**From chemo-prevention to epigenetic regulation: The role of isothiocyanates in skin cancer prevention**

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**Abstract**

Skin cancer incidence is rapidly growing over the last decades and is generally divided into malignant melanoma and non-melanoma (NMSC) with the latter being subdivided into squamous (SCC) and basal cell carcinoma (BCC). Among them, melanoma is the most aggressive type with high mortality rates. On the other hand, aberrant gene expression is a critical step towards malignant transformation. To this end, epigenetic modifications like changes in DNA methylation patterns and miRNA expression profile as well as histone modifications are all capable of inducing an altered gene expression profile involved in various cellular cascades including cell cycle, proliferation and apoptosis. In general, there is an interest about the beneficiary effect of various phytochemicals in the prevention and treatment of skin malignancies. Among them, glucosinolates are an important type of compounds, abundant in cruciferous vegetables, which are hydrolysed by an endogenous enzyme called myrosinase to a range of bioactive compounds including isothiocyanates (ITCs). These are the major biologically active products capable of mediating the anti-cancer effect of cruciferous vegetables. Their chemo-preventive action is mainly attributed to a plurality of anti-cancer properties including regulation of the epigenetic machinery. Current evidence supports the view that ITCs are potent compounds in interacting with the epigenome in order to restore the normal epigenetic landscape in malignant cells. This review article summarizes the current state of knowledge on the epigenetic modifications that lead to malignant transformation and the role of ITCs with respect to their ability to restore the epigenetic landscape that contributes to skin carcinogenesis.

**Keywords:** isothiocyanates; sulforaphane; skin cancer; non-melanoma skin cancer; basal cell carcinoma; squamous cell carcinoma; melanoma; chemoprevention; epigenetic regulation

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**Abbreviations**

A375: Malignant Melanoma Cells

AITC: Allyl Isothiocyanate

BCC: Basal Cell Carcinoma

BITC: Benzyl Isothiocyanate

CPD: Cyclobutane Pyrimidine Dimer

DNMT: DNA methyltransferase

DNMT1: DNA methyltransferase 1

DNMT3A: DNA methyltransferase 3A

DNMT3B: DNA methyltransferase 3B

EZH2: Enhancer of zeste homolog 2

GLs: Glucosinolates

H3K27: Lysine 27 of Histone 3

HAT: Histone Acetyltransferases

HDAC: Histone deacetylases

HT-29: Human Colorectal Adenocarcinoma Cell Line

IBN: Iberin

ITCs: Isothiocyanates

mi-RNA: micro RNA

MMPs: Matrix Metalloproteinases

NF-κB: Nuclear Factor kappa Beta

NMSC: Non-Melanoma Skin Cancer

NQO1: NAD(P)H dehydrogenase [quinone] 1

Nrf2: Nuclear factor erythroid-derived 2-like 2

PA: Plasminogen Activator

PEITC: Phenethyl Isothiocyanate

RASSF1A: Ras-association domain family 1 isoform A

ROS: Reactive Oxygen Species

SCC: Squamous Cell Carcinoma

UV: Ultraviolet

UVA: Ultraviolet Radiation A

UVB: Ultraviolet Radiation B

UVR: Ultraviolet Radiation

VEGF: Vascular Endothelial Growth Factor

# **Introduction**

Skin cancer is considered one of the most common types of cancer worldwide with its rates increasing rapidly over the years (Diepgen & Mahler, 2002; Nguyen & Ho, 2002; Gordon, 2013). There are three main types: i) basal and ii) squamous cell cancer (BCC and SCC respectively both of which arise from keratinocytes) as well as iii) melanoma (which originate from melanocytes) (Erb, et al., 2008). BCC and SCC together are known as non-melanoma skin cancer (NMSC) with BCC being the most common type accounting for about 80% of the disease’s incidence (Madan, et al., 2010; Baxter, et al., 2012). In general, NMSCs have a good prognosis, especially if diagnosed at an early stage in contrast to malignant melanoma which is more aggressive and lethal. Finally, BCCs usually grow locally and rarely metastasize whereas SCCs are more likely to spread to distant areas (Gordon, 2013).

