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GLUTATHIONE AND ITS EFFECTS ON VARIOUS SKIN CELLS: AN OVERVIEW

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Abstract:
Glutathione (GSH) is a ubiquitous tri-peptide in body cells. Beside many ascribed biological effects such as antioxidant and scavenging various free radicals, it plays an important role in prevention of ultraviolet-associated melanomas and premature skin aging. As a cosmeceutical, it has skin whitening effect via three possible mechanisms. Moreover, GSH affects keratinocytes and fibroblasts and accelerates angiogenesis which finally develop wound healing process.

Keywords: *Glutathione, GSH, GSSG, Antioxidant, Oxidative stress, Melanocyte, Melanogenesis, Keratinocyte, Wound healing*

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INTRODUCTION:

Reduced Glutathione (GSH), a tripeptide (y-glutamyl-L-cysteinyl glycin) is one of the major intracellular antioxidants which is present in all cells at high concentrations (between 1 to 10 mM). It plays an important role in prevention of premature skin aging, prevention of cancerous cells formation and development of wound healing process.(Adamson, Schwarz et al. 1996) It has a key role in the process of inactivation or neutralization of intracellular oxidants like hydrogen peroxide. It neutralizes oxidants via receiving an electron.(Kopal, Deveci et al. 2007)

MATERIALS AND METHODS:

Present review highlights the literature on the effects of GSH on various skin cells. The author also emphasizes a variety of effects of this small molecule on skin cells which can be exploited in formulation of cosmetic and cosmeceuticals. Collection of data was carried out through electronic search from Scopus, Web of Science, Google Scholar and Science Direct databases.

Protection against oxidative stress

The cells generate reactive oxygen species (ROS) in response to stressful or damaging stimuli. Exposure of cells to ROS can be damaging whereas normal cells have cytoprotective enzymatic systems including superoxide dismutase (SOD), Glutathione peroxidases (GPXs) and catalase which convert ROS into harmless products.(Arthur 2000) Glutathione redox cycle is a key element in the process of neutralization of oxidant molecules. The defense against ROS can be increased via increment in levels of GSH and GSH-associated enzymatic systems.(Rees, Punch et al. 1993, Rees, Smith et al. 1995, Adamson, Schwarz et al. 1996)

In the process of oxidant inactivation oxidized form of glutathione (GSSG), is produced which is toxic.(Schafer and Werner 2008) GSSG has two fates, first is the degradation to reduced form by glutathione reductase and the second one is to be degraded by glutathione-S-transferase (GST) and then excreted from cell to its outside.(Kopal, Deveci et al. 2007) It is assumed that in vitiligo patients, overproduction of hydrogen peroxide (H2O2) can be induced by NADPH oxidase (NOX) of fibroblasts and keratinocytes and also by metabolism processes of estrogens and catecholamines.(Westerhof and d'Ischia 2007, Schallreuter, Bahadoran et al. 2008) Another important factor that aggravates the oxidative stress is hyperglycemia. It can deplete some antioxidant reservoirs and induce apoptosis of skin cells.(Kopal, Deveci et al. 2007) Increased oxidative stress is supposed to be an induction factor for apoptosis.(Godar 1999) In a study conducted by Walshe et al., all types of solar keratosis (SK) and CSCCs peroxide burden were higher than normal. In addition, activity of GPXs was lower than normal in 3 of 4 types of SK and 4 of 5 types of Cutaneous Squamous Cell Carcinomas (CSCCs).(Walshe, Serewko-Auret et al. 2007)

Protection against ultraviolet radiation (UV)

Findings have revealed that GSH has a protective effect against oxidative stress caused by UV radiation and formation of ROS.(Adamson, Schwarz et al. 1996) So after UV radiation GSH reservoirs depletion is expected in skin cells.(Meloni and Nicolay 2003) CSCCs are high prevalent malignancy of keratinocytes. Outbreak of CSCCs are in sites of skin with more exposure to UV radiation.(Walshe, Serewko-Auret et al. 2007)

