PSORIASIS: THE IMPLICATIONS OF OXIDATIVE STRESS LED PATHOGENESIS FOR DIETETIC INTERVENTIONS

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ABSTRACT

Psoriasis represents the major common dermatosis of multifactorial determination. The fundamental evolutionary biology of environs bearing skin and revelations on multistep involvement of oxidative stress in pathogenic events of psoriasis makes a strong case for medical contemplation. Very clearly the perspectives of dietetics in avoidance and amelioration of psoriasis, emerge as the least addressed in contemporary care, even at specialty level. An attempt is made to discuss the multistep pathogenic indulgence of oxidative stress to emphasize the worth attention to dietetic intervention toward rational and desired management of psoriasis.

Keywords: Psoriasis, Oxidative stress, Antioxidants, Apoptosis, Keratinocyte.

INTRODUCTION

Skin is guardian of homeostasis in the face of varied environmental conditions. The constant renewal of keratinocytes provides protection as a barrier. External insults provoke protective mechanisms, particularly, inflammation. Removal of old cells occurs through biological process of apoptosis. There is a balance between keratinocyte renewal and apoptosis. The horny skin layer made of dead keratinocytes is protective against physical and chemical insults and desquamation sheds microbial contaminants.

THE PROCESS OF APOPTOSIS

Apoptosis is self-regulated cellular suicide controlled at the organ level [1,2]. This process proceeds in several stages. These include reception of apoptotic stimuli, transduction of signal to cell nucleus, activation of lethal or killer genes, and consequent transcription of specific apoptotic proteins. Finally, the endonucleases are activated causing breakdown of DNA. A number of internal as well as external factors control apoptosis. These include hormones, cytokines, antioxidants, reactive oxygen species (ROS), calcium ion fluxes (Ca^{2+}), and different physical and chemical agents [3]. The influence of all these finds way through different signal transduction paths. Complex effects occur on phospholipase, sphingomyelin, tyrosine kinase, and protein kinase pathways that are regulating proliferation and differentiation of keratinocytes.

Oxidative stress is important in modulation of apoptosis [4-8]. Apoptosis is predominantly a gene regulated process with specific provoking [9-11] and blocking [12-14] determinants.

Higher expression of both the apoptotic signal receptors Fas and the anti-apoptotic proteins Bcl-x in skin is demonstrated in psoriasis [8]. This indicates the disturbance in differentiation and programming in apoptosis [15]. In addition, other apoptotic proteins and proliferation molecules are increased in expression in the disease [16]. Psoriasis accompanies activation of apoptotic genes Fas and p53 and anti-apoptotic protective Bcl_2, Bcl_x and Ki67 systems. Metabolic state of keratinocytes is a more responsive to apoptotic signals, through finite mechanism are not yet defined. The process of apoptosis is nevertheless, closely linked to the redox balance in the tissue [7].

KERATINOCYTE HYPERPROLIFERATION

ROS have high reactivity and short life span. They involved in local regulation of proliferation [6,12] vascular tone [17] and induction of specific genes [18]. ROS also participate as second messengers in activating apoptotic genes [5]. Several genes encoding cytokines are activated [4]. Synthesis of cyclic guanosine monophosphate, an important component of intra and extracellular communications is modulated by nitric oxide and carbon monoxide, functioning in tandem with the ROS [17-20].

Enhanced formation of ROS and lipid peroxidation (LPO) is implicated in pathogenesis of variety of diseases, but psoriasis uniquely exhibits low level of LPO. Such state of cell membranes favors ready proliferation. Enhanced synthesis of antioxidant and anti-apoptotic Bcl-x proteins [8,21] may support pathologic shift toward hyperproliferation of keratinocytes, seen in the disease. Conditions triggering differentiation and apoptosis in superficial keratinocytes hold key to pathogenesis of psoriasis and variety of stimuli have a determinant role [3]. Equally the keratinocyte readiness to perceive signals and the antioxidant extracellular milieu [7,21] are important.

Skin evolved in environment of oxygen which naturally impact [5] processes of development, maturation and death of keratinocytes, by continuous exposure to free environment. In psoriasis, keratinocytes grow rapidly within inflammatory environment and low LPO profile. This cuts short the proper differentiation or maturation events. Rapidly the cells face oxidative stress with an expression of apoptotic receptors Fas [15] and p53 [16]. Oxidative stress induced apoptosis of the granular layer cells results in the formation of defective horny layer, the key feature driving skin damage spread and chronicity of the disease.