In recent years, a number of genes (involved in several cellular pathways) were shown to be deregulated and thus contribute to the induction, promotion, progression and metastatic stages of the disease (Bosserhoff, 2006; Greinert, 2009; Hocker, et al., 2008). For instance., BCC is strongly associated with the deregulation of the sonic hedgehog signalling pathway (Athar, et al., 2014) whereas mutations in the p53-regulated pathways are of particular importance for the initiation of SCC (Emmert, et al., 2014). Other genes may also contribute in SCC development including *RAS* and *pl6INK4a* although mutations in these genes are observed at a lower frequency than *p53* (Emmert, et al., 2014; Xie, 2008). In malignant melanoma, various signalling pathways have been shown to be deregulated with the most important one being the RAS-ERK (Dahl & Guldberg, 2007; Ko & Fisher, 2011; Shtivelman, et al., 2014). In particular, mutations in the *BRAF* gene are the most common lesions among melanoma patients (Shtivelman, et al., 2014).

On the other hand, epigenetic modifications can contribute to malignant transformation by means of altering gene expression responsible for abnormal cell proliferation (Sigalotti, et al., 2010). Because epigenetic modifications are reversible (in contrast to genetic mutations) there is a growing interest in identifying agents with the potential to interact with the cancer epigenome and thus restore its “normal” state. In this context, various dietary phytochemicals have been shown to exhibit a plurality of biological properties (e.g. anti-inflammatory, anti-proliferative, anti-mutagenic, anti-oxidant, anti-cancer, etc.) in addition to their capacity of regulating gene expression by means of modulating the epigenetic response (Fitsiou, et al., 2016a; Fitsiou, et al., 2016b; Fitsiou, et al., 2018; Spyridopoulou, et al., 2017; Issa, et al., 2006; Johnson, 2007; Li, et al., 2014; Nohynek, et al., 2006; Ziech, et al., 2012; Li, et al., 2016; Rupasinghe, et al., 2016; Supic, et al., 2013). Among the various types of phytochemicals, isothiocyanates (ITCs) are found abundant in cruciferous vegetables of the *Brassicaceae* family (e.g. cauliflower, cabbage, broccoli, Brussels sprouts, etc.) and have been shown to contribute to cancer prevention through a wide range of mechanisms including modulation of the epigenetic response (Abdull, et al., 2013; Fahey, et al., 1997; Murillo & Mehta, 2001; Sahu & Srivastava, 2009; Talalay & Zhang, 1996; Zhang & Talalay, 1994; Zhang, et al., 1992; Li, et al., 2016).

In this review article, we discuss the current state of knowledge regarding the epigenetic landscape of skin cancer and the importance of such epigenetic alterations in the initiation and progression of the disease. Finally, we discuss the underlying mechanism(s) by which ITCs interact with the skin cancer epigenome in order to restore its normal function.

# **Skin cancer aetiology and pathophysiology**

# **Risk factors**

Skin cancer incidence is multifactorial and its development is based on innate predisposition, inheritable traits, environmental agents and geographical origin all of which play an important role in the disease susceptibility (Chang, et al., 2010; Martin-Gorgojo, et al., 2017; Moan, et al., 2015; Narayanan, et al., 2010). Briefly, ultraviolet radiation (UVR) is considered as the main cause of skin cancer formation and increases the risk of all three main types (Pfeifer & Besaratinia, 2012). People with fair skin, sun sensitivity, red hair, freckles and/or a large number of naevi are more susceptible in addition to those who regularly visit tanning salons. Both the type and extent of exposure are important factors that affect disease type, onset and progression (Armstrong & Kricker, 2001; Diepgen & Mahler, 2002; Martin-Gorgojo, et al., 2017; Moan, et al., 2015; Ting, et al., 2007). At higher risk are also those individuals with a poor immune response due to transplantation and/or are under medication. Moreover, chemical carcinogens (such as those found in tobacco) in addition to medical conditions like chronic ulcers, human papillomavirus infection, immune-suppression and a range of genetic syndromes (e.g. Xeroderma Pigmentosum, Albinism, Gorlin Goltz, Epidermodysplasia verruciformis, etc.) have been associated with an increased risk of NMSC and especially SCC (Devine, et al., 2017; Diepgen & Mahler, 2002).