Accelerating the wound healing process

Several studies have suggested the important role of GSH in wound healing.(Adamson, Schwarz et al. 1996, Mudge, Harris et al. 2002, Aktunc, Ozacmak et al. 2010) Three specific types of cells which play important role in healing the wounds are endothelial cells, keratinocytes and fibroblasts. Successful wound healing requires appropriate parallel processes including production of extracellular matrix, angiogenesis and epithelization. To fulfill these states, some interaction must be established among different structural elements of skin such as inflammatory cells, fibroblasts, keratinocytes and some of their products like growth factors and cytokines. Actually, cytokines build interaction bridges among these cells and accelerate the process of wound healing. Several studies have been shown that ischemia adversely affects the process of wound healing via disrupting the formation of extracellular matrix.(Grinnell and Zhu 1996, Vaalamo, Mattila et al. 1997, Vaalamo, Leivo et al. 1999) Decreased matrix production is a result of overactivity of metalloproteinase (MMPs) that is induced by ischemia.(Shandall, Williams et al. 1986, Mallya, Mookhtiar et al. 1990, Punch, Rees et al. 1992, Wilkins, Rees et al. 1993, Grinnell and Zhu 1996, Vaalamo, Mattila et al. 1997) Moreover, ischemia increases the levels of ROS and consumption of intracellular antioxidants including GSH and depletion of enzymes such as SOD. A study has been revealed that glutathione in both reduced and oxidized form inhibit MMPs especially MMP-2. (Upadhya and Strasberg 2000) A clinical study conducted by Mudge et al. showed that in comparison of healthy patients, lower levels of GSH were present in wound tissue samples of diabetic patients. In addition, GSSG levels were higher in comparison with intact skin sites.(Mudge B 1998)

Effects of glutathione on keratinocytes

Recent studies revealed that loss of adequate GSH can induce keratinocytes apoptosis and this can change the function of stratum corneum.(Telorack, Meyer et al. 2016) Although it has an undeniable role in ROS detoxification, but recent findings showed skin cells can tolerate low levels of GSH due to presence of other intracellular and enzymatic antioxidants. Immunohistochemical analysis of skin of vitiligo patients revealed several differences such as altered expression pattern of cytokines and behavior of keratinocytes before initiation of apoptosis between affected and unaffected areas.(Kostyuk, Potapovich et al. 2010)

As previously mentioned, hypoglycemia itself can increase oxidative stress through depletion of GSH and induce keratinocyte apoptosis. These contingencies all can retard the process of wound healing.(Mudge B 1998)

A study conducted by Kopal et al., revealed more keratinocyte apoptosis at basal layer of epidermis in control group (which had not got any topical GSH).(Kopal, Deveci et al. 2007) More apoptosis rate can reduce the migration of keratinocytes to upper layers which is necessary to successful wound healing.(Lazarus, Cooper et al. 1994, Nwomeh, Yager et al. 1998) Regarding to study conducted by Kostyuk et al., inappropriate control of redox system can cause impaired production of cytokines by keratinocytes.(Kostyuk, Potapovich et al. 2010)

Effects of glutathione on melanocytes

In an animal study which conducted on tortoiseshell guinea pigs it has founded that GSH levels are higher in red and yellow skin in comparison to areas with black skin.(Benedetto, Ortonne et al. 1981)
Some studies conducted on pigmentation revealed important relationships between the skin color and sulfhydryl-containing compounds such as GSH.

In melanogenesis process, tyrosinase (a copper-containing enzyme), a rate limiting step catalyzes the first step of melanin production pathway which converts L-tyrosine to L-DOPA. At next step dopaquinone is produced by this enzyme. Sulfhydryl-containing compounds can switch the process at this point and enter the dopaquinone into alternative pathway to produce thiol-dopa conjugates or a pathway which forms phaeomelanins and trichromes (a mixture of different melanins) which are both lighter pigements.(Sanchez-Ferrer, Rodriguez-Lopez et al. 1995) (Fig.1)

