SciMedCentral

Journal of Dermatology and Clinical Research

Mini Review

Cannabinoids as Therapeutics for Non-Melanoma and Melanoma Skin Cancer

Soliman E[1], Ladin DA[1], and Rukiyah Van Dross[1,2]*

[1]*Department of Pharmacology and Toxicology, East Carolina University, USA*
[2]*Center for Health Disparities, East Carolina University, USA*

***Corresponding author**

Rukiyah Van Dross, Department of Pharmacology and Toxicology, Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA, Tel: 252-744-2744; Email: vandrossr@ecu.edu

Submitted: 30 April 2016

Accepted: 28 May 2016

Published: 01 June 2016

Keywords

- Cannabinoids
- Skin cancer
- Therapeutics
- Carcinogenesis
- Endocannabinoid system

Abstract

Skin cancer has a significant impact on the health care system of many societies. The most common types of skin cancer are Non-Melanoma Skin Cancer (NMSC) and melanoma. In the United States, NMSC incidence is greater than all other cancers combined. Although death is a rare outcome of NMSC, recurrence is fairly common. In contrast, melanoma is highly metastatic, chemoresistant and is often lethal. As such, novel therapeutics are urgently needed for treatment of these malignancies. The therapeutic potential of cannabinoids has been investigated for numerous conditions including skin cancers. The actions of cannabinoids are regulated by components of the endocannabinoid system (ECS) which include cannabinoid receptors, putative transporters, and enzymes involved in endocannabinoid synthesis and degradation. Recent evidence suggests that cannabinoids of endogenous origin perform specific roles in skin cell homeostasis and in the development and elimination of skin cancer. Hence, synthetic cannabinoids (psychoactive and non-psychoactive), phytocannabinoids and endocannabinoids are being investigated as potential therapeutics for skin cancer. In this article, current knowledge regarding the role cannabinoids in skin cancer development and the potential for utilizing cannabinoids as novel therapeutics are reviewed.

ABBREVIATIONS

2-AG: 2-Arachidonoyl Glycerol; ABDH: Alpha/Beta-Hydrolase Domain; AEA: Arachidonoyl Ethanolamide; BBB: Blood-Brain-Barrier; CB1: Cannabinoid Receptor Type 1; CB2: Cannabinoid Receptor Type 2; CNS: Central Nervous System; COX-2: Cyclooxygenase-2; DMBA: Dimethylbenz [a]-Anthracene; ECS: Endocannabinoid System; EMT: Endocannabinoid Membrane Transporter; FAAH: Fatty Acid Amide Hydrolase; MAGL: Monoacylglycerol Lipase; NMSC: Non-Melanoma Skin Cancer; P-450: Cytochrome P-450; Δ^9-THC: Δ^9-Tetrahydrocannabinol; TPA: 12-O-Tetradecanoylphorbol-13-Acetate; TRPV1: Transient Potential Vanilloid Receptor; UVB: Ultraviolet Light B.