# **The role of UVR**

UV irradiation shows a distinct mutation pattern (found very often in skin cancer patients) where adjacent pyrimidines are more sensitive to UV light than other nucleotide combinations (Wikonkal & Brash, 1999). The most commonly observed UVB-induced DNA lesions are the cyclobutane pyrimidine dimer (CPD) and the pyrimidine (6-4) pyrimidone photoproducts (6-4 PPs) both of which have been shown to be mutagenic and lead to tumour development by causing C to T and/or CC to TT substitutions (also known as “UV signature mutations”) (Goto, et al., 2015; Kim, et al., 2013; Wikonkal & Brash, 1999). In general, CPDs occur more frequently than 6-4 PPs and are more mutagenic (Ichihashi, et al., 2003). On the other hand, UVA spectrum has an indirect effect on DNA through generation of reactive oxygen species (ROS) which can cause oxidative damage in guanine molecules thus leading to the formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) photoproducts (Madan, et al., 2010; Sage, et al., 2012; Pfeifer & Besaratinia, 2012; Rünger, 2008; Seebode, et al., 2016). In turn, their existence has been strongly associated with loss of action of *p53* (in SCCs) in addition to other UV-induced mutations in genes like *PTCH1* and *CDKN2* in BCC and melanoma respectively (Freije, et al., 2014; Luo, et al., 2001; Ziegler, et al., 1993; Brash, 2015).

UVR is also a potent modulator of skin immune responses and hence potentially contributing to skin cancer development. More specifically, exposure to UVR is strongly associated with damage to Langerhans cells thus leading to an improper presentation of antigens and consequently to the induction of a Th2 (but not Th1) response in addition to stimulation of UV-induced antigen-specific T regulatory cells (Schwarz, et al., 2010; Welsh, et al., 2011; Yu, et al., 2014). In addition, UV exposure also strongly contributes to immunosuppression via the induction of pro-inflammatory immunosuppressive cytokines, such as interleukin-10 and tumour necrosis factor α (TNFα) (Kanavy & Gerstenblith, 2011; Norval & Halliday, 2011). The release of such pro-inflammatory factors contributes to the induction of an inflammatory response around sun-burned areas. UV-induced inflammation is characterized by leukocyte infiltration of the skin leading to ROS formation and potentially cause further cellular damage, genomic instability and suppression of DNA repair pathways (Halliday, 2005; Meeran, et al., 2008).

# **Glucosinolates and Isothiocyanates**

# **Myrosinase - Glucosinolate system**

Cruciferous vegetables are rich sources of glucosinolates (GLs) which are hydrolysed by myrosinase (Andréasson & Jørgensen, 2003). Inside the plant, the enzyme is physically isolated from their substrates thus allowing the degradation of GLs only when the plant is under stress conditions like pathogen attack or tissue disruption (Andréasson, et al., 2001; Martinez-Ballesta & Carvajal, 2015; Koroleva, et al., 2000). Chewing or cutting leads to the release of the enzyme which comes in contact with GLs and catalyses their hydrolysis (Angelino & Jeffery, 2014; Polat, 2010). Activation of the myrosinase-glucosinolate system (also known as mustard oil bomb) results in the formation of biologically active compounds, such as indoles, nitriles and ITCs (Barba, et al., 2016; Grubb & Abel, 2006) (Figure 1). ITCs are the major biologically active products capable of mediating the anti-cancer effect of cruciferous vegetables. A variety of GLs have been identified giving rise to chemically different ITCs, upon their hydrolysis, including sulforaphane (SFN), iberin (IBN), allyl-ITC (AITC), benzyl-ITC (BITC) and phenethyl-ITC (PEITC) (Figure 2) all of which have been studied for their unique chemo-protective properties (Dinkova-Kostova & Kostov, 2012; Higdon, et al., 2007; Wagner, et al., 2013).