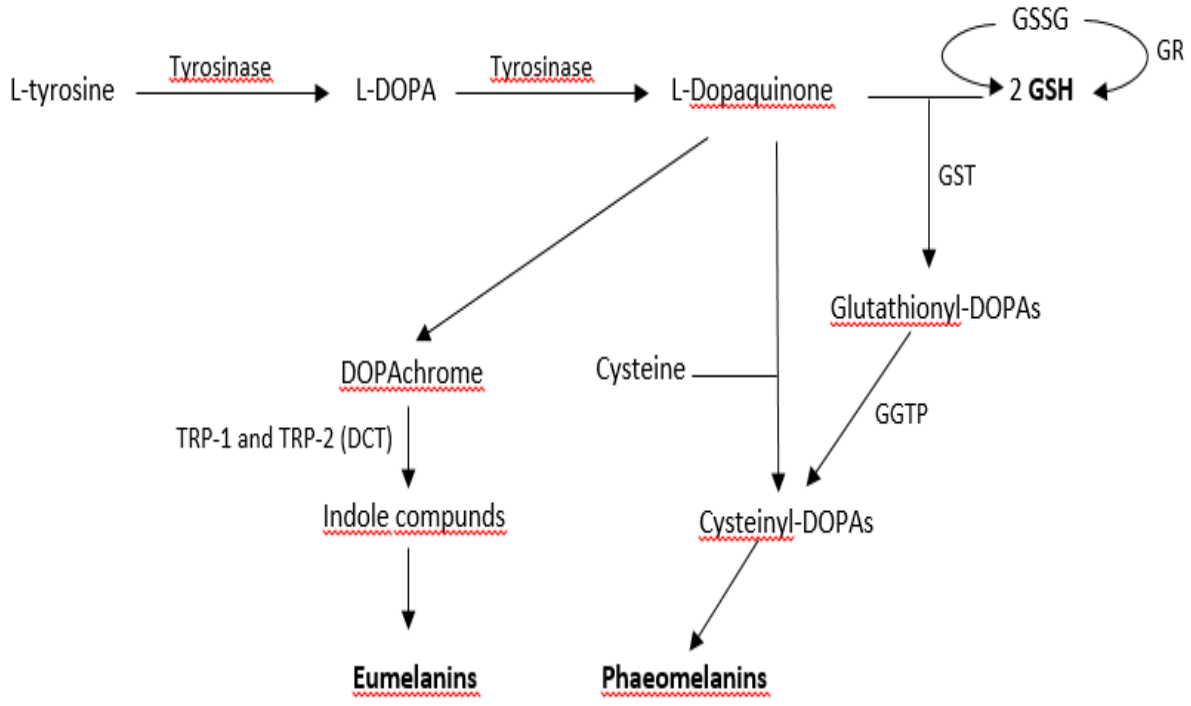

Figure1. Interpretation of the interaction of glutathione (GSH) and cysteine in tyrosinase pathway

Two studies conducted by Rothman et al. and Flesch showed the inhibitory effect of sulfhydryl-containing compounds on melanin production from tyrosine by tyrosinase activity attenuation.(Rothman, Krysa et al. 1946, Flesch 1949)

Ultraviolet radiation, X-ray, heat and inflammation can oxidize sulfhydryl-containing compounds then consequently remove the inhibitory effect on tyrosinase.(Rothman, Krysa et al. 1946)

It is assumed that glutathione affects the melanin production via three mechanisms:

- As a sulfhydryl-containing compound, glutathione may affect melanin production via copper ion chelation which presents on active site of tyrosinase, leading to its inactivation.(Lerner, Fitzpatrick et al. 1950)
- In process of tyrosinase maturation, three forms (T1, T2 and T3) of this enzyme produced.(Iwata and Takeuchi 1977) Melanogenesis initiates via transportation of tyrosinase into premelanosomes. Formation of T3 tyrosinase inhibited by transportation of golgi associated endoplasmic reticulum (GERL)-coated vesicles which contain T1 tyrosinase to premalanosomes..(Korner and Pawelek 1982) Hydrocoumarinic compounds and also alpha-tocopherol indirectly exert antimelanogenic effects by up-regulation of glutathione and subsequently by inhibition of tyrosinase transportation to premelanosomes.(Yamamura, Onishi et al. 2002)
- GSH shift the process to more phaeomelanin production. Reduced level of glutathione can cause a shift to conversion of L-dopaquinone to L-dopachrome, leading to more eumelanin production.(Prota 1980)

Aberrant production of cytokines by keratinocytes can beget defects in melanocyte proliferation and melanogenesis.(Kostyuk, Potapovich et al. 2010)
In the skin of vitiligo patients there is an imbalance between production of ROS and neutralization of them. (12, 13, 35, 46) this imbalance which considered as a cytotoxicity can inactivate melanocytes.

