International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

ROLE OF OXIDATIVE STRESS IN ALLERGIC SKIN DISEASES

Dr. Sonam Thakur[1*] and Prof. Dr. Bai Bingxue[2]

[1]Department of Dermatology, The second affiliated hospital of Harbin Medical University, Harbin, China

[2]Department of Dermatology, Harbin Medical University, The second affiliated hospital of Harbin Medical University, Harbin, P.R.China.

ABSTRACT

Skin is the largest and outermost organ of body which forms the protective boundary of the body and functions in homeostasis mechanism. As it is the outer layer which acts as a edge between the outer environment and body it is more prone to risky effects of outer environmental as well as inner immune mediated responses. The continuous exposure to actions of environmental, physical, chemical and biological factors leads to occurrence of different skin disorders. Allergic skin conditions like Allergic contact dermatitis, Urticaria and Atopic dermatitis are common

variety of skin allergy disorder occurring in recent times. Out of the several factors relative oxygen species(ROS) and oxidative stress has been observed to be significant in skin disorders. In this review the presence of oxidative stress and its role in the pathogenesis of allergic skin diseases has been evaluated for better understanding and control of allergic skin diseases.

INTRODUCTION

Allergy is the defect of immune mechanism which results due to normally undamaging environmental elements known as allergen.[1]Allergic inflammation occurs due to collaboration between various inflammatory cells such as mast cell, basophils, lymphocytes , dendritic cells , eosinophils and neutrophils which later leads to formation of inflammatory mediators like lipids, purines, cytokines and reactive oxygen species(ROS).[2]Among all these factors ROS and oxidative stress has been more significant in recent times. The effect of oxidative stress in allergic skin disease is evaluated in this review.

Ros and oxidative stress:

ROS are oxygen free radicals efficient in producing electron which are formed during breakdown of molecular oxygen such as superoxide anion radical ($O_2^{\bullet g}$), hydroxyl radical ($HO^{\bullet g}$), nitric oxide radical ($NO^{\bullet g}$), nitric dioxide radical ($NO_2^{\bullet g}$), peroxyl radical ($ROO^{\bullet g}$) and non-radical reactive species, such as hydrogen peroxide (H_2O_2), lipid peroxides, hypochlorous acid (HOCl), peroxynitrite ($ONOO^-$) and singlet oxygen ($^1O_2$) .[3] The most important enzyme responsible for ROS production is the membrane–bound enzyme complex NAPDH oxidase (Nox)[4]

Free radicals (ROS) are produced under physiological condition and to maintain the balance of ROS and other free radicals there are antioxidants which helps in maintaining homeostasis of the skin surface. [5]The antioxidants system consist of superoxide dismutase, glutathione peroxidase and peroxiredoxins which are enzyme based system. There are also non enzyme based antioxidants which are vitamins A, C and E and glutathione polyphenols and coenzyme Q10. [6] When there is continuous increase in ROS in comparison with antioxidants the equibilirium condition of homeostasis is disturbed and it give rise to oxidative stress. [4]

Oxidative stress:

The term 'oxidative stress' is known to be a serious imbalance between formation of ROS and antioxidant defences. Sies defined it as "a disturbance in the pro-oxidant–antioxidant balance in favour of the former, leading to potential damage" in the year 1991. [7] Oxidative stress may lead to damage of biomolecules including DNA, lipids and proteins. Oxidative stress leads to a chain of reaction activating transcription factors and signaling pathways like NF-KB and p38 MAPK which further releases inflammatory mediators such as cytokines and chemokines causing inflammation.[8,9] Further increase in ROS causes more damage to cell and causes cell injury ultimately causing cell death.[10] For the assessment of level of oxidative stress certain biomarkers are used which are urine or serum nitrate for nitric oxide , melondialdehyde(MDA) for lipid oxidation and 8-hydroxydeoxyguanosine(8-OHdG) for DNA oxidation.[11]

In recent decades the role of oxidative stress has been observed to be increasing in chronic diseases such as cardiovascular disease, diabetes, neurodegenerative disorders and also in inflammatory disorders. [12,13,14] The incidence of oxidative stress is also in allergic skin conditions such as allergic contact dermatitis, urticarial and atopic dermatitis.

