March 27, 2023

Re: Collagène: Curated Blend and Cellular Absorption Technology Clinical Dossier

Here at THREE, we provide curated proactive wellness solutions using our proprietary Cellular Absorption Technology, proven to help you live a life of greater health and purpose.

This dossier contains peer-reviewed clinical studies both on the curated blend and the Cellular Absorption Technologies used in Collagène that validates its ability to do the following:

- Promote vibrant and youthful looking skin.
- Promote the body's natural ability to produce collagen.
- Support healthy skin, hair, and nails.
- Support healthy immune response and joints.

One thing that you can expect from us here at THREE is that we are always in the process of running clinical studies in elucidating new mechanisms of action by which our products work along with discovering additional areas in which our products can promote human health. We have several exciting clinical studies in the pipeline and will announce these when they are completed.

The clinical studies contained herein, and others that will follow, explain why our products provide the powerful health benefits our customers from all around the world experience every time they use a THREE product.

Thank you for joining us on this journey and for trusting us with your proactive wellness needs.

Be well,

Dr. Dan Gubler
Chief Scientific Officer
Three International

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J Drugs Dermatol. 2019 Jan 1;18(1):9-16.

Oral Collagen Supplementation: A Systematic Review of Dermatological Applications

Franchesca D. Choi, Calvin T. Sung, Margit L.W. Juhasz, Natasha Atanaskova Mesinkovsk

PMID: 30681787

Abstract

Importance: The use of nutraceuticals such as collagen for skincare has been rising, but regulations are lacking on quality, absorption, and efficacy. To address this knowledge gap, clinical studies regarding the potential effects of collagen-based dietary supplements on skin are being completed. Objective: To review the literature and assess available randomized-controlled trials using collagen supplementation for treatment efficacy regarding skin quality, anti-aging benefits, and potential application in medical dermatology. Evidence Review: A literature search was conducted with PubMed using search criteria (collagen) AND (supplement OR food OR nutrition). No lower limit on the year of publication was set. Inclusion criteria were: randomized, placebo-controlled trials using collagen supplementation in human subjects related to dermatology and written in English. Findings: Eleven studies with a total of 805 patients were included for review. Eight studies used collagen hydrolysate, 2.5g/d to 10g/d, for 8 to 24 weeks, for the treatment of pressure ulcers, xerosis, skin aging, and cellulite. Two studies used collagen tripeptide, 3g/d for 4 to 12 weeks, with notable improvement in skin elasticity and hydration. Lastly, one study using collagen dipeptide suggested anti-aging efficacy is proportionate to collagen dipeptide content. Conclusions and Relevance: Preliminary results are promising for the short and long-term use of oral collagen supplements for wound healing and skin aging. Oral collagen supplements also increase skin elasticity, hydration, and dermal collagen density. Collagen supplementation is generally safe with no reported adverse events. Further studies are needed to elucidate medical use in skin barrier diseases such as atopic dermatitis and to determine optimal dosing regimens. J Drugs Dermatol. 2019;18(1):9-16.

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Faculty Opinions

Review Int J Dermatol. 2021 Dec;60(12):1449-1461. doi: 10.1111/ijd.15518.
Epub 2021 Mar 20.

Effects of hydrolyzed collagen supplementation on skin aging: a systematic review and meta-analysis

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Affiliations
PMID: 33742704 DOI: 10.1111/ijd.15518

Abstract

Skin aging has become a recurring concern even for younger people, mainly owing to increased life expectancy. In this context, the use of nutricosmetics as supplements has increased in recent years. Moreover, numerous scientific studies have shown the benefits of hydrolyzed collagen supplementation in improving the signs of skin aging. The objective of this study was to summarize the evidence on the effects of hydrolyzed collagen supplementation on human skin through a systematic review followed by a meta-analysis of clinical trials focusing on the process of skin aging. A literature search was conducted in the Medline, Embase, Cochrane, LILACS (Latin American and Caribbean Health Sciences Literature), and Journal of Negative Results in BioMedicine databases. Eligible studies were randomized, double-blind, and controlled trials that evaluated oral supplementation with hydrolyzed collagen as an intervention and reported at least one of the following outcomes: skin wrinkles, hydration, elasticity, and firmness. After retrieving articles from the databases, 19 studies were selected, with a total of 1,125 participants aged between 20 and 70 years (95% women). In the meta-analysis, a grouped analysis of studies showed favorable results of hydrolyzed collagen supplementation compared with placebo in terms of skin hydration, elasticity, and wrinkles. The findings of improved hydration and elasticity were also confirmed in the subgroup meta-analysis. Based on results, ingestion of hydrolyzed collagen for 90 days is effective in reducing skin aging, as it reduces wrinkles and improves skin elasticity and hydration.