Effects of glutathione on fibroblasts

Proper cellular proliferation is a key factor for wound healing. Glutathione is an essential substance for cellular proliferation. Studies have shown depressed levels of glutathione causes cells to fail enter S-phase, leading to improper cell division.(Hamilos, Zelarney et al. 1989, Atzori, Dypbukt et al. 1990)

These findings are also consonant with the results of the study performed by Takeuchi et al. that have shown decreased levels of glutathione can change the temporal course of wound healing process.(Takeuchi, Okada et al. 1993). In the United States %10 of diabetic patients will develop foot ulcers. Clinical studies which performed on diabetic ulcers suggest impaired cellular metabolism of wound tissues, leading to oxidant generation.(Hansbrough, Morgan et al. 1994, Wilkins, Watson et al. 1994, Steed 1995, Gentzkow, Iwasaki et al. 1996, Sabolinski, Alvarez et al. 1996, Wieman, Smiell et al. 1998)

Wound contraction as a major requisite for wound healing is accomplished by fibroblasts.
It is postulated that wound tissues in diabetic ulcers can't retain redox potential balance due to insufficient amount of GSH.(Mudge, Harris et al. 2002)

A clinical study conducted by Mudge et al., revealed that lower intracellular GSH levels cause poor fibroblasts functions and in this condition the contraction of wound faces disruption.(Mudge B 1998)

More disturbances such as lower activity level of catalase, lower than normal levels of GSH and GSSG in erythrocytes (RBCs) of vitiligo patients have been observed by Kostyuk et al.(Kostyuk, Potapovich et al. 2010) Regarding to the role of GSH in regulation of some metabolic processes such as apoptosis, it seems that there are some more avenues to be explored in direction of GSH application in vitiligo.

CONCLUSION:

GSH is master antioxidant which can be used as the main constituent for the formulation of cosmetic and cosmeceutical preparations. The effects of GSH on melanocytes make it a good candidate for using in whitening formulations with minimum side effects and thyrosinase inhibition rebound. Because of anti-oxidant property and induction of re-epithelization of this molecule, it can be exploited as anti-aging and wound healer. Moreover, GSH can be used in after-sun preparations due to its protective effects on keratinocytes.

Conflict of interest

The author has no conflicts of interest to declare.

REFERENCES:

1. Adamson, B., D. Schwarz, P. Klugston, R. Gilmont, L. Perry, J. Fisher, W. Lindblad and R. Rees (1996). "Delayed repair: the role of glutathione in a rat incisional wound model." J Surg Res **62**(2): 159-164.
2. Aktunc, E., V. H. Ozacmak, H. S. Ozacmak, F. Barut ,M. Buyukates, O. Kandemir and N. Demircan (2010). "N-acetyl cysteine promotes angiogenesis and clearance of free oxygen radicals, thus improving wound healing in an alloxan-induced diabetic mouse model of

