Inherited Variation in Inflammatory Signaling and Cutaneous Photoaging

A Literature Review

Sabrina Frauenschuh[1], Magdalena Behensky[1], René Rohrmanstorfer[1], Thomas Dullnig[1], Daniel Wallerstorfer[1]

[1]*Laboratory, Novogenia GmbH, Salzburg, Austria*

Corresponding Author: Daniel Wallerstorfer (ceo@novogenia.com)

ABSTRACT

Background. Cutaneous photoaging is increasingly recognized as arising not only from cumulative ultraviolet (UV) exposure, but also from the inflammatory response mounted against UV-induced tissue injury. Interindividual genetic variation in key immune regulators, particularly within *TNF*-α, IL-1, and IL-6/IL-6 receptor signaling pathways, may influence the magnitude and persistence of this response and thereby modulate the degree of secondary tissue damage in the skin. This interpretation is supported by evidence showing that UV irradiation induces pro-inflammatory cytokine activity in cutaneous cells, whereas sustained activation of these pathways contributes to extracellular-matrix remodeling, chronic low-grade inflammation, and age-associated skin degeneration (Gahring et al., 1984; Ansary et al., 2021; Salminen et al., 2022).

Methods. Relevant literature was critically evaluated to delineate the contribution of inherited variation in inflammation-regulating pathways to cutaneous photoaging. Emphasis was placed on mechanistic and translational studies addressing common polymorphisms within *TNF*-α-, IL-1-, IL-6/IL-6R- and *CRP*-associated pathways, their effects on cytokine signaling and inflammatory responsiveness, and their relevance to ultraviolet-induced skin injury, extracellular-matrix remodeling, and photoaging. In parallel, studies on selected nutritional and topical bioactives were evaluated for their potential to modulate inflammatory signaling, oxidative stress, and tissue remodeling within this biological framework (Salminen et al., 2022; Pilkington et al., 2011).

Results. The literature indicates that common regulatory variants in TNFA, IL1A, *IL1B*, and *IL6* can influence cytokine expression or inducibility, whereas variation in IL6R may alter soluble receptor abundance and thereby modify the range of IL-6 signaling; variants in *CRP* primarily affect the downstream acute-phase inflammatory response. Mechanistically, such variants may modulate the threshold, magnitude, and resolution of inflammation after UV-induced injury, thereby providing a plausible basis for enhanced inflammatory tissue responses in skin (González et al., 2003; Dominici et al., 2002; Gore et al., 1998; Fishman et al., 1998; Galicia et al., 2004; Obisesan et al., 2004).

Discussion. Inherited variation in inflammation-regulating pathways amplifies the magnitude and persistence of post-UV inflammatory signaling in skin, so that defective genotypes drive an over-aggressive immune response that damages cutaneous tissue. Within this framework, reducing arachidonic-acid-derived inflammatory pressure and increasing omega-3 fatty acid availability provides the most direct nutritional intervention. MSM is mechanistically aligned with the same biology: it exerts anti-inflammatory and antioxidative effects, is absorbed both through the skin and through diet and counteracts a hyper-aggressive immune response in UVB-exposed skin. Resveratrol, vitamin D, vitamin C, and zinc act as further recommended modulators that attenuate oxidative stress, temper inflammatory signaling, improve barrier recovery, and support extracellular-matrix repair. Together these observations support a precision-prevention model in which a pro-inflammatory genetic background strengthens the rationale for combining targeted nutritional and topical strategies with appropriate photoprotection (Pilkington et al., 2011; Berardesca et al., 2008; Chu et al., 2022; Ratz-Łyko and Arct, 2019; Bocheva et al., 2021; Pullar et al., 2017; Schwartz et al., 2005).

Subjects: Genetics, Beauty. **Keywords:** Genetics, Beauty, Polymorphism, Inflammation.

