves MRSS in late-phase DCSS./ decrease in hematologic parameters
Stratum corneum hydration	↑ in CH group compared with controls	Daily CH supplementation may improve skin hydration and elasticity, but concomitant intake of low-dose vitamin C did not enhance the effect of CH on skin properties./not reported
TEWL	↓ in CH group compared with controls	
Skin elasticity	↑ in CH group compared with controls	
Erythema index	NSC	
Melanin index	NSC	
Wrinkle number	↓ compared with placebo group	Ingestion of fish CH improves skin properties and subjective feeling of skin conditions/not reported
Skin dryness	↑ compared with placebo group	
Skin wrinkle volume	↓ compared with placebo group	Oral intake of specific bioactive collagen peptides reduced skin wrinkles and had positive effects on dermal matrix synthesis/No adverse effects were observed
BF type I procollagen	↑ compared with placebo group	
BF elastin	↑ compared with placebo group	
BF fibrillin	NSC	
Facial moisture	↑ in H-CH group compared with L-CH and placebo; ↑ in L-CH group compared with placebo	The collagen hydrolysate with a higher content of Pro-Hyp and Hyp-Gly led to more improvement in facial skin conditions, including facial skin moisture, elasticity, wrinkles, and roughness./no adverse effects were observed
Facial elasticity	↑ in H-CH group compared with L-CH and placebo.	
Facial wrinkle	↓ in H-CH group compared with L-CH and placebo	
Facial roughness	↓ in H-CH group compared with L-CH and placebo; ↓ in L-CH group compared with placebo	
Facial hydration	↑ compared with placebo group	Daily ingestion of 2.5 g of CH improves facial skin hydration, elasticity, and roughness/not reported
Facial elasticity	↑ compared with placebo group	
Facial roughness	↓ compared with placebo group	
Nail moisture	↑ compared with placebo group	Oral ingestion of porcine skin-derived collagen peptide prevents drying by keeping the nail's water retentivity by increasing the intercellular lipids in the nail and improves supple nail flexibility/not reported
Nail hardness	↓ compared with placebo group	
Nail sphingosine	↑ compared with placebo group	
Nail ceramides	↑ compared with placebo group	
Skin hydration	↑ in LMWCH group compared with Placebo	LMWCH can be used as a health functional food ingredient to improve human skin hydration, elasticity, and wrinkling/ no adverse effects were observed
Crow's-feet scores	↓ in LMWCH group compared with placebo	
Skin elasticity	↑ in LMWCH group compared with placebo	
Facial moisture	↑ compared with placebo group	Fish-derived CH holds great promise as a natural supplement with cutaneous anti-aging properties./no adverse effects were observed
Skin elasticity	↑ compared with placebo group	
Periorbital wrinkles	↓ compared with placebo group	
TEWL	↓ compared with placebo group	Collagen peptides derived from porcine skin are effective for skin moisture transpiration/not reported

participants' gender, the mean age of subjects, duration of intervention and dose of collagen supplement, collagen origin, and form), and results (including measured variables, their changes at the end of the intervention, side effects and/or conclusion of the findings). There were different time points for outcome variable values, and we extracted data for the end of the trial.

2.4 | Quality assessment

The quality assessment for the included studies was evaluated by three independent reviewers (MB, AS, and FF) independently. Risk bias for the included studies also was examined using criteria as outlined in the Cochrane Handbook for Systematic Reviews of