INTRODUCTION

The endocannabinoid system

Cannabinoids are utilized therapeutically to prevent pain and chemotherapy-induced emesis. More recently, cannabinoids have been identified as potential therapeutics for conditions including epilepsy, autoimmune disease and cancer [1]. Cannabinoids are a class of structurally diverse hydrophobic compounds that are derived from animals [endocannabinoids, e.g., arachidonoyl ethanolamide (AEA) and 2-arachidonoyl glycerol (2-AG)], plants [phytocannabinoids, e.g., Δ^9-THC: Δ^9-Tetrahydrocannabinol)], or they are chemically synthesized (e.g., WIN 55,212-2 and JWH-015). Cannabinoids activate G-protein-coupled, cannabinoid receptor type 1 (CB1) or cannabinoid receptor type 2 (CB2) which then inhibits cAMP production and decreases intracellular calcium accumulation [2,3]. Other cannabinoid responsive receptors have also been identified including the transient receptor potential cation channel, subfamily V1 (TRPV1) and the orphan G-protein coupled receptor, GRP55 [4,5]. Numerous reports show that cannabinoids can also produce cellular effects independent of the cannabinoid receptors [6,7]. Endocannabinoids enter cells through endocannabinoid membrane transporters (EMT), although the existence of this transporter remains controversial [8]. Once inside cells, the activity of endocannabinoids is terminated by fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL) or alpha/beta hydrolase domain (ABHD) family proteins [9-11]. Other enzymes including cyclooxygenases, lipoxygenases, and P-450 enzymes also convert endocannabinoids to signaling lipids that possess distinct cellular targets and biological activity [12]. The endocannabinoids, cannabinoid receptors, molecular transporters and enzymes involved in cannabinoid synthesis and metabolism are collectively referred to as the endocannabinoid system (ECS). The ECS is widely distributed and has been most extensively characterized in the central nervous system (CNS) and the immune system. Activation of the ECS in the CNS impacts

various processes such as learning and memory, reward and motivation and the appetite primarily through CB1-mediated signaling [13]. Alternatively, the peripheral ECS modulates the immune system, lipid metabolism and other biological activities through both CB1 and CB2 receptors [14].

Unlike neural and immunologic tissues, the physiological function of the ECS in the epidermis is poorly understood. The epidermis is comprised of several cell types including keratinocytes and melanocytes, which are the source of non-melanoma skin cancer (NMSC) and melanoma, respectively [15]. Components of the ECS were found to be present and functional in normal human and animal skin cells. It has been proposed that AEA, the EMT, FAAH and cannabinoid receptors are involved in maintaining skin homeostasis by modulating proliferation and differentiation [16-18]. The cannabinoid receptors are also expressed in neoplastic tissues including NMSC and melanoma [17,19]. Furthermore, exogenous administration of endocannabinoids, phytocannabinoids or synthetic cannabinoids to NMSC or melanoma cells reduces its proliferation and induces apoptosis *in vitro* and *in vivo* [16,17,20]. These collective findings indicate that the ECS is involved in carcinogenic processes and its elements may therefore be appropriate targets for novel skin cancer therapeutics [21,22]. The goal of this review was to examine the literature to gain a greater understanding of the effects of the ECS on skin cancer development and to assess the feasibility of utilizing cannabinoids as novel therapeutics against NMSC and melanoma.

Non melanoma skin cancer (NMSC)

The most common types of NMSC include basal cell carcinoma and squamous cell carcinoma. There are approximately 5.4 million new cases diagnosed each year [23] making NMSC the most frequently acquired cancer in the United States. NMSCs typically appear on sun-exposed areas of the skin such as the face, lips, ears, neck, and backs of the hands (squamous cell carcinoma) as well as the head and neck (basal cell carcinoma) [24]. The major risk factor for developing NMSC is excessive exposure to natural (solar) and artificial (tanning beds) ultraviolet (UV) light as well as contact with chemical carcinogens such as arsenic and the polycyclic aromatic hydrocarbons [25]. Since the incidence of NMSC is continually rising due to increased exposure to UV radiation, novel treatments for NMSC are needed.