Keywords: clinical trials; collagen.

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Review J Cosmet Dermatol. 2020 Nov;19(11):2820-2829. doi: 10.1111/jocd.13435.
Epub 2020 May 21.

Collagen supplementation for skin health: A mechanistic systematic review

Meisam Barati [1], Masoumeh Jabbari [2], Roya Navekar [3], Fariba Farahmand [4], Reihaneh Zeinalian [5], Ammar Salehi-Sahlabadi [6], Nasrin Abbaszadeh [5], Amin Mokari-Yamchi [2], Sayed Hossein Davoodi [7]

Affiliations
PMID: 32436266 DOI: 10.1111/jocd.13435

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: M2-like macrophage; collagen; collagen hydrolysate; oral tolerance; regulatory T cell; skin health.

Related information

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J Laparoendosc Adv Surg Tech A. 2021 Mar;31(3):296-300. doi: 10.1089/lap.2020.0468. Epub 2020 Aug 5.

Hair Loss After Sleeve Gastrectomy and Effect of Biotin Supplements

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PMID: 32762597 DOI: 10.1089/lap.2020.0468

Abstract

Aim: In this study, we aimed to determine the incidence of hair loss in patients who underwent laparoscopic sleeve gastrectomy (LSG), and to observe whether use of Biotin has an impact on hair loss. ***Methods:*** This study included 156 female patients who underwent LSG for obesity and completed a 1-year follow-up. All patients with vitamin deficiency were screened in the pre- and postoperative period. Hair loss was defined as the subjective perception of the women of losing a higher amount of hair when compared with normal situation. ***Results:*** Hair loss was observed in 72% of the patients after LSG (n = 112). Seventy-nine percent of the patients reported hair loss between the third and fourth-month interval, and continued for an average of 5.5 ± 2.6 months. Permanent alopecia was not observed in any of the patients. Patients who experienced hair loss and Biotin deficiency after LSG were prescribed 1000 mcg/day of Biotin for 3 months. Of these 22 patients; only 5 (23%) patients reported a remarkable decline in hair loss. İn addition, 29 patients were found to take 1000 mcg/day of Biotin for average 2.5 months after onset of hair loss by their own initiative, despite optimal blood Biotin levels. Eleven (38%) patients reported a remarkable decline in hair loss. The effect of biotin use on hair loss in patients with and without biotin deficiency was compared. There was no significant difference (P = .2). ***Conclusion:*** Temporary hair loss after LSG is common. It was found that biotin supplementation used to prevent hair loss does provide low efficacy.

Keywords: bariatric surgery; biotin supplements; hair loss; sleeve gastrectomy.

Related information

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PubChem Compound (MeSH Keyword)

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Atypon

Other Literature Sources

Biochem Pharmacol. 2021 Mar;185:114454. doi: 10.1016/j.bcp.2021.114454. Epub 2021 Feb 3.

The anti-melanogenic effects of ellagic acid through induction of autophagy in melanocytes and suppression of UVA-activated α-MSH pathways via Nrf2 activation in keratinocytes

Hsin-Ling Yang [1], Chia-Pei Lin [2], Yugandhar Vudhya Gowrisankar [2], Pei-Jane Huang [3], Wan-Lin Chang [2], Sirjana Shrestha [1], You-Cheng Hseu [4]

Affiliations

PMID: 33545118 DOI: 10.1016/j.bcp.2021.114454

Abstract

Ellagic acid (EA) is a natural phenol antioxidant in different fruits, vegetables, and nuts. As a copper iron chelator from the tyrosinase enzyme's active site, EA was reported to inhibit melanogenesis in melanocytes. Here, we demonstrated the anti-melanogenic mechanisms of EA through autophagy induction in melanoma B16F10 cells and the role of Nrf2 and UVA (3 J/cm^2)-activated α-melanocyte stimulating hormone (α-MSH) pathways in keratinocyte HaCaT cells. In vitro data showed that EA suppressed the tyrosinase activity and melanogenesis by suppressing cAMP-mediated CREB and MITF signaling mechanisms in α-MSH-stimulated B16F10 cells. ERK, JNK, and AKT pathways were involved in this EA-regulated MITF downregulation. Notably, EA induced autophagy in B16F10 cells was evidenced from increased LC3-II accumulation, p62/SQSTM1 activation, ATG4B downregulation, acidic vesicular organelle (AVO) formation, PI3K/AKT/mTOR inhibition, and Beclin-1/Bcl-2 dysregulation. Interestingly, 3-MA (an autophagy inhibitor) pretreatment or LC3 silencing (siRNA transfection) of B16F10 cells significantly reduced EA-induced anti-melanogenic activity. Besides this, in UVA-irradiated keratinocyte HaCaT cells, EA suppressed ROS production and α-MSH generation. Moreover, EA mediated the activation and nuclear translocation of Nrf2, leading to antioxidant γ-GCLC, HO-1, and NQO-1 protein expression in HaCaT cells. However, Nrf2 knockdown has significantly impaired this effect, and there was an uncontrolled ROS generation following UVA irradiation. JNK, PKC, and ROS pathways were involved in the activation of Nrf2 in HaCaT cells. In vivo experiments using the zebrafish model confirmed that EA inhibited tyrosinase activity and endogenous pigmentation. In conclusion, ellagic acid is an effective skin-whitening agent and might be used as a topical applicant.