OXIDATIVE STRESS IN ALLERGIC SKIN DISEASES:

Contact dermatitis:

Contact dermatitis is an inflammatory, occupational and environmental disease which occurs due to exposure to chemical allergens. [15] It is of two types (a)Allergic contact dermatitis(ACD) which is a delayed type hypersensitivity reaction mediated by reactive T helper and interferon (IFN)-c producing $CD8^+$ T cells (Tc1), (b)Irritant contact dermatitis (ICD)which occurs by the primary contact with allergen and is not mediated by lymphocytes. [16,17]

ACD is more common than ICD being prevalent in 15-20% of general population to minimum one chemical, nickel being most common of them. Genetic predisposition is also evident in ACD. [115,19] The exact mechanism and pathways of ROS is not fully understood in case of contact dermatitis but it plays a significant role in pathogenesis of allergic dermatitis. Chemicals inducing ACD are haptens. These chemical allergens induce ROS .skin when exposed to chemical allergens ROS is triggered and further causes electrophilic and oxidative stress. ROS also triggers the production of inflammatory mediators like IL-4 and IFN-g Under electrophilic stress condition there is accumulation of transcription factor Nrf2 which also plays major role in ACD. [18] The evidence of oxidative stress in contact dermatitis are explained in previous studies as in explained by Okayama et al. [20] In another study by Kaur et al it is explained that systemic effect of contact dermatitis is better measured by oxidative stress parameters like TPX (Total peroxide concentration) and OSI (Oxidative stress indices) as compared to inflammatory markers and adipokine level. [21] In a recent study it is explained the effect of long term exposure of a type of environmental toxin as in phthalates leading to allergic dermatitis and also the role of oxidative stress in aggravating the condition. [22]

Urticaria:

Urticaria is a common variety of allergic diseases presenting with pruiritic, oedematous and erythematous lesion of different size which blanches under pressure. [23] It occurs mostly in adults. The exact pathogenesis of both acute and chronic urticarial is still not properly understood but it's association with oxidative stress has been observed in recent studies. Urticaria is an allergic disease of which mast cells are main effected cells. [16] Superoxide dismutase activity (SOD) is increased in case of CIU. [24,25] The antioxidants are lower in case of urticaria. Catalase activity is also decreased in physical urticaria. [26)] In the recent studies the association of oxidative stress is explained by analysis of biomarkers such as TAS and TOS. [23,27)] There are not many studies on urticaria done so more work should be done for proper understanding of urticarial.

Atopic dermatitis:

Atopic dermatitis is a chronic recurring inflammatory condition of skin clinically characterized by intense itching, dryness, erythema, papules, lichenification, exudation and discoloration. [28,29] There is history of respiratory allergy and raised level of IgE in AD. There is high prevalence in childhood which mostly persists in adolescence and adulthood affecting the quality of life of AD patients. [30]

Atopic dermatitis is multifactorial and complex in etiology. The exact pathogenesis is still not clearly understood. However, the interrelation between genetic predisposition, environmental factors, immunological, pharmacological factors and skin barrier defect are the most probable etiology of AD [31] Genetic predisposition is very common in case of AD with high incidence of family history of allergic conditions like asthma and allergic rhinitis. [31,32]

The variety of defects in the inborn immune mechanism varying from barrier defects to reduced AMP release to genetic polymorphism in PRRRs collectively affects the development and severity of AD. [32] Mutation of several genes manifested as Th2 dominance and raised IgE levels such as IL-4, IL-4 receptors, IL-13, IL-22, distorted cutaneous inflammation such as mast cell are involved in systemic atopic response. Th2 and Th22 cytokines degenerates the skin barrier by reducing filaggrin expression. Mutation in SPINK5(serine protease inhibitor kazal type 5) gene also associated with disrupted epidermis differentiation and skin barrier function. [33-37]