The efficiency of conversion of GLs to ITCs is key in controlling their health-promoting properties. Briefly, the consumption of raw vegetables leads to the hydrolysis of GLs as opposed to vegetables cooked for a long time where no GL hydrolysis occurs due to myrosinase being heat-inactivated (Verkerk & Dekker, 2004; Oliviero, et al., 2018). Moreover, consumption of shortly cooked vegetables could be of greater health benefit than consumption of raw vegetables (Matusheski, et al., 2004; Oliviero, et al., 2018). Also, acidic and alkaline conditions as well as water dilution (as part of cooking preparations) can lead to achieving higher ITC concentrations (Hanschen, et al., 2017; Oliviero, et al., 2018). Finally, the role of various food components on ITCs bioavailability has been the subject of intense research. More specifically, ITCs can react with specific functional groups of proteins (e.g. free amino groups and sulfhydryl side chains) and thus reduce their accessibility (Kroll, et al., 1994; Oliviero, et al., 2018). However, ITC absorption can be up to 5-fold higher in a meal-containing meat compared to one without (Rungapamestry, et al., 20017; Oliviero, et al., 2018) which, in turn, relates to the presence of fat that increases the absorption of lipophilic compounds (Ippoushi, et al., 2013; Ippoushi, et al., 2014; Oliviero, et al., 2018). Furthermore, dietary fiber can also impact the bioavailability of ITCs by means of encapsulating (and postponing their absorption) and/or changing their “digesta rheology” (Howarth, et al., 2001; Oliviero, et al., 2018).

On another note, the gastrointestinal microflora can also convert GLs to ITCs and thus acts as a significant factor (either limiting or augmenting) for the health-promoting benefits associated with the consumption of cruciferous vegetables. Overall, the bioavailability of ITCs from GLs is relatively constant but could vary substantially between individuals. Only recently ITC conversion rates were shown to be significantly higher during the day than at night, an observation that leads to an association between diurnal cycles of gut microbial metabolism and daily cycling of enzymes involved in carcinogenesis like DNA repair. If so, it may be that circadian rhythmicity may have significant impact in cancer prevention (Fahey, et al., 2012; Oliviero, et al., 2018).

# **Biological activities**

ITCs exert a plurality of biological properties including anti-microbial, anti-inflammatory, anti-carcinogenic, etc. For instance, many studies have shown that ITCs exert both bacteriostatic and bactericidal potencies thus resulting in a wide range of usages like natural antibiotic agents, additives in foods and/or pesticides (Drobnica, et al., 1967; Freitas, et al., 2013; Kaiser, et al., 2017; Park, et al., 2013; Tierens, et al., 2001; Zou, et al., 2013; Ko, et al., 2016; Kurepina, et al., 2013; Luciano & Holley, 2009; Manyes, et al., 2015). In addition, they have shown to exert a protective effect against pathogens including disruption of cell membrane(s), deregulation of respiratory and enzymatic processes as well as induction of heat shock proteins and oxidative stress (Dufour, et al., 2015).