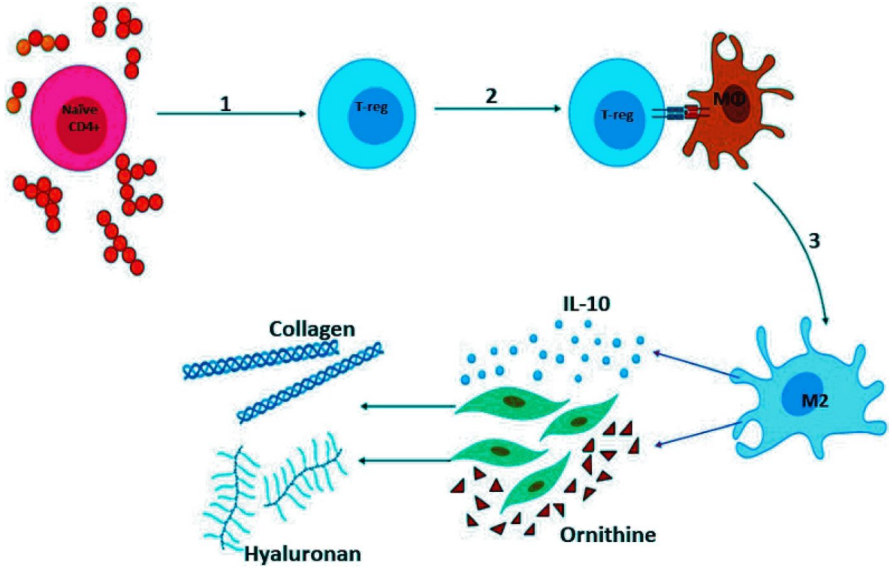

FIGURE 2 The effects of orally originated collagen-derived fragments on production of extracellular matrix by fibroblasts. 1: Differentiation of naive CD4+ immune cells to Tregs after exposure to collagen-derived fragments; 2: migration of Tregs to peripheral tissue and make cross-link with macrophages; and 3: polarization of macrophages toward M2-like macrophages. CD: cluster of differentiation; Treg: regulatory T cell. MΦ: macrophage; M2: M2-like macrophage; IL-10: interleukin 10

Interventions[24] by review manager software (ver. 5.3). Any discrepancy was resolved by the third investigator (SHD).

3 | RESULTS

3.1 | Literature search

Figure 1 shows the flow diagram of the systematic literature search and screening for the present study. At the first step of search in database, 9057 items were obtained. After removal of duplicate items, 6531 publications remained. Further screening by title and/or abstract resulted in removal of 6500 items. Finally, full texts of the 31 remained items were assessed for eligibility and 10 publications were included in this review.[2,3,12-15,25-28] Table 1 shows the features of selected studies which assessed the effect of collagen (intact or hydrolyzed) supplementation on skin health or aging parameters. The results of quality assessment are summarized in S Figure 1.

3.2 | Findings from the systematic review

All of the included articles were RCTs (Table 1). The RCTs were performed on healthy subjects (n = 9) and DCSS patients (n = 1). Bovine (n = 1), fish (n = 4), and porcine skin (n = 2) were the main sources of the collagen that were used for the interventions. Three RCTs did not report the source of their used supplement. Ten g/d (n = 1), 5 g/d (n = 3), 3 g/d (n = 2), 2.5 g/d (n = 2), 1 g/d (n = 1), and 500 μg/d (n = 1) were the collagen doses that were used in the RCTs. It should be noted that both CH (n = 9) and intact collagen (n = 1) were used for the interventions. The duration of the interventions was 12 months (n = 1), 12 weeks (n = 4), and 8 weeks (n = 5). From the included articles, seven papers worked on female subjects and three on both genders. The details of the quality score for every study are shown in Figure S1. The articles enrolled healthy subjects, which did not report any adverse effects after collagen supplementation, but Postlethwaite et al[13] reported that during 1-year supplementation with intact type I collagen, CNS-related adverse effects including headache significantly decreased and hematologic side effects increased, compared to placebo-receiving group.

All of the included studies reported beneficial effects of intact or hydrolyzed collagen on skin health parameters including moisture, elasticity, wrinkle number, dryness, and the modified Rodnan skin score (MRSS). There are no inconsistencies about collagen supplementation and skin health between included studies. We comprehensively discussed possible mechanisms for these findings. In brief, it seems the connection between oral collagen administration, the gut immune regulatory T cells, and M_2 macrophages is the main possible mechanism for findings of the summarized RCTs (Table 1).

4 | DISCUSSION

As mentioned before, all of the included studies reported the beneficial effects of collagen supplementation on skin health parameters without any adverse effects, especially in healthy subjects. Therefore, no inconsistencies exist between the included studies in this regard. Although, over the last decade, researchers used intact or hydrolyzed collagen for improving parameters related to skin health, no specific mechanism has been introduced yet. So, in this section, we are going to talk about the possible mechanisms for findings of the current systematic review. Concerning the possible mechanisms related to oral collagen administration and skin health, three different possible mechanisms could be suggested in this regard: (a) Collagen fragments can be a precursor for collagen synthesis in the skin; (b) collagen fragments can stimulate collagen and proteoglycans production in the skin; and (c) collagen and its fragments can increase skin turnover by induction of regulatory T cells (Tregs) and M2 macrophages.