Learning points

- Increased proliferation and apoptosis of keratinocytes is well known in psoriasis.
- It is increased sensitivity, mediated by metabolic effects and induced antioxidant enzymes that propells apoptosis in psoriasis. ROS are the obvious causal factors for such changes in psoriasis. They involve directly and also through various other secondary effective molecular processes crucial in hyper proliferation and apoptosis.

IMMUNE DYSFUNCTION

Current findings in psoriasis indicate to autoimmune pathogenesis. Elevated circulating immune complexes correlate duration and severity of the disease. Injuries by scratches provoke inflammation. Intense proliferation associating inflammation with activated proteolysis uncovers latent skin antigens liable to activating synthesis of autoantibodies. Normally, the lymphocyte clones engaging in synthesis of autoantibodies are eliminated by regulatory immune mechanism. The low LPO in psoriatic keratinocytes and ROS involved apoptosis impairs immunological regulatory mechanisms [22]. The vicious circle perpetuates to spread psoriasis lesions.

Inflammation and leukocyte activation are initiated with the release of inflammatory mediators following deposition of immune complexes and binding of complement components in cutaneous microvasculature. Intense inflammation results in local hypoxia and lower antioxidant profile further stimulating of keratinocyte proliferation.

Psoriasis represents a genotypic multifactorial dermatosis. Genes encoding apoptotic receptor Fas and anti-apoptotic Bcl_2 and Bcl_x proteins, as well as enzymatic and nonenzymatic antioxidant mechanisms are prominently at focus of psoriasis molecular biology [15,23,24]. Clonal selection of autoantibody-producing cells is affected by changes in LPO and disturbances in apoptosis. On the other hand, activation of antioxidant mechanisms in reaction to infection only aggravates psoriasis. The infectious and immunological concept of psoriasis is based on such revelations.

> **Learning points**
> - Autoimmune mechanisms are believed to be involved in pathogenesis of psoriasis. The current therapies attempt to control their effects and effectors but not the causal factors.
> - ROS are linked to autoimmunity by exposing latent skin antigens as well as causing impairment of immune regulatory mechanisms. They have major causal relation to autoimmunity in psoriasis.

NEURO-ENDOCRINE DISORDER

The development of psoriasis with emotional and autonomic disturbances calls attention to role of Neuroendocrine mechanisms in pathogenesis. The pituitary-adrenal system has intricate role in the regulation of stress responses and inflammation [25]. The process of apoptosis is subject to hormonal influences and its disorder is crucial in the pathogenesis of psoriasis. This is confounded by psychophysiological disruptions consequent to stigma [26,27] and an impact of adverse personal habits [28]. Subtle impacts of the neuroendocrine disturbances may compromise microcirculation in skin hypoxia triggers paracrine mechanisms aggravating pathology with major involvement of ROS [29,30].

> **Learning points**
> - Stress is well known to associate with and aggravate psoriasis.
> - The neuro-endocrine activity of stress affects microcirculation and is trigger to pathogenic mechanisms involving major role of oxidative stress.

INTERPLAY OF ROS, ANTIOXIDANTS AND CYTOKINES

Redox state (i.e., the balance between pro and anti-oxidant activities) of cells is regulator of fundamental process as signal transduction, gene expression, inflammation, and apoptosis [31,32]. Among the bio-molecules generated by influence of oxidative stress, cytokines are the major regulators of immune responses and are involved in driving inflammation, carcinogenesis, and apoptosis [33,34]. Antioxidant defense includes enzymes and low molecular compounds. Enzymes are superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Low molecular antioxidants are glutathione, contributing to recycling of other oxidized antioxidants, uric acid, ascorbic acid,

and lipid soluble α-tocopherol. Keratinocytes produce some cytokines physiologically but can be induced to produce and release pro-inflammatory cytokines that involve ROS as mediators [35]. Among the multiple cytokines produced, interleukin 1β and tumor necrosis factor-α (TNF-α) are known to induce cellular production of ROS. The relationship between the redox state and cytokines has a key role in cutaneous pathophysiology via cellular pathways. These pathways contain phosphorylation and gene expression which are mediated mainly by NFκB, nitric oxide radicals and proteins kinases [36].