incisional wound." Clin Exp Dermatol **35**(8): 902.909-
3. Arthur, J. R. (2000). "The glutathione peroxidases." Cell Mol Life Sci **57**(13-14): 1825-1835.
4. Atzori, L., J. M. Dypbukt, K. Sundqvist, I. Cotgreave, C. C. Edman, P. Moldeus and R. C. Grafstrom (1990). "Growth-associated modifications of low-molecular-weight thiols and protein sulfhydryls in human bronchial fibroblasts." J Cell Physiol **143**(1): 165-171.
5. Benedetto, J. P., J. P. Ortonne, C. Voulot, C. Khatchadourian, G. Prota and J. Thivolet (1981). "Role of thiol compounds in mammalian melanin pigmentation: Part I. Reduced and oxidized glutathione." J Invest Dermatol **77**(5): 402-405.
6. Flesch, P. (1949). "Inhibitory action of extracts of mammalian skin on pigment formation." Proc Soc Exp Biol Med **70**(1): 136-140.
7. Gentzkow, G. D., S. D. Iwasaki, K. S. Hershon , M. Mengel, J. J. Prendergast, J. J. Ricotta, D. P. Steed and S. Lipkin (1996). "Use of dermagraft, a cultured human dermis, to treat diabetic root ulcers." Diabetes Care **19**(4): 350-354.
8. Godar, D. E. (1999). "Light and death: photons and apoptosis." J Investig Dermatol Symp Proc **4**(1): 17-23.
9. Grinnell, F. and M. Zhu (1996). "Fibronectin degradation in chronic wounds depends on the relative levels of elastase, alpha1-proteinase inhibitor, and alpha2-macroglobulin." J Invest Dermatol **106**(2): 335-341.
10. Hamilos, D. L., P. Zelarney and J. J. Mascali (1989). "Lymphocyte proliferation in glutathione-depleted lymphocytes: direct relationship between glutathione availability and the proliferative response." Immunopharmacology **18**(3): 223-235.
11. Hansbrough, J. F., J. Morgan, G. Greenleaf, M. Parikh, C. Nolte and L. Wilkins (1994). "Evaluation of Graftskin composite grafts on full-thickness wounds on athymic mice." J Burn Care Rehabil **15**(4): 346-353.
12. Iwata, K. and T. Takeuchi (1977). "Granule-bound tyrosinase: solubilization and its relation to the soluble form of tyrosinase." J Invest Dermatol **68**(2): 88-92.
13. Kopal, C., M. Deveci, S. Ozturk and M. Sengezer (2007). "Effects of topical glutathione treatment in rat ischemic wound model." Ann Plast Surg **58**(4): 449-455.
14. Korner, A. and J. Pawelek (1982). "Mammalian tyrosinase catalyzes three reactions in the biosynthesis of melanin." Science **217**(4565): 1163-1165.
15. Kostyuk, V. A., A. I. Potapovich, E. Cesareo, S. Brescia, L. Guerra, G. Valacchi, A. Pecorelli, I. B. Deeva, D. Raskovic, C. De Luca, S. Pastore and L. G. Korkina (2010). "Dysfunction of glutathione S-transferase leads to excess 4-hydroxy-2-nonenal and H(2)O(2) and impaired cytokine pattern in cultured keratinocytes and blood of vitiligo patients." Antioxid Redox Signal **13**(5): 607-620.
16. Lazarus, G. S., D. M. Cooper, D. R. Knighton, D. J. Margolis, R. E. Pecoraro, G. Rodeheaver and M. C. Robson (1994). "Definitions and guidelines for assessment of wounds and evaluation of healing." Arch Dermatol **130**(4): 489-493.
17. Lerner ,A. B., T. B. Fitzpatrick, E. Calkins and W. H. Summerson (1950). "Mammalian tyrosinase; the relationship of copper to enzymatic activity." J Biol Chem **187**(2): 793-802.
18. Mallya, S. K., K. A. Mookhtiar, Y. Gao, K. Brew, M. Dioszegi, H. Birkedal-Hansen and H . E. Van Wart (1990). "Characterization of 58-kilodalton human neutrophil collagenase: comparison with human fibroblast collagenase." Biochemistry **29**(47): 10628-10634.
19. Meloni, M. and J. F. Nicolay (2003). "Dynamic monitoring of glutathione redox status in UV-B irradiated reconstituted epidermis: effect of antioxidant activity on skin homeostasis." Toxicol In Vitro **17**(5-6): 609-613.
20. Mudge B, H. C., Rees R (1998). "Altered glutathione status in two examples of chronic human wounds." Surg Forum **46**: 629.
21. Mudge, B. P., C. Harris, R. R. Gilmont, B. S. Adamson and R. S. Rees (2002). "Role of glutathione redox dysfunction in diabetic wounds." Wound Repair Regen **10**(1): 52-58.
22. Nwomeh, B. C., D. R. Yager and I. K. Cohen (1998). "Physiology of the chronic wound." Clin Plast Surg **25**(3): 341-356.
23. Prota, G. (1980). "Recent advances in the chemistry of melanogenesis in mammals." J Invest Dermatol **75**(1): 122-127.
24. Punch, J., R. Rees, B. Cashmer, E. Wilkins, D. J. Smith and G. O. Till (1992). "Xanthine oxidase: its role in the no-reflow phenomenon." Surgery **111**(2): 169-176.
25. Rees, R., J. Punch, K. Shaheen, B. Cashmer, K. Guice and D. J. Smith, Jr. (1993). "The stress response in skin: the role of neutrophil products in preconditioning." Plast Reconstr Surg **92**(1): 110-117; discussion 118-119.
26. Rees, R. S., D. J. Smith, Jr., B. Adamson, M. Im and D. Hinshaw (1995). "Oxidant stress: the role of the glutathione redox cycle in skin preconditioning." J Surg Res **58**(4): 395-400.
27. Rothman, S., H. F. Krysa and A. M. Smiljanic (1946). "Inhibitory-action of human epidermis