INTRODUCTION

Cutaneous photoaging is increasingly understood as the consequence of both cumulative ultraviolet (UV) exposure and the host inflammatory response to UV-induced tissue injury. Beyond causing direct oxidative and genotoxic damage, UV radiation activates cytokine signaling, immune remodeling, and matrix metalloproteinase-dependent extracellular-matrix degradation, thereby linking acute photodamage to progressive structural deterioration of the skin. Recurrent episodes of injury followed by incomplete resolution promote collagen fragmentation, elastotic change, and a persistent state of low-grade inflammation that resembles cutaneous inflammaging (Salminen et al., 2022; Ansary et al., 2021).

Within this framework, interindividual differences in photoaging susceptibility can reflect inherited variation in inflammatory pathways. Common allelic variation functions as a modifier of inflammatory tone, thereby influencing the magnitude, duration, and resolution of cytokine-driven responses after UV exposure. Such variation may affect cytokine transcriptional activity, receptor-mediated signaling behavior, or downstream inflammatory output, thereby altering the extent of secondary tissue damage that accompanies cutaneous repair. This perspective shifts the emphasis from isolated genetic findings to the functional behavior of integrated inflammatory networks.

Photoaging may therefore be regarded as a biologically heterogeneous process arising from the interplay between environmental UV exposure and genetically determined inflammatory responsiveness, with pathway-level mechanisms linking these factors to extracellular-matrix remodeling and age-associated cutaneous degeneration (Salminen et al., 2022; Ansary et al., 2021).

INFLAMMATORY MEDIATOR PATHWAYS AS MODIFIERS OF CUTANEOUS PHOTOAGING

TNFA, *IL1A*, *IL1B*, *IL6*, and *IL6R* constitute an integrated inflammatory signaling network with direct relevance to the pathobiology of cutaneous photoaging. *TNFA*, *IL1A*, *IL1B*, and *IL6* encode key mediators of the early innate response to tissue injury, while *IL6R* shapes the spatial and functional range of IL-6 signaling, partly through its effects on soluble receptor abundance. *CRP*, by contrast, primarily reflects downstream acute-phase activation and may therefore be regarded as an integrated readout of upstream cytokine tone. Considered together, these loci are best viewed as modulators of inflammatory intensity, persistence, and spatial propagation during cutaneous repair (Fishman et al., 1998; Galicia et al., 2004; Lakka et al., 2006; Obisesan et al., 2004).

In skin, this network is engaged early after UV exposure. Epidermal IL-1 production increases, *TNF*-α is induced in keratinocytes, and IL-6 levels rise in irradiated tissue, with downstream effects on leukocyte recruitment, oxidative stress, vascular activation, and MMP induction. Under physiological conditions, these responses contribute to the clearance of damaged cells and restoration of tissue integrity; when excessive or prolonged, however, they may promote collateral tissue injury, extracellular-matrix degradation, and delayed resolution, thereby favoring the structural alterations characteristic of photoaging (Gahring et al., 1984; Bashir et al., 2009a, 2009b; Schneider et al., 2017; Salminen et al., 2022).

FUNCTIONAL IMPLICATIONS OF COMMON POLYMORPHISMS IN KEY INFLAMMATORY GENES

A key mechanistic issue is whether common allelic variation modifies the magnitude and inducibility of inflammatory signaling rather than generating qualitatively distinct inflammatory pathways. Promoter polymorphisms in *IL6* have been shown to influence transcriptional activity and inducible expression, and association studies support the broader physiological relevance of this variation in human inflammatory and metabolic phenotypes (Fishman et al., 1998; Illig et al., 2004; Huth et al., 2006). For *IL1A*, promoter-region polymorphism has been linked to altered transcriptional regulation, whereas *IL1B* variants have been associated with inflammatory disease phenotypes, including meta-analytic evidence in periodontal disease. Likewise, promoter variation in *TNFA* has been associated with enhanced *TNF*-α production and greater inflammatory activity in vivo, while experimental and meta-analytic data further support relationships between *TNFA* regulatory variation, stimulated *TNF*-α production, and broader inflammatory/metabolic phenotypes (Dominici et al., 2002; Gore et al., 1998; Nikolopoulos et al., 2008; González et al., 2003; Louis et al., 1998; Sookoian et al., 2005).