In recent times the role of oxidative stress in AD has been observed in many studies. These studies have determined the presence of oxidative stress in AD as well as in acute exacerbation of AD and also implicated lack of antioxidant status and increased oxidative stress as responsible factor in pathogenesis of AD. The urinary biomarkers of oxidative stress such as 8-OHdG, nitrate, selenium were found to be changed in children in AD implicating disturbed equilibrium of oxygen/nitrogen radicals and oxidative stress as a significant factor in pathogenesis of childhood AD.[38] In a recent study impairment of the serum oxidant and antioxidant balance was observed in patients of AD.[39] Urinary biomarkers of oxidative stress like 8-OHdG and malondialdehyde are used as parameters estimating severity of AD. [38]In the case –control studies by Amin et al and Sivaranjani lipid peroxidation measured by MDA was observed to be high whereas the antioxidant parameters like SOD, catalase ,vitamin A, C and E were significantly low indicating the role of high lipid peroxidation and low antioxidant status in rise of oxidative stress leading to AD. [40,5]The relation of oxidative stress and altered antioxidant defence in children with exacerbation of atopic dermatitis was observed by Tsukahara et al and also demonstrated the level of pentosidine, glycation end product and urinary concentration of 8-OHdG which were higher in AD exacerbation in children. [41,42,] In another study by Chung et al the association of Glutathione-S-transferase polymorphism with AD risk was analysed in preschool going children. [43] Supporting the role of lacking antioxidant defence system Kirino et al demonstrated the action of Hemeoxygenase-1(HO-1) an inducible antioxidant in attenuating the development of AD like lesions in mice. [44] Environmental factors are very important triggering factor for production of oxidative stress. Air pollutants like smoke, volatile organic compounds, tobacco, chemical allergens, formaldehyde etc are risk factors in AD by inducing oxidative stress in skin causing skin barrier disruption. [45] Psychological stress also act as triggering factor in skin barrier disruption leading to AD. [46] The association between depression and AD has found to be significant in recent studies. [47] Recently the relation between physical activity, increase oxidative stress and increase of proinflammatory mediators has been observed. [48]

The hallmark of the AD is an acute, sub-acute or chronic dermatitis of nondisjunctive type. [35] In AD patient's pro-inflammatory cells like tumor necrosis factor and IL-4, IL-9, IL-22 is raised. The dermis and epidermis go through various secondary changes like edema, spongiosis, cell layer parakeratosis, hyperkeratosis and dyskeratosis.

The stratum corneum functioning as defensive mechanism is lost in AD. [35,37] Keratinocytes facilitates the pro inflammatory cytokines and chemokines in inducing cellular infiltration which further aggravates the cell mediated T-lymphocytes cytokine profile. [49]

Irregular production of pro inflammatory mediators increase severity of AD.

Controlling measures for oxidative stress in allergic skin diseases:

The role of increased oxidative stress and decrease antioxidants status in pathophysiology of Allergic skin disease is very significant as reported above. So for management of allergic skin disease reduction of oxidative stress can be used as one of the strategies. It can be obtained by reducing free radical production,rise in antioxidant capacity, decrease in inflammatory and pro-inflammatory mediators, removal or avoidance of environmental and psychosocial stress and application of skin emollients in maintaining skin barrier. The combination of skin emollients, anti-inflammatory agents, immunomodulatory drugs and antioxidants would be most prominent therapeutic approach.

Melatonin:

Melatoninis an indolamine produced in pineal gland. [50] MT1 and MT2 are the melatonin receptors expressed in skin. Antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase which are significantly low in allergic skin disease are encouraged by melatonin. It also functions as protector from lipid peroxidation and act as neutralizing agent of toxic radicals. It also acts as a potent anti-inflammatory agent as documented in both in vivo and in vitro studies. [50,52] It can be helpful in regulating circadian rhythms for sleep inducing activity as well as visual, reproductive cerebrovascular, neuroendocrine function and also has immunological and immunomodulatory effects in allergic diseases. [50-53] However the melatonin is rarely used in allergic skin disease.

Heme Oxygenase-1(HO-1):

Heme oxygenase-1 (HO-1) is a 32-KD stress induced and rate limiting enzyme that catalyzes the conversion of heme into carbon monoxide, ferrous ion and biliverdin (which later converted to bilirubin). [54,55] It is a heat shock protein which is expressed in response to various stimuli and stress. [56] HO-1 provides cytoprotective effect against oxidative stress. HO-1 deficiency cases were manifested as systemic inflammation, abnormalities of coagulation, developmental failure, intravascular hemolysis, nephropathy and vascular endothelial injury. [57,58] It is an inducible antioxidant which was expressed by Kirino et al in a study where chemical induction of HO-1 attenuates the development of AD like lesion in mice suggesting the protective role against inflammation. [44] Anti-inflammatory action of HO-1 is aided by action of byproduct of HO-1 activity. The byproducts of heme degeneration which are CO, the anti-oxidant property of biliverdin and sequestration of free iron by ferritin combinely contribute to the anti-inflammatory effect with HO-1. [55,59] The inhibitory

action of HO-1 against NADPH activity and superoxide induced oxidative stress has been used as therapeutic measure in kidney disease and also as antihypertensive. [60] However therapeutic role of HO-1 has not been properly explored in case of allergic skin disease.