The redox state and cytokines play a major role in redox cutaneous homeostasis and interference in ROS-induced immune modulation can associate immune disorder of skin [37]. Since antioxidant imbalance is implicated in the pathogenesis of inflammatory skin disease, supplementation of antioxidants appeals as a rational approach to restore homeostasis. Pro-inflammatory cytokines interleukin-8, TNF-α, and interferon-γ produced in excess from psoriatic keratinocytes also promote inducible nitric oxide synthase expression in the cell [38]. Under influence of the stated cytokines, the enzyme produces nitric oxide radicals which play a key role in recruiting T-lymphocytes and neutrophils. The immune-mediated inflammation is thus established and perpetuated.

> **Learning points**
> - Dominant role of cytokines in pathology of psoriasis is established.
> - It is the relationship between the cytokines and the oxidative stress that plays a pivotal role in pathophysiology of psoriasis via diverse cellular pathways of immune and inflammatory mechanisms.

PROSPECTS FOR PROTECTIVE/AMELIORATIVE DIETETICS

The dietetic perspectives based on contemporary understanding were earlier reviewed [36]. Psoriasis has distinct pathogenesis yet bears strong association with co-morbidity of metabolic syndrome [39]. This has to be based on the causative elements of metabolic syndrome and psoriasis sharing inflammation as feature [40]. There are reports of benefit of fasting and calories restriction in psoriasis also [41]. The specific dietetic perspective need to adapt to the same concerns that envisage advances in future psoriasis therapy [42]. There is need to develop phenotypic understanding toward refining preventive and ameliorative strategies in drugs and dietetic management. Focus is to be on bioregulatory agents that only check aberrant and not normal immune/inflammatory and proliferative function. These should target signaling pathways, regulate balance of lymphocyte subset functions, specifically counter aggressive cytokines, and mediators of various facets in disease pathogenesis.

The inflammatory triggers release arachidonic acid from membrane phospholipids to generate 2-carbon series of potent inflammatory eicosanoid mediators. Meat products are rich in arachidonic acid. Mixed vegetable oils and sunflower oil contribute to linoleic acid consumption which gets converted to arachidonic acid. Monounsaturated fat, e.g., olive oil consumption avoids this. The omega-3 fats and gamma linolenic acid produce 1 and 3 carbon anti-inflammatory eicosanoids. Omega-3 fat Eicosapentaenoic acid is available in fish oil and cold water fish. Flax seed provides alfa-linolenic acid that gets converted to the eicosapentaenoic acid. Borage seed oil, black current oil, evening primrose oil all promote 1-C series eicosanoid synthesis [43-46].

Antioxidant micronutrients as vitamin C, vitamin E, selenium, beta-carotene, etc., as well as vitamin B, especially B_6 and magnesium, selenium, serve as cofactors and coenzymes to enhance synthesis of the anti-inflammatory 1-C and 3-C series eicosanoids. These also to an extent disrupt inflammatory processes provoked by cytokine TNF-α [47].

Bioactive compounds in many herbs are directly inhibitory to enzymes cyclo-oxygenase and lipoxygenases which make inflammatory 2-C

series eicosanoids from arachidonic acid. Such usefulness is seen with curcumin, ginger, boswellia, white willow, etc., all of which are edible [48-50].

Inflammatory cytokines, e.g., TNF-α activate transcription factor NFκB which then upregulates genes coding inflammatory proteins and hyperproliferative mediators as interleukins-1, 6, 8, etc. Natural agents as curcumin, quercetin, vitamin B_6 and catechins can downregulate TNF-α and NFκB in over activated inflammatory cells as macrophages, without affecting blissfully, the normal level inflammatory capability. The effect is uniquely bioregulatory. Again the stated bioactive agents are easily available from edible plant resource. Reishi mushrooms and astragalus are very effective too [51].

Vitamin D has unique role to benefit immune-mediated inflammatory state by promoting formation of anti-inflammatory cytokines interleukin 4 and anti-microbial peptides, again exhibiting bio-regulatory effect [52]. Folate is found to be particularly scavenger of peroxynitrile radicals, so important in psoriatic inflammation [53].

Prebiotics and probiotics exert a significant immunomodulatory effect as well [54,55]. The reports emphasize crucial need to improve micronutrients in diet. This may summarily be helped by increasing consumption of fruits, nuts, seeds, non-starchy vegetables, and fish. Cruciferous vegetables are particularly protective. On the contrary above information suggests need to avoid excess dairy products, meat consumption, sugary refined foods and drinks. Very prudent is to give up alcohol and smoking.