IL6R warrants consideration because receptor-related polymorphisms may influence signaling not only through receptor abundance, but also through altered receptor shedding and circulating soluble IL-6 receptor levels. In this context, common variation in *IL6R* may expand the tissue compartment capable of responding to IL-6. By contrast, polymorphisms in *CRP* appear primarily to influence baseline *CRP* concentrations and are therefore more appropriately interpreted as modifiers of downstream inflammatory output. This interpretation is consistent with evidence linking *TNFA* promoter variation to higher circulating *CRP* concentrations in chronically distressed subjects, supporting the view that upstream cytokine variation may be reflected in downstream acute-phase burden (Jeanmonod et al., 2004). Overall, a pro-inflammatory allelic pattern across these loci is most plausibly regarded as a modifier of inflammatory amplitude, duration, and persistence (Galicia et al., 2004; Lakka et al., 2006; Obisesan et al., 2004).

IMPLICATIONS FOR SUSCEPTIBILITY TO INFLAMMATION-DRIVEN PHOTOAGING

If less favorable inflammatory variants increase cytokine inducibility, the most likely cutaneous consequence is not constitutive inflammation at baseline, but an exaggerated response to UV challenge. In this setting, *TNF*-α, IL-1, and IL-6 augment NF-κB- and AP-1-dependent transcriptional programs, increase MMP activity, and accelerate disorganization of collagen and elastin architecture. The expected phenotype would therefore include greater susceptibility to collateral matrix damage, slower restoration of tissue homeostasis, and a stronger transition from acute photodamage to chronic photoaging (Salminen et al., 2022; Ansary et al., 2021).

Prominent studies show evidence that is best interpreted as mechanistically inferential: functional cytokine polymorphisms influence inflammatory biology in humans, UV-induced cytokine signaling is central to photoaging, and inflammatory skin disorders also show associations with cytokine-related genetic variation, including associations between promoter variation in *TNFA* and acne susceptibility. On this basis, a pro-inflammatory cytokine genotype acts as a modifier of vulnerability to inflammation-driven photoaging, particularly under conditions of sustained UV burden, without implying that accelerated cutaneous aging is inevitable in the absence of environmental exposure (Li et al., 2015; Salminen et al., 2022; Ansary et al., 2021).

MECHANISTICALLY ALIGNED ACTIVE INGREDIENTS AND NUTRITIONAL STRATEGIES

The active ingredients used in inflammation-associated photoaging are organized by their position in the pathogenic cascade. Omega-3 fatty acids and moderation of arachidonic-acid-derived signaling act on upstream inflammatory tone and lipid-mediator balance. Methylsulfonylmethane, resveratrol, vitamin D, vitamin C, and zinc act on downstream processes such as oxidative stress, immunomodulation, barrier maintenance, and extracellular-matrix repair. In a pro-inflammatory biological background, the amplified post-UV inflammatory response increases the burden of secondary tissue damage, which is why both upstream and downstream interventions are combined in the recommended regimen (Pilkington et al., 2011; Chu et al., 2022; Ratz-Łyko and Arct, 2019; Bocheva et al., 2021; Pullar et al., 2017; Schwartz et al., 2005).

OMEGA-3 FATTY ACIDS AND MODULATION OF ARACHIDONIC-ACID-DERIVED INFLAMMATORY SIGNALING

Omega-3 fatty acids represent a mechanistically direct nutritional approach within the context of inflammation-driven photoaging. Arachidonic acid serves as a precursor for multiple eicosanoids capable of amplifying inflammatory activity, whereas eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compete with arachidonic acid at membrane and enzymatic levels and favor the generation of less inflammatory or pro-resolving lipid mediators. In skin biology, omega-3 fatty acids have been characterized as photoprotective nutrients, and broader dermatologic literature supports anti-inflammatory effects of omega-3-derived mediators. Human nutrigenetic studies further suggest that fatty-acid milieu can interact with inflammatory genetic variation, although most available data derive from systemic metabolic phenotypes rather than cutaneous photoaging specifically. Collectively, these observations support omega-3 enrichment, together with moderation of arachidonic-acid-rich dietary patterns, as the most direct nutritional approach for attenuating inflammation-associated susceptibility to photoaging (Simopoulos, 2002; Pilkington et al., 2011; Sawada et al., 2021; Norde et al., 2018; Jourdan et al., 2011).