Vitamin A:

Vitamin A is not synthesized inside body so required Vitamin A is obtained from dietary intake. It plays important role in vision, immunity and hair follicle development as well as in carcadianrhythm and oxidative stress. It helps in regulating certain antioxidant enzymes and its capacity. [61] Also effects lipid oxidation and maintenance of skin barrier function. [51]

Vitamin D:

A steroid hormone which can be produced in a body in a chemical reaction catalyzed by UV radiation exposure.In absence of UV exposure can be obtained through diet.It's antioxidant capacity in skin is not clear but in some cases it has upregulated antioxidant genes in prostate cells such as SOD, thioredioden reductase and G6PD.Also protects prostate cells from H2O2 induced cell death. [620However no clinical efficacy of similar responses has been found in allergic skin disease.

Vitamin E:

Plevnik Kapun et al [63] observed reduced Vitamin E concentration in canine atopic dermatitis. The levels of oxidative stress markers showed marked improvement on dogs receiving Vitamin E. In humans however no such studies are done but it has been used in skin aging.

Others:

Other methods in treatment of allergic skin diseases especially in AD also apply their antioxidant capabilities. Coal tar has been used. In a recent study it is demonstrated that coal tar induces AhR dependent skin barrier repair by inducing epidermal gene and potent expression in filaggrin in AD patients. [64] Hydrogen water a potent and harmless antioxidant as explained by Yoon et al showed positive effect in relieving AD. [65] Zinc oxide (ZNO) functions asskin protective functionalized textiles as tested by Wiegand et al. [66]

Theoritically dietary antioxidant supplementation looks promising but has not been clinically efficient. [67] An ultimate approach would encompass analysis of severity and quality of life, assessment and management of environmental, physical and psychological aspects, recognition and treatment of infection and restoration of skin barrier function. [68] Additional large scale and well-designed studies are required to evaluate its role in controlling allergic skin disease.

CONCLUSION

Oxidative stress is one of the important factors in pathogenesis of allergic skin diseases.The increased oxidative stress along with low antioxidant status triggers the skin inflammationand also disruption of skin barrier function.For the further management of allergic skin diseases one of the strategies should be reduction of oxidative stress and increased antioxidant capacity. This treatment goal can be achieved by (a) avoidance of

environmental and psychological stress(b) improving skin barrier function by skin emollients. (c)use of anti-inflammatory and immunomodulatory agents. (d)using oral antioxidants supplements such as melatonin and vitamins.Also therapeutic role of HO-1 should be explored more in relation with skin diseases. Further well designed studies are required for better understanding the role of oxidative stress in skin diseases for further evaluation of cause of allergic skin disease and proper management that is not only symptomatically but overall improvent of quality of life of patients of allergic skin disease.

REFERENCES

1. Nakai K, Yoneda K, Kubota Y. Oxidative stress in allergic and irritant dermatitis: from basic research to clinical management. Recent patents on inflammation & allergy drug discovery. 2012 Sep 1;6(3):202-9.
2. Barnes PJ. Pathophysiology of allergic inflammation. Immunological reviews. 2011 Jul 1;242(1):31-50.
3. Bickers DR, Athar M. Oxidative stress in the pathogenesis of skin disease. Journal of Investigative Dermatology. 2006 Dec 31;126(12):2565-75.
4. Wagener FA, Carels CE, Lundvig D. Targeting the redox balance in inflammatory skin conditions. International journal of molecular sciences. 2013 Apr 26;14(5):9126-67.
5. Sivaranjani N, Rao SV, Rajeev G. Role of reactive oxygen species and antioxidants in atopic dermatitis. Journal of clinical and diagnostic research: JCDR. 2013 Dec;7(12):2683.
6. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. Toxicology. 2011 May 10;283(2):65-87.
7. Sies H. Oxidative stress: introduction. Oxidative stress: oxidants and antioxidants. 1991;23:21-48.
8. Halliwell B. Biochemistry of oxidative stress.
9. Kouretas D, Tsatsakis AM, Domingo JL, Wallace HA. Mechanisms involved in oxidative stress regulation. Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association. 2013 Nov;61:1.
10. Kannan K, Jain SK. Oxidative stress and apoptosis. Pathophysiology. 2000 Sep 30;7(3):153-63.
11. Nakai K, Yoneda K, Maeda R, Munehiro A, Fujita N, Yokoi I, Moriue J, Moriue T, Kosaka H, Kubota Y. Urinary biomarker of oxidative stress in patients with psoriasis vulgaris and atopic dermatitis. Journal of the European Academy of Dermatology and Venereology. 2009 Dec 1;23(12):1405-8.
12. Ferroni P, Riondino S, Buonomo O, Palmirotta R, Guadagni F, Roselli M. Type 2 diabetes and breast cancer: the interplay between impaired glucose metabolism and oxidant stress. Oxidative medicine and cellular longevity. 2015 Jun 11;2015.
13. Dizdaroglu M. Oxidatively induced DNA damage and its repair in cancer. *Mutation Research/Reviews in Mutation Research*
14. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocrine reviews. 2002 Oct 1;23(5):599-622.