Role of the ECS in NMSC Development and Treatment

An accumulating body of evidence implicates the ECS in NMSC development. It has been reported that CB1 and CB2 receptors were expressed in a number of human and murine transformed epidermal cell lines as well as in skin tumors (e.g. papilloma, basal cell carcinoma, squamous cell carcinoma) [17]. Furthermore, the expression of orphan receptor, GPR55 was higher in human squamous cell carcinoma samples than in normal skin [26]. NMSC is typically studied using cultured transformed keratinocytes and by utilizing two well-known animal models, the UVB-light protocol [27] or the two-stage chemical carcinogenesis protocol with dimethylbenz [a]-anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA) [28]. Using the UVB-light tumorigenesis model, Zheng et al, demonstrated that CB1 and CB2 receptor deficient mice ($CB1/2^{-/-}$) developed fewer papillomas than the corresponding wild-type ($CB1/2^{+/+}$) animals under conditions where UVB light increased the activity of both receptor types [29]. Moreover, acute exposure of $CB1/2^{+/+}$ but not $CB1/2^{-/-}$ animals to UVB resulted in elevated inflammation consistent with the known role of inflammation in cancer promotion [29]. However, a different study showed that the synthesis of AEA and 2-AG and the cell membrane localization of CB1 and CB2 were reduced after UVB exposure indicating that the ECS might be protective against tumor development [30]. In contrast to studies conducted with UVB-light, CB1 and CB2 receptors did not modulate tumor development initiated by DMBA/TPA. Both $CB1/2^{+/+}$ and $CB1/2^{-/-}$ mice developed papillomas with no significant difference in tumor multiplicity or incidence [31]. However, GPR55 receptors were required for DMBA/TPA-induced skin carcinogenesis. Specifically, it was determined that $GPR55^{-/-}$ mice were more resistant to papilloma formation than wild type mice [26]. Thus, the available data suggests that the involvement of the cannabinoid receptors in tumor development is stimulus-dependent.

The potential therapeutic effect of synthetic cannabinoids on NMSC has been examined. Synthetic cannabinoid, WIN-55 212–2 (mixed CB1/CB2 agonist) and the non-psychotropic synthetic, JWH-133 (selective CB2 agonist) reduced the growth of murine epidermal tumor cells in PDV.C57 xenograft experiments [17]. In this model, impairment in tumor vascularization and a reduction in the expression of various proangiogenic factors were also observed. Complementary *in vitro* studies demonstrated that WIN-55 212–2 and JWH-133, increased DNA fragmentation and death in PDV.C57 cells which was reversed by selective CB1 and CB2 receptor antagonists [17]. More recently, the chemopreventive activity of other synthetic cannabinoids was tested in the DMBA/TPA skin carcinogenesis model [32]. Topical application of JWH-018, JWH-122, and JWH-210 (mixed CB1/CB2 agonists), thirty minutes before each TPA administration, resulted in a significant reduction in tumor incidence and multiplicity compared to vehicle treated animals.

Other studies show that the endocannabinoid, AEA, effectively eliminates NMSC cells. NMSC over expresses the enzyme, cyclooxygenase-2 (COX-2), differentiating it from normal keratinocytes. It was determined that AEA was metabolized by COX-2 to a novel metabolite, 15deoxy, $\Delta^{12,14}$ prostaglandin-ethanolamide J2 (15d-PGJ2-EA) whose production was required for AEA cell death [33]. AEA-induced apoptosis in NMSC cells was mediated by the initiation of oxidative stress and endoplasmic reticulum (ER) stress. Furthermore, inhibition of AEA degradation with the FAAH inhibitor, URB597, increased J-series prostaglandin synthesis and AEA cytotoxicity [34]. However, selective antagonist of CB1, CB2, and TRPV1 receptors did not inhibit AEA-induced ER stress and apoptosis [7]. Since the endogenous levels of COX-2 are low in non-tumorigenic keratinocytes compared to tumorigenic keratinocytes, the data suggest that AEA is selectively toxic towards tumor cells.

The results of these reports suggest that cannabinoid receptor stimulation by chemical carcinogens and UVB light promotes tumor development but that exogenously administered cannabinoid ligands induce tumor cell death. These seemingly opposing effects are possibly explained by the concentration-

dependent effects of cannabinoids on skin cancer cell viability. Whereas the endogenous levels of endocannabinoids (nanomolar range) associated with carcinogen exposure increases tumor growth, the exogenous administration of cannabinoids (micromolar range) decreases tumor growth. This suggestion is consistent with our previous studies demonstrating that low concentrations of anandamide (< 10 μM) increased NMSC cell proliferation while high concentrations (> 10 μM) caused cell death and apoptosis [35]. Collectively, the data suggest that ECS components are functional in keratinocytes and can be targeted to bring about tumor cell death.