Methylsulfonylmethane

Methylsulfonylmethane (MSM) is a natural sulfur compound with anti-inflammatory and antioxidative effects in skin-related settings. MSM counteracts a genetically over-aggressive immune response and is absorbed both through the skin and through the diet, which makes it suitable for use as a topical and as a dietary intervention. A topical formulation including MSM has shown benefit in rosacea, supporting relevance in inflammatory facial dermatoses, while an experimental murine study demonstrated attenuation of UVB-induced wrinkle formation and other photoaging-associated changes. Review literature further characterizes MSM as an anti-inflammatory dietary supplement with a favorable safety profile (Berardesca et al., 2008; Chu et al., 2022; Butawan et al., 2017).

Resveratrol

Resveratrol is best regarded as an adjunctive compound in this context. Its relevance lies chiefly in antioxidative and anti-inflammatory activity, particularly through modulation of NF-κB- and AP-1-associated pathways implicated in photoaging. Current evidence supports its use as a dermo cosmetic adjunct in settings characterized by oxidative stress and inflammatory amplification. Its pleiotropic activity profile makes resveratrol a biologically attractive component of multimodal strategies aimed at limiting cumulative inflammatory and oxidative damage in photo exposed skin. In this regard, its value lies less in targeting a single pathway than in providing broader support against convergent mechanisms involved in cutaneous aging (Ratz-Łyko and Arct, 2019).

Vitamin D

Vitamin D represents a biologically relevant adjunct within this framework owing to its immunomodulatory and photoprotective functions in skin. Review literature supports antiaging and photoprotective effects of vitamin D metabolites in skin. A human interventional study showed that high-dose oral vitamin D attenuated experimental sunburn inflammation and reduced pro-inflammatory mediators, including *TNF*-α. In a pro-inflammatory biological context, vitamin D may therefore be considered a rational immunomodulatory cofactor (Bocheva et al., 2021; Scott et al., 2017).

Vitamin C

Vitamin C acts downstream of inflammatory predisposition but remains highly relevant to the cutaneous phenotype. It contributes to antioxidant defense, collagen biosynthesis, and recovery from UV-driven oxidative injury. Reviews of skin biology support both systemic and topical relevance, while controlled human studies have shown clinical improvement of photodamaged skin together with enhancement of collagen-associated endpoints after topical application. Vitamin C is therefore best interpreted as a matrix-preserving and repair-supportive measure (Pullar et al., 2017; Al-Niaimi and Chiang, 2017; Humbert et al., 2003).

Zinc

Zinc is most appropriately considered a supportive micronutrient for barrier maintenance, wound repair, and inflammatory regulation. Dermatologic literature emphasizes its importance for keratinocyte function, immune homeostasis, and orderly healing. Within the context of genetically modulated photoaging, zinc acts primarily by supporting barrier stability and tissue repair, thereby mitigating the downstream consequences of inflammatory injury. Its relevance is therefore likely greatest in settings of recurrent inflammatory stress, in which restoration of epithelial integrity and controlled immune responses are essential for limiting secondary tissue damage. Within this framework, zinc is best regarded as a supportive component of cutaneous resilience rather than a primary modulator of upstream cytokine signaling (Schwartz et al., 2005).