Learning points

• Dietary items are known to have pro- and anti-inflammatory potentials and in psoriasis anti-inflammatory foods are preferable while pro-inflammatory food is avoidable.

• There are evolutionary and biochemical/immunological bases of choosing from available dietary options. The role of dietary factors in epigenome function is crucial to appreciate and consider in individual cases.

• The micronutrient balanced or enriched nutrition is suggestive of critical significance in management and prevention of psoriasis.

• Convergence with dietetic selection and application is integral to rational psoriasis management.

EPILOGUE

Traditionally, the topical agents as corticosteroids, retinoids, and vitamin D_3 analogs, systemic methotrexate, ciclosporin, and retinoids as well as phototherapy form therapeutic means. Their inconvenience and adverse effects compromise the adherence to and success of therapy, particularly in early mild disease. The immunologicals developed through biotechnology advances are visibly too slow to find favor in dermatology practice at large. There is interest in immune-modulatory – anti-inflammatory less toxic and acceptable oral agents such as fumarate [56], cannabinoids, allopurinol, and loratadine [57] and new class of the phosphodiesterase-4 inhibitors [58]. The overview of events in psoriasis pathogenesis reveals the significance of resting derailed index of cutaneous redox state for therapeutic rationale. Such a shift would reduce inflammation and improve microcirculation and proper tissue respiration, reducing risk of vascular endothelial growth factor production, which appears to be important in persistence and spread of psoriatic skin lesion [59]. Modern emphasis of evolving systems approach is on attempting personalized therapeutics [60]. The technical aids for the same are only developing. High and low responders to oxidative stress may involve genetic determinants but also nutrition shall answer such challenge. The advances in understanding on protective nutrients and harmful nutrients are impressive and represent very logical intervention to comprehensive rational management of psoriasis.