Melanoma

Melanoma is the most aggressive and deadly cutaneous neoplasm in the United States. It is estimated that more than 76,000 new cases of melanoma will be diagnosed and that over 10,000 patients will die from this disease in 2016 [36]. Like NMSC, UV radiation exposure is a primary risk factor for developing melanoma [37]. In addition, individuals with family history, poor immune function or rare genetic abnormalities such as xeroderma pigmentosum may be at increased risk of developing this malignancy [38]. Unlike other forms of skin cancer, melanoma is especially dangerous due to its highly metastatic nature and resistance to chemotherapy [39]. Melanoma incidence has steadily risen over the last 10 years and novel therapeutic approaches must be identified.

Role of the ECS in melanoma development and treatment

Recent research suggests that the ECS plays a critical role in melanoma development and progression. Cannabinoid receptors CB1 and CB2 are expressed in human melanomas and numerous melanoma cell lines suggesting functional endocannabinoid signaling in this cancer type [19]. Indeed, plasma concentrations of 2-AG were elevated in patients with metastatic melanoma suggesting a link between endocannabinoid regulation and melanoma development [40]. The data also indicates that endocannabinoids act in a concentration-dependent manner. At low levels (<10 μM), endocannabinoids released from tumor cells including melanoma, act on immune cell cannabinoid receptors, leading to immune suppression and tumor cell mediated immune evasion [41-43]. High endocannabinoid levels (>10 μM) in the tumor microenvironment are suggested to suppress tumor growth and migration [44,45]. As such, the therapeutic potential of cannabinoids in melanoma skin cancer has been investigated.

Melanoma is typically studied using cultured melanoma cells or subcutaneous tumor models. Using these experimental approaches, several reports indicate that phytocannabinoids are potent inducers of melanoma cell death. Armstrong et al. demonstrated that Δ^9-THC induced apoptosis in melanoma cell lines including A357, SK-MEL-28, and CHL-1 through an autophagic-dependent mechanism [46]. In this study, the cytotoxicity of Δ^9-THC was further increased in melanoma cells co-treated with cannabidiol (CBD). Furthermore, the anti-tumor effects were replicated in a melanoma xenograft mouse model [46]. Similarly, Glodde's group reported that Δ^9-THC decreased the growth of melanoma *in vitro* and *in vivo* and that this effect was not observed in mice lacking CB1 and CB2 receptors, pointing to a CB receptor-dependent mechanism [31]. Interestingly, a different report demonstrated that Δ^9-THC preferentially eliminated melanoma compared to non-tumorigenic melanocytes by inhibiting the activity of the pro-survival proteins, Akt and pRb [19]. As such, phytocannabinoids may emerge as a selective and effective class of anti-melanoma agents.

Synthetic cannabinoids have helped to reveal the role CB1 and CB2 receptors in melanoma and the potential of CB receptors as therapeutic targets. Activation of CB1/CB2 with WIN55,212-2 decreased melanoma cell viability, melanoma xenograft growth and metastasis [19,47]. In contrast, CB2 receptor activation with JWH-133 had no effect on melanoma cell viability but decreased melanoma cell migration across the blood brain barrier suggesting specific roles for CB1 and CB2 in melanoma metastasis [48,49]. The synthetic, metabolically stable analogs of AEA such as arachidonyl-2'-chloroethylamide (ACEA) and met-anandamide (m-AEA) have also been examined for their anti-melanoma properties. In contrast to other synthetic cannabinoids, these agents possessed moderate toxicity in human melanoma cell lines but failed to significantly decrease tumor size in mouse melanoma xenografts [50].