TABLE 1: SELECTED GENETIC AND FUNCTIONAL POLYMORPHISM STUDIES HIGHLIGHTING INFLAMMATION-DRIVEN SUSCEPTIBILITY TO CUTANEOUS PHOTOAGING

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Dominici et al., 2002	**Design:** Functional promoter / transcription-regulatory study. **Population:** In vitro cloning and reporter analysis of the IL1A transcriptional regulatory region. **SNP:** IL1A promoter polymorphism −889 C/T (rs1800587).	Demonstrated functional allelic differences in the transcription-regulatory region of IL1A, supporting altered transcriptional control as a mechanism for interindividual inflammatory variability.
Gore et al., 1998	**Design:** Case-control association study. **Population:** Adults with periodontitis and control subjects. **SNP:** *IL1B* +3953 C/T (allele 2; rs1143634).	Reported that +3953 allele 2 of *IL1B* was associated with inflammatory disease status, supporting the biological relevance of *IL1B* variation to high-inflammatory phenotypes.

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
González et al., 2003	**Design:** Clinical genetic association study. **Population:** Patients with Crohn's disease, including fistulizing phenotype. **SNP:** TNFA −308 G/A (rs1800629).	Showed that the −308A promoter variant was associated with enhanced *TNF*-α production and greater inflammatory activity in vivo, supporting functional relevance of TNFA regulatory variation.
Lakka et al., 2006	**Design:** Genetic association study within exercise cohort. **Population:** 688 healthy adults (456 White, 232 Black) in the HERITAGE Family Study undergoing a 20-week exercise program. **SNP:** TNFA G−308A (rs1800629).	The AA genotype was associated with higher plasma *CRP* levels and a less favorable *CRP* response to exercise, linking TNFA variation to downstream inflammatory burden.
Li et al., 2015	**Design:** Meta-analysis of case-control studies. **Population:** 5 studies; 728 acne cases and 825 controls. **SNP:** TNFA 308 G>A (rs1800629).	Reported a significant association between TNFA 308 G>A and acne susceptibility, providing dermatologic support for TNFA-linked inflammatory predisposition.

CONCLUSION

Cutaneous photoaging is best understood as the product of both cumulative ultraviolet (UV) exposure and the inflammatory response to UV-induced tissue injury. Collectively, common variation in *TNFA*, *IL1A*, *IL1B*, *IL6*, *IL6R*, and *CRP* contributes to interindividual differences in inflammatory tone. By influencing cytokine inducibility, receptor-related signaling behavior, and downstream acute-phase output, these loci influence the magnitude, duration, and resolution of post-UV inflammatory responses in skin. Such effects provide a mechanistic basis for enhanced leukocyte recruitment, oxidative stress, matrix metalloproteinase activation, extracellular-matrix degradation, and delayed tissue recovery, thereby increasing susceptibility to inflammation-driven photoaging (Salminen et al., 2022; Ansary et al., 2021; Dominici et al., 2002; Gore et al., 1998; González et al., 2003; Fishman et al., 1998; Galicia et al., 2004; Obisesan et al., 2004).

The evidence supports a pathway-level interpretation in which inherited inflammatory responsiveness drives susceptibility to inflammation-driven photoaging. Within this framework, omega-3 fatty acids combined with moderation of arachidonic-acid-derived inflammatory signaling form the most direct nutritional intervention, and methylsulfonylmethane (MSM) is recommended as a sulfur-based anti-inflammatory and antioxidative compound that is absorbed both through the skin and through the diet. Resveratrol, vitamin D, vitamin C, and zinc are further recommended actives that attenuate oxidative stress, temper inflammatory amplification, improve barrier recovery, and support extracellular-matrix repair. Taken together, a precision-prevention model in which a pro-inflammatory genetic background strengthens the rationale for combining targeted nutritional and topical strategies with appropriate photoprotection is clearly supported (Pilkington et al., 2011; Berardesca et al., 2008; Chu et al., 2022; Ratz-Łyko and Arct, 2019; Bocheva et al., 2021; Pullar et al., 2017; Schwartz et al., 2005).