Keywords: Anti-melanogenesis; Autophagy; Ellagic acid; Keratinocytes; Melanoma cells; ROS.

Related information

MedGen

Randomized Controlled Trial Planta Med. 2020 Jul;86(11):749-759.
doi: 10.1055/a-1170-7785. Epub 2020 May 19.

Phenolic-rich Pomegranate Peel Extract: In Vitro, Cellular, and In Vivo Activities for Skin Hyperpigmentation Treatment

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Affiliations
PMID: 32428937 DOI: 10.1055/a-1170-7785

Abstract

The pomegranate phenolics are reported to have cutaneous benefits and to be effective in treating skin disorders, including hyperpigmentation. In this context, a preparation method was developed by which to obtain phenolic-rich pomegranate peel extract. Sinapic acid was presented as the major pomegranate peel phenolics, followed by gallic and ellagic acids, and 4 additional phenolics. The extract exhibited strong antioxidant activity with an *in vitro* tyrosinase inhibitory effect. The skin hyperpigmentation treating potency was confirmed by the suppression of cellular melanogenesis through tyrosinase and TRP-2 inhibitions as examined in the B16F10 melanoma cells. Cellular antioxidant and proliferative activities of the extract toward human dermal fibroblasts were evidenced, as well as an inhibitory effect against MMP-2. The extract was developed into the stable serum and mask. The products were proved to be non-irritated in 30 Thai volunteers participating in a single application closed patch test. A split-face, randomized, double-blind, placebo-controlled test of the skin lightening effect was evaluated in the 30 volunteers over 28 consecutive daily treatments and monitored by the Mexameter MX 18. The active serum and mask were better in facial skin lightening efficacy than the placebo ($p < 0.005$). That was in accordance with the sensory evaluation scored by the volunteers. Phenolic-rich pomegranate peel extract is evidenced as a safe herbal derived material promising for skin hyperpigmentation treatment. Supportive information regarding chemical and biological profiles is presented with the confirmed safety and cutaneous benefits in volunteers.

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Int J Mol Sci. 2021 Jan 28;22(3):1277. doi: 10.3390/ijms22031277.

Anti-Inflammatory Effects of Ellagic Acid on Keratinocytes via MAPK and STAT Pathways

Tae-Young Gil [1], Chul-Hee Hong [2], Hyo-Jin An [1]

Affiliations

PMID: 33525403 PMCID: PMC7865693 DOI: 10.3390/ijms22031277

Free PMC article

Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is characterized by an impaired skin barrier and intense itchiness, which decreases the individual's quality of life. No fully effective therapeutic agents have prevailed for AD due to an insufficient grasp of the complex etiology. Ellagic acid (EA), a natural compound, has anti-inflammatory properties in chronic diseases. The effects of EA on AD have not yet been explored. The present study investigated the effects of EA on TNF-α/IFN-γ-stimulated HaCaT keratinocytes and house dust mite-induced AD-like skin lesions in NC/Nga mice. Treatment with EA suppressed inflammatory responses in keratinocytes by regulating critical inflammatory signaling pathways, such as mitogen-activated protein kinases and signal transducers and activators of transcription. In vivo studies using a DfE-induced AD mouse model showed the effects of EA administration through ameliorated skin lesions via decremented histological inflammatory reactions. These results suggest that EA could be a potential therapeutic alternative for the treatment of AD by inhibiting inflammatory signaling pathways.

Keywords: MAPKs; STATs; atopic dermatitis; chronic disease; ellagic acid; inflammation.

Figures

Food Chem Toxicol. 2012 May;50(5):1245-55. doi: 10.1016/j.fct.2012.02.020. Epub 2012 Feb 22.