The endocannabinoid AEA shows promise as a potential anti-melanoma agent. Consistent with observations in NMSC, AEA appears to promote tumor death through a receptor independent pathway [50,51]. Adinolfi et al. showed that AEA caused melanoma cell death that was partially reversed by pretreatment with a CB1 antagonist [48]. Furthermore, the FAAH inhibitor, URB597, potentiated the anti-melanoma properties of AEA and inhibition of COX-2 significantly reversed AEA-mediated cytotoxicity [48]. These findings suggest that COX-2 metabolized AEA to cytotoxic prostaglandin-ethanolamides in melanoma as well as NMSC. In the same study, disruption of cellular lipid rafts reversed the effect of AEA on melanoma cell viability suggesting that these organization centers were important for the activity of AEA [48]. Taken together, these reports indicate that endocannabinoids may induce tumor cell toxicity through mechanisms distinct from other classes of cannabinoid compounds.

CONCLUSION

An assessment of the available findings indicates that components of the ECS play an important role in the development of NMSC and melanoma which have a higher incidence than all other cancers combined. The ECS is involved in the formation of UVB-induced NMSC and melanoma.

Endocannabinoids, synthetic cannabinoids and phytocannabinoids decrease NMSC and melanoma growth *in vitro* and *in vivo* through CB receptor dependent and independent pathways (Table 1). This suggests that molecules which make up the ECS are potential targets for development of novel skin cancer therapeutics. Because NMSC and melanoma rates are rapidly increasing, new therapeutic options are needed. The studies cited herein indicate that a more detailed assessment of the effect of cannabinoids on skin cancer is warranted and that agents which

Table 1: Anticancer activity of cannabinoids.

	Cannabinoids	Type of cancer	Experimental model	Findings	References
Endocannabinoids	AEA	NMSC	Murine JWF2 cells- *in vitro*	AEA is metabolized by COX-2 to 15d-PGJ2-EA causing ER stress- and oxidative stress-dependent apoptosis CB receptor independent activity	[7,34,35]
	AEA	Melanoma	Human A375 and HT168-MI cells- *in vitro* Murine B16 cells- *in vitro*	Decreased cell proliferation and increased apoptosis in a COX-2 dependent and CB receptor independent manner. FAAH inhibition potentiated AEA cytotoxicity	[48,50,51]
Synthetic cannabinoids	JWH-133	NMSC	Murine PDV.C57 cells- *in vitro* and *in vivo*	*In vitro*: CB receptor-dependent cell death and DNA fragmentation *In vivo*: reduced tumor growth and angiogenesis	[17]
	JWH-133	Melanoma	Human A375 cells- *in vitro* Human A2058 and murine B16- *in vivo*	*In vitro:* No effect on melanoma cell viability. *In vivo:* JWH decreased tumor growth and metastasis by inhibiting BBB penetration	[19,48,49]
	JWH-018, JWH-122, and JWH-210	NMSC	DMBA/TPA skin carcinogenesis- *in vivo*	Decreased tumor incidence and multiplicity	[32]
	WIN-55,212–2	NMSC	Murine PDV.C57 cells- *in vitro* and *in vivo*	*In vitro:* CB receptor-dependent cell death and DNA fragmentation *In vivo:* reduced tumor growth and angiogenesis	[17]
	WIN-55,212-2	Melanoma	Human COLO38, SKMEL28, uveal OCM1A, and A375 cells- *in vitro* Murine B16 cells- *in vivo*	*In vitro:* decreased cell proliferation in melanoma but not melanocytes (melan-c Hermes 2b) Lipid raft dependent and CB receptor independent in COLO38 cells *In vivo:* decreased tumor growth and metastasis	[19,47]
	Met-AEA ACEA	Melanoma	Human HT168-MI cells- *in vitro* Human HT168-MI and A375 cells- *in vitro* Human HT168-MI cells- *in vivo*	I*n vitro :* decreased cell proliferation *In vivo:* decreased liver metabolism.	[50] [48,50]
Phyto cannabinoids	Δ^9-THC	Melanoma	Murine B16 and HCmel12 cells- *in vitro* Human A357, SK-MEL-28 and CHL-1 cells- *in vitro*	In vitro: decreased cell proliferation in melanoma cell lines but not melanocytes (melan-c Hermes 2b) CB receptor dependent toxicity Involvement of Akt, pRb and autophagy in toxicity	[19,31,46]

modulate ECS components may be effective in clinical settings.