on melanin formation." Proc Soc Exp Biol Med **62**(2): 208.
28. Sabolinski, M. L., O. Alvarez, M. Auletta, G. Mulder and N. L. Parenteau (1996). "Cultured skin as a 'smart material' for healing wounds: experience in venous ulcers." Biomaterials **17**(3): 311-320.
29. Sanchez-Ferrer, A., J. N. Rodriguez-Lopez, F. Garcia-Canovas and F. Garcia-Carmona (1995). "Tyrosinase: a comprehensive review of its mechanism." Biochim Biophys Acta **1247**(1): 1-11.
30. Schafer, M. and S. Werner (2008). "Oxidative stress in normal and impaired wound repair." Pharmacol Res **58**(2): 165-171.
31. Schallreuter, K. U., P. Bahadoran, M. Picardo, A. Slominski, Y. E. Elassiuty, E. H. Kemp, C. Giachino, J. B. Liu, R. M. Luiten, T. Lambe, I. C. Le Poole, I. Dammak, H. Onay ,M. A. Zmijewski, M. L. Dell'Anna, M. P. Zeegers, R. J. Cornall, R. Paus, J. P. Ortonne and W. Westerhof (2008). "Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else?" Exp Dermatol ;139-140 :(2)17 discussion 141-160.
32. Shandall, A. A., G. T. Williams, M. B. Hallett and H. L. Young (1986). "Colonic healing: a role for polymorphonuclear leucocytes and oxygen radical production." Br J Surg **73**(3): 225-228.
33. Steed, D. L. (1995). "Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group." J Vasc Surg **21**(1): 71-78; discussion 79-81.
34. Takeuchi, K., M. Okada, K. Ueshima, T. Ohuchi and S. Okabe" .(1993) Endogenous sulfhydryls in healing gastric mucosal injury induced by HCl in the rat." Digestion **54**(2): 91-97.
35. Telorack, M., M. Meyer, I. Ingold, M. Conrad, W. Bloch and S. Werner (2016). "A Glutathione-Nrf2-Thioredoxin Cross-Talk Ensures Keratinocyte Survival and Efficient Wound Repair." PLoS Genet **12**(1): e1005800.
36. Upadhya, G. A. and S. M. Strasberg (2000). "Glutathione, lactobionate, and histidine: cryptic inhibitors of matrix metalloproteinases contained in University of Wisconsin and histidine/tryptophan/ketoglutarate liver preservation solutions." Hepatology **31**(5): 1115-1122.
37. Vaalamo, M., T. Leivo and U. Saarialho-Kere (1999). "Differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing." Hum Pathol **30**(7): 795-802.
38. Vaalamo, M., L. Mattila, N. Johansson, A. L. Kariniemi, M. L. Karjalainen-Lindsberg, V. M. Kahari and U. Saarialho-Kere (1997). "Distinct populations of stromal cells express collagenase-3 (MMP-13) and collagenase-1 (MMP (1-in chronic ulcers but not in normally healing wounds." J Invest Dermatol **109**(1): 96-101.
39. Walshe, J., M. M. Serewko-Auret, N. Teakle, S. Cameron, K. Minto, L. Smith, P. C. Burcham, T. Russell, G. Strutton, A. Griffin, F. F. Chu, S. Esworthy, V. Reeve and N. A. Saunders (2007). "Inactivation of glutathione peroxidase activity contributes to UV-induced squamous cell carcinoma formation." Cancer Res **67**(10): 4751-4758.
40. Westerhof, W. and M. d'Ischia (2007). "Vitiligo puzzle: the pieces fall in place." Pigment Cell Res **20**(5): 345-359.
41. Wieman, T. J., J. M. Smiell and Y. Su (1998). "Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study." Diabetes Care **21**(5): 822-827.
42. Wilkins, E. G., R. S. Rees, D. Smith, B. Cashmer, J. Punch, G. O. Till and D. J. Smith, Jr. (1993). "Identification of xanthine oxidase activity following reperfusion in human tissue." Ann Plast Surg **31**(1): 60-65.
43. Wilkins, L. M., S. R. Watson, S. J. Prosky, S. F. Meunier and N. L. Parenteau (1994). "Development of a bilayered living skin construct for clinical applications." Biotechnol Bioeng **43**(8): 747-756.
44. Yamamura, T ,.J. Onishi and T. Nishiyama (2002). "Antimelanogenic activity of hydrocoumarins in cultured normal human melanocytes by stimulating intracellular glutathione synthesis." Arch Dermatol Res **294**(8): 349-354.