REFERENCES

- Gahring LC, Baltz ML, Pepys MB, Daynes RA. Effect of ultraviolet radiation on production of epidermal cell thymocyte-activating factor/interleukin 1 in vivo and in vitro. Proc Natl Acad Sci U S A. 1984;81(4):1198-1202.
- Ansary TM, Hossain MR, Kamiya K, Komine M, Ohtsuki M. Inflammatory molecules associated with ultraviolet radiation-mediated skin aging. Int J Mol Sci. 2021;22(8):3974.
- Salminen A, Kaarniranta K, Kauppinen A. Photoaging: UV radiation-induced inflammation and immunosuppression accelerate the aging process in the skin. Inflamm Res. 2022;71(7-8):817-831.
- Pilkington SM, Watson REB, Nicolaou A, Rhodes LE. Omega-3 polyunsaturated fatty acids: photoprotective macronutrients. Exp Dermatol. 2011;20(7):537-543.
- González S, Rodrigo L, Martínez-Borra J, López-Vázquez A, Fuentes D, Niño P, et al. *TNF*-alpha -308A promoter polymorphism is associated with enhanced *TNF*-alpha production and inflammatory activity in Crohn's patients with fistulizing disease. Am J Gastroenterol. 2003;98(5):1101-1106.
- Dominici R, Cattaneo M, Malferrari G, Archi D, Mariani C, Grimaldi LM, et al. Cloning and functional analysis of the allelic polymorphism in the transcription regulatory region of interleukin-1 alpha. Immunogenetics. 2002;54(2):82-86.
- Gore EA, Sanders JJ, Pandey JP, Palesch Y, Galbraith GM. Interleukin-1beta+3953 allele 2: association with disease status in adult periodontitis. J Clin Periodontol. 1998;25(10):781-785.
- Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest. 1998;102(7):1369-1376.
- Galicia JC, Tai H, Komatsu Y, Shimada Y, Akazawa K, Yoshie H. Polymorphisms in the IL-6 receptor (IL-6R) gene: strong evidence that serum levels of soluble IL-6 receptor are genetically influenced. Genes Immun. 2004;5(6):513-516.
- Obisesan TO, Leeuwenburgh C, Phillips T, Ferrell RE, Phares DA, Prior SJ, et al. C-reactive protein genotypes affect baseline, but not exercise training-induced changes, in C-reactive protein levels. Arterioscler Thromb Vasc Biol. 2004;24(10):1874-1879.
- Berardesca E, Cameli N, Cavallotti C, Levy JL, Piérard GE, de Paoli Ambrosi G. Combined effects of silymarin and methylsulfonylmethane in the management of rosacea: clinical and instrumental evaluation. J Cosmet Dermatol. 2008;7(1):8-14.
- Chu SG, Chang YJ, Ryu JY, Lee JS, Choi KY, Chung HY, et al. Effects of methylsulfonylmethane on UVB-induced skin damage: an experimental study in a mouse model. In Vivo. 2022;36(6):2714-2721.
- Ratz-Łyko A, Arct J. Resveratrol as an active ingredient for cosmetic and dermatological applications: a review. J Cosmet Laser Ther. 2019;21(2):84-90.
- Bocheva G, Slominski RM, Slominski AT. The impact of vitamin D on skin aging. Int J Mol Sci. 2021;22(16):9097.
- Pullar JM, Carr AC, Vissers MCM. The roles of vitamin C in skin health. Nutrients. 2017;9(8):866.
- Schwartz JR, Marsh RG, Draelos ZD. Zinc and skin health: overview of physiology and pharmacology. Dermatol Surg. 2005;31(7 Pt 2):837-847.
- Lakka HM, Lakka TA, Rankinen T, Rice T, Rao DC, Leon AS, Skinner JS, et al. The *TNF*-alpha G-308A polymorphism is associated with C-reactive protein levels: the HERITAGE Family Study. Vascul Pharmacol. 2006;44(5):377-383.
- Bashir MM, Sharma MR, Werth VP. *TNF*-alpha production in the skin. Arch Dermatol Res. 2009a;301(1):87-91.
- Bashir MM, Sharma MR, Werth VP. UVB and proinflammatory cytokines synergistically activate *TNF*-alpha production in keratinocytes through enhanced gene transcription. J Invest Dermatol. 2009b;129(4):994-1001.
- Schneider LA, Raizner K, Wlaschek M, Brenneisen P, Gethöffer K, Scharffetter-Kochanek K. UVA-1 exposure in vivo leads to an IL-6 surge within the skin. Exp Dermatol. 2017;26:830-832.