REFERENCES

1. Vriz S, Reiter S, Galliot B. Cell death: A program to regenerate. Curr Top Dev Biol 2014;108:121-51.
2. Alison MR, Sarraf CE. Apoptosis: A gene-directed programme of cell death. J R Coll Physicians Lond 1992;26(1):25-35.
3. Thatte U, Dahanukar S. Apoptosis: Clinical relevance and pharmacological manipulation. Drugs 1997;54(4):511-32.
4. Fidelus RK. The generation of oxygen radicals: A positive signal for lymphocyte activation. Cell Immunol 1988;113(1):175-82.
5. Cerutti PA. Oxidant stress and carcinogenesis. Eur J Clin Invest 1991;21:1-5.
6. Allen RG. Oxygen-reactive species and antioxidant responses during development: The metabolic paradox of cellular differentiation. Proc Soc Exp Biol Med 1991;196:117-29.
7. Chaudhuri J, Chowdhury AA, Biswas N, Manna A, Chatterjee S, Mukherjee T, *et al.* Superoxide activates mTOR-eIF4E-Bax route to induce enhanced apoptosis in leukemic cells. Apoptosis 2014;19(1):135-48.
8. Whitacre CM, Cathcart MK. Oxygen free radical generation and regulation of proliferative activity of human mononuclear cells responding to different mitogens. Cell Immunol 1992;144(2):287-95.
9. Bissonnette RP, McGahon A, Mahboubi A, Green DR. Functional Myc-Max heterodimer is required for activation-induced apoptosis in T cell hybridomas. J Exp Med 1994;180(6):2413-8.
10. Lane DP, Lu X, Hupp T, Hall PA. The role of the p53 protein in the apoptotic response. Philos Trans R Soc Lond B Biol Sci 1994;345(1313):277-80.
11. Lowe SW, Schmitt EM, Smith SW, Osborne BA, Jacks T. p53 is required for radiation-induced apoptosis in mouse thymocytes. Nature 1993;362(6423):847-9.
12. Hockenbery D, Nunez G, Milliman C, Schreiber RD, Korsmeyer SJ. Bcl2 is an inner mitochondrial membrane protein that blocks programmed cell death. Nature 1980;348(6299):334-6.
13. Korsmeyer SJ, Yin XM, Oltvai ZN, Veis-Novack DJ, Linette GP. Reactive oxygen species and the regulation of cell death by the Bcl-2 gene family. Biochim Biophys Acta 1995;1271(1):63-6.
14. Osawa T, Kato Y. Protective role of antioxidative food factors in oxidative stress caused by hyperglycemia. Ann N Y Acad Sci 2005;1043:440-51.
15. Jost M, Class R, Kari C, Jensen PJ, Rodeck U. A central role of Bcl-X(L) in the regulation of keratinocyte survival by autocrine EGFR ligands. J Invest Dermatol 1999;112(4):443-9.
16. Batinac T, Zamolo G, Jonjic N, Gruber F, Petrovecki M. p53 protein expression and cell proliferation in non-neoplastic and neoplastic proliferative skin diseases. Tumori 2004;90(1):120-7.
17. Moncada S, Palmer RM, Higgs EA. Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43(2):109-42.
18. Bowden GT, Schneider B, Domann R, Kulesz-Martin M. Oncogene activation and tumor suppressor gene inactivation during multistage mouse skin carcinogenesis. Cancer Res 1994;54 7 Suppl:1882s-5.
19. Verma A, Hirsch DJ, Glatt CE, Ronnett GV, Snyder SH. Carbon monoxide: A putative neural messenger. Science 1993;259(5093):381-4.
20. Chávez MD, Lakshmanan N, Kavdia M. Impact of superoxide dismutase on nitric oxide and peroxynitrite levels in the microcirculation – A computational model. Conf Proc IEEE Eng Med Biol Soc 2007;2007:1022-6.
21. Rashedi I, Panigrahi S, Ezzati P, Ghavami S, Los M. Autoimmunity and apoptosis – Therapeutic implications. Curr Med Chem 2007;14(29):3139-51.
22. Cohen JJ. Programmed cell death and apoptosis in lymphocyte development and function. Chest 1993;103 2 Suppl:99S-101.
23. Feldman GM, Rosenthal LA, Liu X, Hayes MP, Wynshaw-Boris A, Leonard WJ, *et al.* Stat-5A deficient mice demonstrate a defect in granulocyte-macrophase colony stimulating factor induced proliferation and gene expression. Blood 1997;90(5):1768-76.
24. Takahashi H, Tsuji H, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Cell proliferation and cytokine induction by TNF-alpha of psoriatic keratinocytes are not different from normal keratinocytes *in vitro*. Indian J Dermatol 2009;54(3):237-9.
25. Weigl BA. The significance of stress hormones (glucocorticoids, catecholamines) for eruptions and spontaneous remission phases in psoriasis. Int J Dermatol 2000;39(9):678-88.
26. Chaturvedi SK, Singh G, Gupta N. Stigma experience in skin disorders: An Indian perspective. Dermatol Clin 2005;23(4):635-42.
27. Fried RG, Friedman S, Paradis C, Hatch M, Lynfield Y, Duncanson C, *et al.* Trivial or terrible? The psychosocial impact of psoriasis. Int J

Dermatol 1995;34(2):101-5.

28. Higgins E. Alcohol, smoking and psoriasis. Clin Exp Dermatol 2000;25(2):107-10.

29. Kim YW, Byzova TV. Oxidative stress in angiogenesis and vascular disease. Blood 2014;123(5):625-31.

30. Zhou C, Yu X, Cai D, Liu C, Li C. Role of corticotropin-releasing hormone and receptor in the pathogenesis of psoriasis. Med Hypotheses 2009;73(4):513-5.

31. Dröge W. Free radicals in the physiological control of cell function. Physiol Rev 2002;82(1):47-95.

32. Lavrovsky Y, Chatterjee B, Clark RA, Roy AK. Role of redox-regulated transcription factors in inflammation, aging and age-related diseases. Exp Gerontol 2000;35(5):521-32.

33. Das RP, Jain AK, Ramesh V. Current concepts in the pathogenesis of psoriasis. Indian J Dermatol 2009;54(1):7-12.

34. Raychaudhury SP. Recent advances in psoriasis: Bench to bedside. Indian J Dermatol 2010;55(2):150.

35. Lima HC, Kimball AB. Targeting IL-23: Insights into the pathogenesis and the treatment of psoriasis. Indian J Dermatol 2010;55(2):171-5.

36. Pandey G, Pandey AK. Nutrition research perspectives in immune mediated inflammatory disorders. Indian J Rheumatol 2013;8:30-6.