ACKNOWLEDGEMENTS

This work was supported with funds from a Golfer's Against Cancer Grant and an Internal Seed Grant from the Division of Research and Graduate Studies, East Carolina University.

REFERENCES

1. Murnion B. Medicinal cannabis. Aust Prescr. 2015; 38: 212-215.
2. Romani C, Di Betta AM, Tsouknida E, Olson A. Lexical and nonlexical processing in developmental dyslexia: a case for different resources and different impairments. Cogn Neuropsychol. 2008; 25: 798-830.
3. Rao GK, Zhang W, Kaminski NE. Cannabinoid receptor-mediated regulation of intracellular calcium by delta(9)-tetrahydrocannabinol in resting T cells. J Leukoc Biol. 2004; 75: 884-892.
4. Liu B, Song S, Jones PM, Persaud SJ. GPR55: from orphan to metabolic regulator? Pharmacol Ther. 2015; 145: 35-42.
5. Mickle AD, Shepherd AJ, Mohapatra DP. Sensory TRP channels: the key transducers of nociception and pain. Prog Mol Biol Transl Sci. 2015; 131: 73-118.

6. Van Dross R, Soliman E, Jha S, Johnson T, Mukhopadhyay S. Receptor-dependent and receptor-independent endocannabinoid signaling: a therapeutic target for regulation of cancer growth. Life Sci. 2013; 92: 463-466.

7. Soliman E, Van Dross R. Anandamide-induced endoplasmic reticulum stress and apoptosis are mediated by oxidative stress in non-melanoma skin cancer: Receptor-independent endocannabinoid signaling. Mol Carcinog. 2015.

8. Nicolussi S, Gertsch J. Endocannabinoid transport revisited. Vitam Horm. 2015; 98: 441-485.

9. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996; 384: 83-87.

10. Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, et al. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci U S A. 2002; 99: 10819-10824.

11. Blankman JL, Simon GM, Cravatt BF. A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. Chem Biol. 2007; 14: 1347-1356.

12. Urquhart P, Nicolaou A, Woodward DF. Endocannabinoids and their oxygenation by cyclo-oxygenases, lipoxygenases and other oxygenases. Biochim Biophys Acta 2015; 1851: 366-376.

13. Skaper SD, Di Marzo V. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. Philos Trans R Soc Lond B Biol Sci. 2012; 367: 3193-3200.

14. Klein TW, Cabral GA. Cannabinoid-induced immune suppression and modulation of antigen-presenting cells. J Neuroimmune Pharmacol. 2006; 1: 50-64.

15. Linares MA, Zakaria A, Nizran P. Skin Cancer. Prim Care. 2015; 42: 645-659.

16. Maccarrone M, Di RM, Battista N, Gasperi V, Guerrieri P, Rossi A, et al. The endocannabinoid system in human keratinocytes. Evidence that anandamide inhibits epidermal differentiation through CB1 receptor-dependent inhibition of protein kinase C, activation protein-1, and transglutaminase. J Biol Chem. 2003; 278: 33896-33903.

17. Casanova ML, Blázquez C, Martínez-Palacio J, Villanueva C, Fernández-Aceñero MJ, Huffman JW, et al. Inhibition of skin tumor growth and angiogenesis *in vivo* by activation of cannabinoid receptors. J Clin Invest. 2003; 111: 43-50.

18. Wilkinson JD, Williamson EM. Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. J Dermatol Sci. 2007; 45: 87-92.

19. Blázquez C, Carracedo A, Barrado L, Real PJ, Fernández-Luna JL, Velasco G, et al. Cannabinoid receptors as novel targets for the treatment of melanoma. FASEB J. 2006; 20: 2633-2635.