4.1 | Collagen fragments act as precursor for collagen synthesis

In the first view, it looks that collagen fragments act as precursor for collagen synthesis. But protein synthesis has its specific mechanisms and does not need any primer for its beginning. Also, during protein synthesis, tRNAs have key role to prepare specific amino acid for protein synthesis. The tRNAs carry only the amino acids and not peptides.[29] Therefore, the first possible mechanism for the association of intact or hydrolyzed collagen with skin health parameters is rejected; because neither endogenous nor exogenous peptides can participate in the protein translation process directly. Although collagen fragments could not be involved in protein synthesis directly, recent studies showed they could affect extracellular matrix metabolism.[30] The following subsections describe the indirect effects of collagen fragments on extracellular matrix turnover.

4.2 | Collagen fragments have role in extracellular matrix components synthesis

Although limited studies have been done to find the exact mechanism of the diet-derived collagen fragments' effects (low molecular weight collagen-derived peptides) on synthesis of extracellular matrix components, many studies evaluated the effects of endogenous collagen fragments (high molecular weight collagen-derived fragments) on metabolism of extracellular matrix and its possible mechanisms. Jennings et al in an in vitro study evaluated the effects of type II collagen fragments on factors related to extracellular matrix metabolism. They revealed that exposure of the collagen fragments significantly inhibits chondrocytes attachment to matrix, and inhibits collagen synthesis and matrix degradation induction.[31] In a similar study, Varani et al[32] revealed that collagen fragments produced by photodamage negatively correlated with procollagen synthesis. On the other hand, Röck et al[33] showed that collagen peptides inhibit hyaluronan synthesis in skin fibroblasts. Against what is summarized in Table 1, the mentioned in vitro studies reported detrimental effects of collagen fragments on skin health parameters including hyaluronan and collagen synthesis. There are several reasons for the mentioned inconsistency between the in vitro and the RCTs results. The most important cause of this inconsistency may be the molecular weight of the peptides which were used. While in vitro studies evaluated the effects of high molecular weight collagen fragments, the RCTs administered oral low molecular weight CPs which undergo further breakdown during intestinal digestion and absorption. During the gut protein digestion processes, di- and tri-peptides are the main free amino acids that are made.[34] Ohara et al[30] in an in vitro study showed that exposure of dermal fibroblasts to Pro-Hyp significantly increases synthesis of hyaluronic acid. So, this mechanism also could be a suitable mechanism for explaining the beneficial effects of CH on skin health parameters.

4.3 | CPs increase skin turnover by induction of Tregs and M2 macrophages

In the processes of tissue remodeling, proper removal and manipulation of older collagen scaffolds are critical issues. However, there are still many unknown related aspects in turnover of these plentiful components of the extracellular matrix in vivo. Recent in vivo researches have suggested that in collagen turnover, cellular uptake mediated by receptor is so important. Also, it has been shown that M2-like macrophages have a key role in this regard.[35-37]

Macrophages have pivotal role in extracellular matrix turnover and remodeling. For instance, after myocardial infarction, M1-like macrophages facilitate the clearance of dead cells and M2-like macrophages are working to resolve inflammation and rebuild cardiac tissue.[38] Researchers are strictly investigating about the association between M2 macrophages and Tregs. Also, the immune tolerance and role of M2 macrophages in its maintenance have been under