37. Trouba KJ, Hamadeh HK, Amin RP, Germolec DR. Oxidative stress and its role in skin disease. Antioxid Redox Signal 2002;4(4):665-73.

38. Bruch-Gerharz D, Fehsel K, Suschek C, Michel G, Ruzicka T, Kolb-Bachofen V. A proinflammatory activity of interleukin 8 in human skin: Expression of the inducible nitric oxide synthase in psoriatic lesions and cultured keratinocytes. J Exp Med 1996;184(5):2007-12.

39. Tidman MJ. Improving outcomes in patients with psoriasis. Practitioner 2013;257(1757):27-30, 3.

40. Pandey AK, Pandey G, Pandey SS, Pandey BL. Human biology of diet and lifestyle linked chronic inflammatory non-communicable disease epidemic - A review. Hum Biol Rev 2014;3:25-42.

41. Wolters M. The significance of diet and associated factors in psoriasis. Hautarzt 2006;57(11):999-1004.

42. Wippel-Slupetzky K, Stingl G. Future perspectives in the treatment of psoriasis. Curr Probl Dermatol 2009;38:172-89.

43. Azzini M, Girelli D, Olivieri O, Guarini P, Stanzial AM, Frigo A, *et al.* Fatty acids and antioxidant micronutrients in psoriatic arthritis. J Rheumatol 1995;22(1):103-8.

44. Basavaraj KH, Seemanthini C, Rashmi R. Diet in dermatology: Present perspectives. Indian J Dermatol 2010;55(3):205-10.

45. Ziboh VA. Implications of dietary oils and polyunsaturated fatty acids in the management of cutaneous disorders. Arch Dermatol 1989;125(2):241-5.

46. Ziboh VA, Miller CC, Cho Y. Metabolism of polyunsaturated fatty acids by skin epidermal enzymes: Generation of antiinflammatory and antiproliferative metabolites. Am J Clin Nutr 2000;71 1 Suppl:361S-6.

47. Greenberger S, Harats D, Salameh F, Lubish T, Harari A, Trau H, *et al.* 9-cis-rich ß-carotene powder of the alga Dunaliella reduces the severity of chronic plaque psoriasis: A randomized, double-blind, placebo-controlled clinical trial. J Am Coll Nutr 2012;31:320-6.

48. Reuter J, Merfort I, Schempp CM. Botanicals in dermatology: An evidence-based review. Am J Clin Dermatol 2010;11(4):247-67.

49. Lv H, She G. Naturally occurring diarylheptanoids. Nat Prod Commun 2010;5(10):1687-708.

50. Maioli E, Valacchi G. Rottlerin: Bases for a possible usage in psoriasis. Curr Drug Metab 2010;11(5):425-30.

51. Wolters M. Diet and psoriasis: Experimental data and clinical evidence. Br J Dermatol 2005;153(4):706-14.

52. Reinholz M, Schauber J. Vitamin D and innate immunity of the skin. Dtsch Med Wochenschr 2012;137(46):2385-9.

53. McCarty MF, Barroso-Aranda J, Contreras F. High-dose folate and dietary purines promote scavenging of peroxynitrite-derived radicals – Clinical potential in inflammatory disorders. Med Hypotheses 2009;73(5):824-34.

54. Schley PD, Field CJ. The immune-enhancing effects of dietary fibres and prebiotics. Br J Nutr 2002;87 Suppl 2:S221-30.

55. Solis-Pereyra B, Lemonnier D. Induction of human cytokines by bacteria used in dairy foods. Nutr Res 1993;13:1127-40.

56. Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: More than a dietary curiosity. Trends Mol Med 2005;11(1):43-8.

57. Namazi MR. Cannabinoids, loratadine and allopurinol as novel additions to the antipsoriatic ammunition. J Eur Acad Dermatol Venereol 2005;19:319-22.

58. Wittmann M, Helliwell PS. Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. Dermatol Ther (Heidelb) 2013;3(1):1-15.

59. Canavese M, Altruda F, Ruzicka T, Schauber J. Vascular endothelial growth factor (VEGF) in the pathogenesis of psoriasis – A possible target for novel therapies? J Dermatol Sci 2010;58(3):171-6.

60. Ryan C, Menter A, Warren RB. The latest advances in pharmacogenetics and pharmacogenomics in the treatment of psoriasis. Mol Diagn Ther 2010;14(2):81-93.