20. Ständer S, Schmelz M, Metze D, Luger T, Rukwied R. Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. J Dermatol Sci. 2005; 38: 177-188.

21. Kupczyk P, Reich A, Szepietowski JC. Cannabinoid system in the skin - a possible target for future therapies in dermatology. Exp Dermatol. 2009; 18: 669-679.

22. Bíró T, Tóth BI, Haskó G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. Trends Pharmacol Sci. 2009; 30: 411-420.

23. Key statistics for basal and squamous cell skin cancers. http://m.cancer.org/cancer/skincancer-basalandsquamouscell/detailedguide/skin-cancer-basal-and-squamous-cell-key-statistics

24. Lazareth V. Management of non-melanoma skin cancer. Semin Oncol Nurs. 2013; 29: 182-194.

25. Schwarz M, Münzel PA, Braeuning A. Non-melanoma skin cancer in mouse and man. Arch Toxicol. 2013; 87: 783-798.

26. Pérez-Gómez E, Andradas C, Flores JM, Quintanilla M, Paramio JM, Guzmán M, et al. The orphan receptor GPR55 drives skin carcinogenesis and is upregulated in human squamous cell carcinomas. Oncogene. 2013; 32: 2534-2542.

27. Fischer SM, Pavone A, Mikulec C, Langenbach R, Rundhaug JE. Cyclooxygenase-2 expression is critical for chronic UV-induced murine skin carcinogenesis. Mol Carcinog. 2007; 46: 363-371.

28. Kiraly AJ, Soliman E, Jenkins A, Van Dross RT. Apigenin inhibits COX-2, PGE2, and EP1 and also initiates terminal differentiation in the epidermis of tumor bearing mice. Prostaglandins Leukot Essent Fatty Acids. 2016; 104: 44-53.

29. Zheng D, Bode AM, Zhao Q, Cho YY, Zhu F, Ma WY, et al. The cannabinoid receptors are required for ultraviolet-induced inflammation and skin cancer development. Cancer Res. 2008; 68: 3992-3998.

30. Gegotek A, Biernacki M, Ambrozewicz E, Surazynski A, Wronski A, Skrzydlewska E. The cross-talk between electrophiles, antioxidant defence and the endocannabinoid system in fibroblasts and keratinocytes after UVA and UVB irradiation. J Dermatol Sci. 2016; 81: 107-117.

31. Glodde N, Jakobs M, Bald T, Tüting T, Gaffal E. Differential role of cannabinoids in the pathogenesis of skin cancer. Life Sci. 2015; 138: 35-40.

32. Nakajima J, Nakae D, Yasukawa K. Structure-dependent inhibitory effects of synthetic cannabinoids against 12-O-tetradecanoylphorbol-13-acetate-induced inflammation and skin tumour promotion in mice. J Pharm Pharmacol. 2013; 65: 1223-1230.

33. Soliman E, Henderson KL, Danell AS, Van Dross R. Arachidonoyl-ethanolamide activates endoplasmic reticulum stress-apoptosis in tumorigenic keratinocytes: Role of cyclooxygenase-2 and novel J-series prostamides. Mol Carcinog. 2016; 55: 117-130.

34. Kuc C, Jenkins A, Van Dross RT. Arachidonoyl ethanolamide (AEA)-induced apoptosis is mediated by J-series prostaglandins and is enhanced by fatty acid amide hydrolase (FAAH) blockade. Mol Carcinog. 2012; 51: 139-149.

35. Van Dross RT. Metabolism of anandamide by COX-2 is necessary for endocannabinoid-induced cell death in tumorigenic keratinocytes. Mol Carcinog. 2009; 48: 724-732.

36. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66: 7-30.

37. Vogel RI, Ahmed RL, Nelson HH, Berwick M, Weinstock MA, Lazovich D. Exposure to indoor tanning without burning and melanoma risk by sunburn history. J Natl Cancer Inst. 2014; 106.