15. Corsini E, Galbiati V, Nikitovic D, Tsatsakis AM. Role of oxidative stress in chemical allergens induced skin cells activation. Food and chemical toxicology. 2013 Nov 30;61:74-81.
16. Fonacier LS, Dreskin SC, Leung DY. Allergic skin diseases. Journal of Allergy and Clinical Immunology. 2010 Feb 28;125(2):S138-49.
17. Fuchs J, Zollner TM, Kaufmann R, Podda M. Redox-modulated pathways in inflammatory skin diseases. Free Radical Biology and Medicine. 2001 Feb 15;30(4):337-53.
18. El Ali Z, Gerbeix C, Hemon P, Esser PR, Martin SF, Pallardy M, Kerdine-Römer S. Allergic skin inflammation induced by chemical sensitizers is controlled by the transcription factor Nrf2. toxicological sciences. 2013 Apr 5;134(1):39-48.
19. Martin SF. Contact dermatitis: from pathomechanisms to immunotoxicology. Experimental dermatology. 2012 May 1;21(5):382-9.
20. Okayama Y. Oxidative stress in allergic and inflammatory skin diseases. Current Drug Targets-Inflammation & Allergy. 2005 Aug 1;4(4):517-9.
21. Kaur S, Zilmer K, Leping V, Zilmer M. Allergic contact dermatitis is associated with significant oxidative stress. Dermatology research and practice. 2014 Aug 11;2014
22. Shen S, Li J, You H, Wu Z, Wu Y, Zhao Y, Zhu Y, Guo Q, Li X, Li R, Ma P. Oral exposure to diisodecyl phthalate aggravates allergic dermatitis by oxidative stress and enhancement of thymic stromal lymphopoietin. Food and Chemical Toxicology. 2017 Jan 31;99:60-9.
23. Ozkaya E, Yazıcı M, Erenberk U, Dilek F, Dundaroz R. Oxidative Stress in Children with Noninfectious Acute Urticaria. Pediatric Allergy, Immunology, and Pulmonology. 2016 Mar 1;29(1):13-6.
24. Sagdic A, Sener O, Bulucu F, Karadurmus N, Yamanel L, Tasci C, Naharci I, Ocal R, Aydin A. Oxidative stress status in patients with chronic idiopathic urticaria. Allergologia et immunopathologia. 2011 Jun 30;39(3):150-3.
25. Cassano N, Raho G, Filieri M, D'Argento V, Amoruso A, Filotico R, Vena GA. Influence of desloratadine on oxidative stress markers in patients with chronic idiopathic urticaria. International journal of dermatology. 2006 Apr 1;45(4):394-6.
26. Briganti S, Cristaudo A, D'argento V, Cassano N, Turbino L, Guarrera M, Vena G, Picardo M. Oxidative stress in physical urticarias. Clinical and experimental dermatology. 2001 May 1;26(3):284-8.
27. Dilek F, Ozceker D, Ozkaya E, Guler EM, Yazici M, Tamay Z, Kocyigit A, Guler N. Elevated Nitrosative Stress in Children with Chronic Spontaneous Urticaria. International Archives of Allergy and Immunology. 2017;172(1):33-9.
28. Ji H, Li XK. Oxidative stress in atopic dermatitis. Oxidative medicine and cellular longevity. 2016 Feb 23;2016.
29. Corren J. Inflammatory Disorders Associated with Allergy: Overview of Immunopathogenesis and Implications for Treatment. Immunology and Allergy Clinics of North America. 2017 Mar 3.

30. Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy. 2015 Jul 1;70(7):836-45.
31. Leung DY. Pathogenesis of atopic dermatitis. Journal of Allergy and Clinical Immunology. 1999 Sep 30;104(3):S99-108.
32. Brown SJ, McLean WI. Eczema genetics: current state of knowledge and future goals. Journal of Investigative Dermatology. 2009 Mar 31;129(3):543-52.
33. De Benedetto A, Agnihothri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects?. Journal of Investigative Dermatology. 2009 Jan 31;129(1):14-30.
34. Furue M, Chiba T, Tsuji G, Ulzii D, Kido-Nakahara M, Nakahara T, Kadono T. Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies. Allergology International. 2017 Jan 2.
35. Pasparakis M, Haase I, Nestle FO. Mechanisms regulating skin immunity and inflammation. Nature Reviews Immunology. 2014 May 1;14(5):289-301.
36. Cheung PF, Wong CK, Ho AW, Hu S, Chen DP, Lam CW. Activation of human eosinophils and epidermal keratinocytes by Th2 cytokine IL-31: implication for the immunopathogenesis of atopic dermatitis. International immunology. 2010 Apr 21;22(6):453-67.
37. Darlenski R, Kazandjieva J, Tsankov N. Skin barrier function: morphological basis and regulatory mechanisms. J Clin Med. 2011;4(1):36-45.
38. Omata N, Tsukahara H, Ito S, Ohshima Y, Yasutomi M, Yamada A, Jiang M, Hiraoka M, Nambu M, Deguchi Y, Mayumi M. Increased oxidative stress in childhood atopic dermatitis. Life sciences. 2001 Jun 1;69(2):223-8.
39. Uysal P, Avcil S, Abas Bİ, Yenisey Ç. Evaluation of Oxidant-Antioxidant Balance in Children with Atopic Dermatitis: A Case-Control Study. American journal of clinical dermatology. 2016 Oct;17(5):527-37.
40. Amin MN, Liza KF, Sarwar MS, Ahmed J, Adnan MT, Chowdhury MI, Hossain MZ, Islam MS. Effect of lipid peroxidation, antioxidants, macro minerals and trace elements on eczema. Archives of dermatological research. 2015 Sep 1;307(7):617.
41. Tsukahara H, Shibata R, Ohshima Y, Todoroki Y, Sato S, Ohta N, Hiraoka M, Yoshida A, Nishima S, Mayumi M. Oxidative stress and altered antioxidant defenses in children with acute exacerbation of atopic dermatitis. Life sciences. 2003 Apr 18;72(22):2509-16.
42. Tsukahara H, Shibata R, Ohta N, Sato S, Hiraoka M, Ito S, Noiri E, Mayumi M. High levels of urinary pentosidine, an advanced glycation end product, in children with acute exacerbation of atopic dermatitis: relationship with oxidative stress. Metabolism. 2003 Dec 31;52(12):1601-5.
43. Chung J, Oh SY, Shin YK. Association of glutathione-S-transferase polymorphisms with atopic dermatitis risk in preschool age children. Clinical chemistry and laboratory medicine. 2009 Dec 1;47(12):1475-81.
44. Kirino M, Kirino Y, Takeno M, Nagashima Y, Takahashi K, Kobayashi M, Murakami S, Hirasawa T, Ueda A, Aihara M, Ikezawa Z. Heme oxygenase 1 attenuates the development of atopic dermatitis–like lesions in

mice: Implications for human disease. Journal of Allergy and Clinical Immunology. 2008 Aug 31;122(2):290-7.