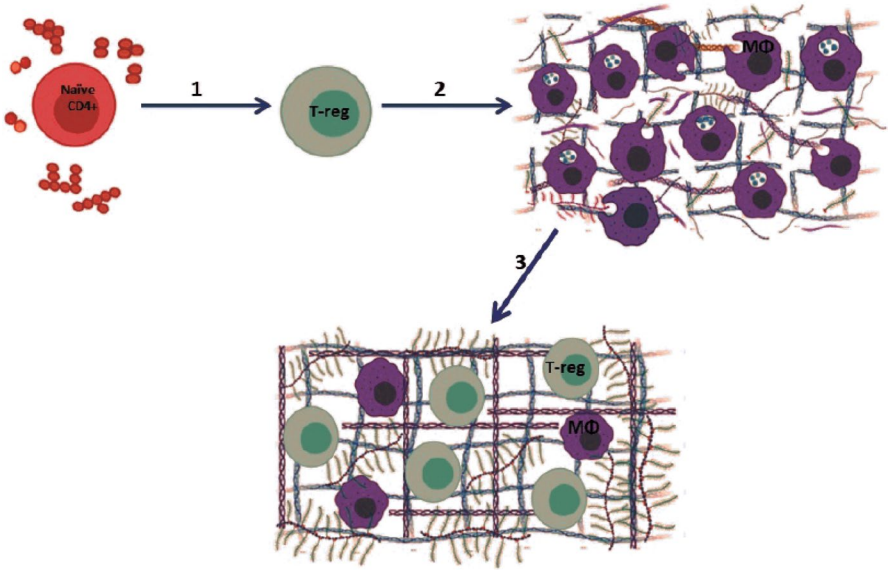

FIGURE 3 The effects of orally originated collagen-derived fragments on suppression of autoimmune response against endogenous collagen. 1: Differentiation of naive CD4+ immune cells to specific colony of Tregs after exposure to collagen-derived fragments; 2: migration of the formed Tregs to autoimmune destructed tissue; and 3: suppression of autoimmune responses by Treg presence and recovery of damaged tissue; CD: cluster of differentiation; Treg: regulatory T cell. MΦ: macrophage

investigation. On the other hand, there are some evidences about the significant role of Tregs/macrophage interaction in the modulation of host immune responses. Treg depletion causes to amplification of macrophage activation.[39]

There are increasing interests about the role of M2 macrophages in the inflammation. These macrophages have immunomodulatory role, and it has been suggested that in the presence of two cytokines including interleukin 10 (IL-10) and transforming growth factor β (TGF-β)—major cytokines correlated with Treg function—they have a regulatory phenotype. In a process which is associated with IL-10 and TGF-β, Tregs can lead differentiation of macrophages to the M2 regulatory phenotype.[40-42] Also, there are some other different suggested mechanisms involved in the Treg-induced regulatory phenotype in macrophages.[43,44] M2-like macrophages by IL-10 and ornithine secretion increase extracellular matrix production by fibroblasts (Figure 2).[45-47]

The oral administration of CH and intact collagen is closely related to induction of Tregs, and the exact mechanisms are widely demonstrated over the last decade. Two main mechanisms are presented for induction of collagen-mediated Tregs: (a) tolerance-mediated mechanisms and (b) nontolerance-mediated mechanisms.

4.3.1 | Oral tolerance-mediated mechanism

Oral tolerance is a type of peripheral tolerance in which systemic immune unresponsiveness to food antigens occurs. Induction of Tregs is the main mechanism for oral tolerance.[48] During digestion and absorption processes, gut immune system samples the gut lumen content continuously and assesses the food antigens. After identifying the food-derived antigens, the immune response against them is suppressed.[49] In DCSS—an autoimmune disease—the immune system responses against the skin antigens.[50] Type I collagen is a skin antigen in which immune system responses against it in DCSS.[51] Surprisingly, Postlethwaite et al[13] in their RCT showed that oral administration of intact type I collagen with dose of 500 μg/d for 1 year reduces MRSS in late-phase DCSS. In fact, oral administration of type I collagen induces colony-specific Tregs that suppress any immune response versus type I collagen in any site of the whole body. Autoimmunity against type V collagen has pivotal role in lung allograft rejection.[52] In an animal model of lung allograft transplantation, Yasufuku et al[11] revealed that oral administration of type V collagen significantly reduces allograft rejection. Similar results were obtained from animal models of arthritis when oral collagen was administered.[23,53] Therefore, after oral administration of collagen, especially intact collagen, specific Treg colonies are formed and suppress immune response against collagen in any site of the whole body (Figure 3). It should be noted that in this kind of mechanism, the proteins are not necessarily absorbed and only sampling of protein content by gut immune system could induce Treg colonies formation.[48,49]

4.3.2 | Nontolerance-mediated mechanism

Before talking about this mechanism, it should be noted that the evidence about this mechanism is limited. When dietary proteins enter the gut, digestion begins. During digestion of dietary proteins, free amino acids, di-, tri-, and tetra-peptides (the major absorbable protein-derived structures) are formed.[34] Di- and tri-peptides derived from dietary collagen are the major players of nontolerance-mediated mechanism. Nishikimi et al[22] in an ex vivo study revealed that hydroxylproline-containing dipeptides, Pro-Hyp and Hyp-Gly, promote Treg expansion in response to antigen stimulation in the presence of TGF-β.

5 | CONCLUSION

All of the included studies reported the beneficial effects of collagen supplementation on skin aging parameters in both healthy and unhealthy subjects, without any inconsistency. In this systematic review, two different mechanisms of action were clarified for the findings. Direct exposure of collagen-derived peptides after intestinal absorption to fibroblasts could increase synthesis of extracellular matrix. On the other hand, collagen and its fragments could induce regulatory T cells and the induced cells improve skin health parameters by macrophage polarization toward M2-like macrophages and suppression of immune response against endogenous collagen.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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