38. Stamataki Z, Brunton L, Lorigan P, Green AC, Newton-Bishop J, Molassiotis A. Assessing the impact of diagnosis and the related supportive care needs in patients with cutaneous melanoma. Support Care Cancer. 2015; 23: 779-789.

39. Niezgoda A, Niezgoda P, Czajkowski R. Novel Approaches to Treatment of Advanced Melanoma: A Review on Targeted Therapy and Immunotherapy. Biomed Res Int. 2015; 2015: 851387.

40. Sailler S, Schmitz K, Jäger E, Ferreiros N, Wicker S, Zschiebsch K, et al. Regulation of circulating endocannabinoids associated with cancer and metastases in mice and humans. Oncoscience. 2014; 1: 272-282.

41. Cabral GA, Toney DM, Fischer-Stenger K, Harrison MP, Marciano-Cabral F. Anandamide inhibits macrophage-mediated killing of tumor

necrosis factor-sensitive cells. Life Sci. 1995; 56: 2065-2072.

42. Klegeris A, Bissonnette CJ, McGeer PL. Reduction of human monocytic cell neurotoxicity and cytokine secretion by ligands of the cannabinoid-type CB2 receptor. Br J Pharmacol. 2003; 139: 775-786.

43. Eisenstein TK, Meissler JJ, Wilson Q, Gaughan JP, Adler MW. Anandamide and Delta9-tetrahydrocannabinol directly inhibit cells of the immune system via CB2 receptors. J Neuroimmunol. 2007; 189: 17-22.

44. Joseph J, Niggemann B, Zaenker KS, Entschladen F. Anandamide is an endogenous inhibitor for the migration of tumor cells and T lymphocytes. Cancer Immunol Immunother. 2004; 53: 723-728.

45. Ramer R, Hinz B. Inhibition of cancer cell invasion by cannabinoids via increased expression of tissue inhibitor of matrix metalloproteinases-1. J Natl Cancer Inst. 2008; 100: 59-69.

46. Armstrong JL, Hill DS, McKee CS, Hernandez-Tiedra S, Lorente M, Lopez-Valero I, et al. Exploiting cannabinoid-induced cytotoxic autophagy to drive melanoma cell death. J Invest Dermatol. 2015; 135: 1629-1637.

47. Scuderi MR, Cantarella G, Scollo M, Lempereur L, Palumbo M, Saccani-Jotti G, et al. The antimitogenic effect of the cannabinoid receptor agonist WIN55212-2 on human melanoma cells is mediated by the membrane lipid raft. Cancer Lett. 2011; 310: 240-249.

48. Adinolfi B, Romanini A, Vanni A, Martinotti E, Chicca A, Fogli S, et al. Anticancer activity of anandamide in human cutaneous melanoma cells. Eur J Pharmacol. 2013; 718: 154-159.

49. Haskó J, Fazakas C, Molnár J, Nyúl-Tóth Á, Herman H, Hermenean A, et al. CB2 receptor activation inhibits melanoma cell transmigration through the blood-brain barrier. Int J Mol Sci. 2014; 15: 8063-8074.

50. Kenessey I, Bánki B, Márk A, Varga N, Tóvári J, Ladányi A, et al. Revisiting CB1 receptor as drug target in human melanoma. Pathol Oncol Res. 2012; 18: 857-866.

51. Hamtiaux L, Masquelier J, Muccioli GG, Bouzin C, Feron O, Gallez B, et al. The association of N-palmitoylethanolamine with the FAAH inhibitor URB597 impairs melanoma growth through a supra-additive action. BMC Cancer. 2012; 12: 92.

Cite this article

Soliman E, Ladin DA, Van Dross R (2016) Cannabinoids as Therapeutics for Non-Melanoma and Melanoma Skin Cancer. J Dermatolog Clin Res 4(2): 1069.