45. Ahn K. The role of air pollutants in atopic dermatitis. Journal of Allergy and Clinical Immunology. 2014 Nov 30;134(5):993-9.
46. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. Current opinion in allergy and clinical immunology. 2005 Feb 1;5(1):23-9.
47. Sanna L, Stuart AL, Pasco JA, Jacka FN, Berk M, Maes M, O'Neil A, Girardi P, Williams LJ. Atopic disorders and depression: findings from a large, population-based study. Journal of affective disorders. 2014 Feb 28;155:261-5.
48. Kruk J, Duchnik E. Oxidative stress and skin diseases: possible role of physical activity. Asian Pac J Cancer Prev. 2014 Jan 1;15(2):561-8.
49. Albanesi C. Keratinocytes in allergic skin diseases. Current opinion in allergy and clinical immunology. 2010 Oct 1;10(5):452-6.
50. Marseglia L, D'Angelo G, Manti S, Salpietro C, Arrigo T, Barberi I, Reiter RJ, Gitto E. Melatonin and atopy: role in atopic dermatitis and asthma. International journal of molecular sciences. 2014 Aug 4;15(8):13482-93.
51. Ndiaye MA, Nihal M, Wood GS, Ahmad N. Skin, reactive oxygen species, and circadian clocks. Antioxidants & redox signaling. 2014 Jun 20;20(18):2982-96.
52. Mauriz JL, Collado PS, Veneroso C, Reiter RJ, González-Gallego J. A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives. Journal of pineal research. 2013 Jan 1;54(1):1-4.
53. Sánchez A, Calpena AC, Clares B. Evaluating the oxidative stress in inflammation: role of melatonin. International journal of molecular sciences. 2015 Jul 27;16(8):16981-7004.
54. Pae HO, Chung HT. Heme oxygenase-1: its therapeutic roles in inflammatory diseases. Immune network. 2009 Feb 28;9(1):12-9.
55. Rushworth SA, O'Connell MA. Haem oxygenase-1 in inflammation.
56. Abraham NG, Kappas A. Pharmacological and clinical aspects of heme oxygenase. Pharmacological reviews. 2008 Mar 1;60(1):79-127.
57. Radhakrishnan N, Yadav SP, Sachdeva A, Wada T, Yachie A. Human Heme Oxygenase-1 Deficiency Presenting with Hemolysis, Bleeding, Nephritis, Asplenia and Inflammation.
58. Yachie A, Niida Y, Wada T, Igarashi N, Kaneda H, Toma T, Ohta K, Kasahara Y, Koizumi S. Oxidative stress causes enhanced endothelial cell injury in human heme oxygenase-1 deficiency. Journal of Clinical Investigation. 1999 Jan 1;103(1):129.
59. Alam J, Stewart D, Touchard C, Boinapally S, Choi AM, Cook JL. Nrf2, a Cap'n'Collar transcription factor, regulates induction of the heme oxygenase-1 gene. Journal of Biological Chemistry. 1999 Sep 10;274(37):26071-8.

60. Datla SR, Dusting GJ, Mori TA, Taylor CJ, Croft KD, Jiang F. Induction of Heme Oxygenase-1 In Vivo Suppresses NADPH Oxidase–Derived Oxidative Stress. Hypertension. 2007 Oct 1;50(4):636-42.
61. Ponce IT, Rezza IG, Delgado SM, Navigatore LS, Bonomi MR, Golini RL, Gimenez MS, Anzulovich AC. Daily oscillation of glutathione redox cycle is dampened in the nutritional vitamin A deficiency. Biological rhythm research. 2012 Aug 1;43(4):351-72.
62. Bao BY, Ting HJ, Hsu JW, Lee YF. Protective role of 1α, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. International Journal of Cancer. 2008 Jun 15;122(12):2699-706.
63. Kapun AP, Salobir J, Levart A, Kalcher GT, Svete AN, Kotnik T. Vitamin E supplementation in canine atopic dermatitis: improvement of clinical signs and effects on oxidative stress markers. Veterinary Record. 2014 Sep 9;175(22):560.
64. van den Bogaard EH, Bergboer JG, Vonk-Bergers M, van Vlijmen-Willems IM, Hato SV, van der Valk PG, Schröder JM, Joosten I, Zeeuwen PL, Schalkwijk J. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. The Journal of clinical investigation. 2013 Feb 1;123(2):917.
65. Yoon YS, Sajo ME, Ignacio RM, Kim SK, Kim CS, Lee KJ. Positive Effects of hydrogen water on 2, 4-dinitrochlorobenzene-induced atopic dermatitis in NC/Nga mice. Biological and Pharmaceutical Bulletin. 2014 Sep 1;37(9):1480-5.
66. Wiegand C, Hipler UC, Boldt S, Strehle J, Wollina U. Skin-protective effects of a zinc oxide-functionalized textile and its relevance for atopic dermatitis. Clinical, cosmetic and investigational dermatology. 2013;6:115.
67. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. Cochrane Database of Systematic Reviews. 2005;2.
68. Hon KL, Leung AK, Barankin B. Barrier repair therapy in atopic dermatitis: an overview. American journal of clinical dermatology. 2013 Oct 1;14(5):389.