Ellagic acid protects human keratinocyte (HaCaT) cells against UVA-induced oxidative stress and apoptosis through the upregulation of the HO-1 and Nrf-2 antioxidant genes

You-Cheng Hseu [1], Chih-Wei Chou, K J Senthil Kumar, Ke-Ting Fu, Hui-Min Wang, Li-Sung Hsu, Yueh-Hsiung Kuo, Chi-Rei Wu, Ssu-Ching Chen, Hsin-Ling Yang

Affiliations

PMID: 22386815 DOI: 10.1016/j.fct.2012.02.020

Abstract

UV radiation from the sun is a potent environmental risk factor in the pathogenesis of skin damage. Much of the skin damage caused by ultraviolet A (UVA) irradiation from the sun is associated with oxidative stress. The aim of this study was to investigate the protective role of ellagic acid (25-75 μM), a natural antioxidant, against UVA (5-20 J/cm(2))-induced oxidative stress and apoptosis in human keratinocyte (HaCaT) cells and to reveal the possible mechanisms underlying this protective efficacy. Ellagic acid pre-treatment markedly increased HaCaT cell viability and suppressed UVA-induced ROS generation and MDA formation. Moreover, ellagic acid pre-treatment prevented UVA-induced DNA damage as evaluated by the comet assay. Ellagic acid treatment also significantly inhibited the UVA-induced apoptosis of HaCaT cells, as measured by a reduction of DNA fragmentation, mitochondria dysfunction, ER stress, caspase-3 activation, and Bcl-2/Bax deregulation. Notably, the antioxidant potential of ellagic acid was directly correlated with the increased expression of HO-1 and SOD, which was followed by the downregulation of Keap1 and the augmented nuclear translocation and transcriptional activation of Nrf2 with or without UVA irradiation. Nrf2 knockdown diminished the protective effects of ellagic acid. Therefore, ellagic acid may be useful for the treatment of UVA-induced skin damage.

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Randomized Controlled Trial J Nutr Sci Vitaminol (Tokyo). 2006 Oct;52(5):383-8.
doi: 10.3177/jnsv.52.383.

Effects of oral administration of ellagic acid-rich pomegranate extract on ultraviolet-induced pigmentation in the human skin

Kouichi Kasai [1], Mineka Yoshimura, Takuro Koga, Masayuki Arii, Satoru Kawasaki

Affiliations
PMID: 17190110 DOI: 10.3177/jnsv.52.383
Free article

Abstract

We performed a double-blind, placebo-controlled trial to clinically evaluate the protective and ameliorative effects of ellagic acid-rich pomegranate extract on pigmentation in the skin after ultraviolet ray (UV) irradiation, using female subjects in their 20s to 40s. Thirteen healthy volunteers per group were randomly assigned to three groups; namely, high dose (200 mg/d ellagic acid), low dose (100 mg/d ellagic acid) and control (0 mg/d ellagic acid: placebo). Each group received the respective test foods for 4 wk. Each subject received a 1.5 MED (minimum erythema dose) of UV irradiation on an inside region of the right upper arm, based on the MED value measured on the previous day. Luminance (L), melanin and erythema values were measured before the start of the test food intake, and after 1, 2, 3 and 4 wk following the start of the test food intake. Further, questionnaires were conducted regarding the condition of the skin before the start of the test food intake and at the termination of the test food intake. As a result, decreasing rates of L values from the baseline in the low- and high-dose groups were inhibited by 1.35% and 1.73% respectively, as compared to the control group. Further, a stratified analysis using subjects with a slight sunburn revealed an inhibited decrease of L values compared with the control group at 1, 2 ($p<0.01$, respectively) and 4 wk ($p<0.05$) after the start of the test food intake in the low-dose group, and at 2 and 3 wk ($p<0.05$) in the high-dose group. Furthermore, the results of questionnaires showed ameliorating tendencies due to the test food, in some items such as "brightness of the face" and "stains and freckles." Based on the above-mentioned results, it is suggested that ellagic acid-rich pomegranate extract, ingested orally, has an inhibitory effect on a slight pigmentation in the human skin caused by UV irradiation.

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Exp Dermatol. 2010 Aug;19(8):e182-90. doi: 10.1111/j.1600-0625.2009.01044.x.