- Illig T, Bongardt F, Schöpfer A, Müller-Scholze S, Rathmann W, Koenig W, et al. Significant association of the interleukin-6 gene polymorphisms C-174G and A-598G with type 2 diabetes. J Clin Endocrinol Metab. 2004;89(10):5053-5058.
- Huth C, Heid IM, Vollmert C, Gieger C, Grallert H, Wolford JK, et al. *IL6* gene promoter polymorphisms and type 2 diabetes: joint analysis of individual participants' data from 21 studies. Diabetes. 2006;55(10):2915-2921.
- Nikolopoulos GK, Dimou NL, Hamodrakas SJ, Bagos PG. Cytokine gene polymorphisms in periodontal disease: a meta-analysis of 53 studies including 4178 cases and 4590 controls. J Clin Periodontol. 2008;35(9):754-767.
- Louis E, Franchimont D, Piron A, Gevaert Y, Schaaf-Lafontaine N, Roland S, et al. Tumour necrosis factor (*TNF*) gene polymorphism influences *TNF*-alpha production in lipopolysaccharide (LPS)-stimulated whole blood cell culture in healthy humans. Clin Exp Immunol. 1998;113(3):401-406.
- Sookoian SC, González C, Pirola CJ. Meta-analysis on the G-308A tumor necrosis factor alpha gene variant and phenotypes associated with the metabolic syndrome. Obes Res. 2005;13(12):2122-2131.
- Jeanmonod P, von Känel R, Maly FE, Fischer JE. Elevated plasma C-reactive protein in chronically distressed subjects who carry the A allele of the *TNF*-alpha -308 G/A polymorphism. Psychosom Med. 2004;66(4):501-506.
- Li L, Wu Y, Li L, Cai YF, Geng L, Gao XH, et al. The tumour necrosis factor-alpha 308G>A genetic polymorphism may contribute to the pathogenesis of acne: a meta-analysis. Clin Exp Dermatol. 2015;40(6):682-687.
- Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr. 2002;21(6):495-505.
- Sawada Y, Saito-Sasaki N, Nakamura M. Omega 3 fatty acid and skin diseases. Front Immunol. 2021;11:623052.
- Norde MM, Oki E, Ferreira Carioca AA, Teixeira Damasceno NR, Fisberg RM, Lobo Marchioni DM, et al. Influence of *IL1B*, *IL6* and IL10 gene variants and plasma fatty acid interaction on metabolic syndrome risk in a cross-sectional population-based study. Clin Nutr. 2018;37(2):659-666.
- Jourdan C, Kloiber S, Nieters A, Becker N, Linseisen J, Boeing H, et al. Gene-PUFA interactions and obesity risk. Br J Nutr. 2011;106(8):1263-1272.
- Butawan M, Benjamin RL, Bloomer RJ. Methylsulfonylmethane: applications and safety of a novel dietary supplement. Nutrients. 2017;9(3):290.
- Scott JF, Das LM, Ahsanuddin S, Qiu Y, Binko AM, Traylor ZP, et al. Oral vitamin D rapidly attenuates inflammation from sunburn: an interventional study. J Invest Dermatol. 2017;137(10):2078-2086.
- Al-Niaimi F, Chiang NYZ. Topical vitamin C and the skin: mechanisms of action and clinical applications. J Clin Aesthet Dermatol. 2017;10(7):14-17.
- Humbert PG, Haftek M, Creidi P, Lapière CM, Nusgens BV, Richard A, et al. Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation: double-blind study vs. placebo. Exp Dermatol. 2003;12(3):237-244.