Dietary compound ellagic acid alleviates skin wrinkle and inflammation induced by UV-B irradiation

Ji-Young Bae [1], Jung-Suk Choi, Sang-Wook Kang, Yong-Jin Lee, Jinseu Park, Young-Hee Kang

Affiliations

PMID: 20113347 DOI: 10.1111/j.1600-0625.2009.01044.x

Free article

Abstract

Ellagic acid, a polyphenol compound present in berries and pomegranate, has received attention as an agent that may have potential bioactivities preventing chronic diseases. This study examined photoprotective effects of ellagic acid on collagen breakdown and inflammatory responses in UV (ultraviolet)-B irradiated human skin cells and hairless mice. Ellagic acid attenuated the UV-B-induced toxicity of HaCaT keratinocytes and human dermal fibroblasts. Non-toxic ellagic acid markedly prevented collagen degradation by blocking matrix metalloproteinase production in UV-B-exposed fibroblasts. Anti-wrinkle activity of ellagic acid was further investigated in hairless mice exposed to UV-B, in which it attenuated UV-B-triggered skin wrinkle formation and epidermal thickening. Topical application of 10 micromol/l ellagic acid diminished production of pro-inflammatory cytokines IL-1beta and IL-6, and blocked infiltration of inflammatory macrophages in the integuments of SKH-1 hairless mice exposed to UV-B for 8 weeks. In addition, this compound mitigated inflammatory intracellular cell adhesion molecule-1 expression in UV-B-irradiated keratinocytes and photoaged mouse epidermis. These results demonstrate that ellagic acid prevented collagen destruction and inflammatory responses caused by UV-B. Therefore, dietary and pharmacological interventions with berries rich in ellagic acid may be promising treatment strategies interrupting skin wrinkle and inflammation associated with chronic UV exposure leading to photoageing.

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Ovid Technologies, Inc.

Controlled Clinical Trial Skin Pharmacol Physiol. 2013;26(3):147-54.
doi: 10.1159/000350833. Epub 2013 May 24.

Dose-dependent vitamin C uptake and radical scavenging activity in human skin measured with in vivo electron paramagnetic resonance spectroscopy

Anna-Christina Lauer [1], Norbert Groth, Stefan F Haag, Maxim E Darvin, Jürgen Lademann, Martina C Meinke

Affiliations
PMID: 23689595 DOI: 10.1159/000350833

Abstract

Vitamin C is a potent radical scavenger and a physiological part of the antioxidant system in human skin. The aim of this study was to measure changes in the radical-scavenging activity of human skin in vivo due to supplementation with different doses of vitamin C and at different time points. Therefore, 33 volunteers were supplemented with vitamin C or placebo for 4 weeks. The skin radical-scavenging activity was measured with electron paramagnetic resonance spectroscopy. After 4 weeks, the intake of 100 mg vitamin C/day resulted in a significant increase in the radical-scavenging activity by 22%. Intake of 180 mg/day even resulted in a significant increase of 37%. No changes were found in the placebo group. A part of the study population was additionally measured after 2 weeks: in this group radical scavenging had already reached maximal activity after 2 weeks. In conclusion, orally administered vitamin C increases the radical-scavenging activity of the skin. The effect occurs fast and is enhanced with higher doses of vitamin C.

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S. Karger AG, Basel, Switzerland

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Review Actas Dermosifiliogr. 2023 Feb;114(2):114-124. doi: 10.1016/j.ad.2022.09.014.
Epub 2022 Oct 4.

Oral Supplementation and Systemic Drugs for Skin Aging: A Narrative Review

[Article in English, Spanish]

D Morgado-Carrasco [1], J Gil-Lianes [2], E Jourdain [3], J Piquero-Casals [4]

Affiliations

PMID: 36206809 DOI: 10.1016/j.ad.2022.09.014

Free article

Abstract

Skin aging is influenced by intrinsic and extrinsic factors and involves multiple pathogenic mechanisms. The most widely used treatments are topical products and minimally invasive procedures. Evidence on the benefits of systemic therapy is limited for several reasons: Reliance on mostly small and predominantly female samples, short study durations, methodologic heterogeneity, and a lack of consensus on which outcome measures are clinically relevant. Furthermore, systemic drugs and oral supplements are not without adverse effects. Oral hydrolyzed collagen and oral hyaluronic acid are well tolerated, and numerous clinical trials show they can mitigate some signs of skin aging. Low-dose oral isotretinoin is another option, but it has a higher risk of adverse effects. Evidence is lacking on the effects of the many dietary supplements on offer, such as vitamins, flavonoids, plant extracts, and trace elements. The future of skin aging management would appear to lie in the use of senolytic and senomorphic agents targeting senescent cells in the skin.

Keywords: Colágeno hidrolizado oral; Envejecimiento cutáneo; Fotoenvejecimiento; Hyaluronic acid; Oral; Oral hydrolyzed collagen; Photoaging; Skin aging; Tratamiento; Treatment; Ácido hialurónico.

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Ediciones Doyma, S.L.

Medical