Moreover, various studies reported that ITCs modulate the activity of antioxidant enzymes through activation of the nuclear factor erythroid-derived 2-like 2 (Nrf2) pathway (Hu, et al., 2006; Johnson, et al., 2017; Keum, et al., 2003; McWalter, et al., 2004; Xu, et al., 2006). To this end, a recent study has documented that ITCs increased the expression of GSTA1/2 (glutathione S-transferase alpha class A1/2), GSTA3 (glutathione S-transferase alpha class 3), GSTM1/2 (glutathione S-transferase alpha class 1/2) and NQO1 (NAD(P)H dehydrogenase [quinone] 1) in wild-type (but not Nrf2-knockdown) mice as well as in various mouse cell lines (McWalter, et al., 2004). As such, various cellular pathways have been identified to contribute to ITC-induced activation of Nrf2, including those of ERK, JNK and Akt all of which can lead to Nrf2 phosphorylation and induction of the transcriptional activity of the antioxidant response element (ARE) (Cheung & Kong, 2010; Ernst, et al., 2011; Jakubíková, et al., 2005; Xu, et al., 2006b).

Moreover, ITCs have been reported to mediate an anti-inflammatory response mainly by modulating the NF-κB pathway which regulates the expression of pro-inflammatory molecules like COX-2 and iNOS as well as the anti-apoptotic proteins Bcl-Xl, Bcl-2 and Bcl-3 (Shan, et al., 2012; Surh & Na, 2008; Del Prete, et al., 2011). To this end, AITC has been shown to exhibit a potent anti-inflammatory activity by significantly decreasing the levels of TNFα, interleukin-1β, inducible nitric oxide synthase (iNOS), p65 (a nuclear protein subunit of the transcription factor NF-κB) and miRNA-155 in addition to increasing the levels of Nrf2 and heme-oxygenase 1 in murine RAW264.7 macrophages (Wagner, et al., 2012). Currently, a number of other studies have proposed the involvement of Nrf2 and macrophage migration inhibitory factor (MIF) pathways as novel targets of ITC-induced anti-inflammatory responses (Greaney, et al., 2016; Crichlow, et al., 2012; Qu, et al., 2015; Yang, et al., 2016; Spencer, et al., 2015).

# **Anti-cancer activity and cancer chemoprevention**

Chemo-prevention refers to the usage of synthetic, natural and/or biological agents to reverse, suppress and/or prevent the multi-stage process of carcinogenesis (Kang, et al., 2011; Weng & Yen, 2012). The ability of ITCs to act as chemo-preventive agents is documented in a number of cancer studies including breast (Pledgie-Tracy, et al., 2007; Xiao, et al., 2008; Xiao, et al., 2006; Xie, et al., 2017), prostate (Cho, et al., 2016; Khurana, et al., 2017; Zhang, et al., 2016), brain (Chou, et al., 2015), colon (Liu, et al., 2017; Pappa, et al., 2006) and skin (Abel, et al., 2013; Kerr, et al., 2018; Mantso, et al., 2016). In addition, many *in vitro* and *in vivo* studies have shown evidence of the mechanistic basis underlining the potential of these compounds to act as chemo-protective agents including: i) modulation of phase I and phase II enzymes, ii) induction of cell cycle growth arrest and cell death, iii) prevention of metastasis and angiogenesis as well as iv) regulation of the epigenetic machinery (Figure 3).

In general, it has been proposed that ITCs modulate the detoxification process by down-regulating the phase I cytochrome P450 enzymes in order to inhibit carcinogen activation while up-regulating phase II enzymes such as glutathione S-transferases (GSTs), UDP-glucuronosyl transferase and NADPH quinine reductases in order to further enhance detoxification and prevent ROS-induced cellular damage (Keum, et al., 2004; Munday, 2002; Talalay & Fahey, 2001; Telang & Morris, 2010; von Weymarn, et al., 2006). The effect of ITCs in regulating the activity of the detoxifying enzymes has been documented in several other studies by showing their increased activation in acute myeloid leukaemia (Gao, et al., 2010), breast carcinoma (Wang, et al., 2005), lung adenocarcinoma (Tan, et al., 2010), hepatocellular carcinoma (Basten, et al., 2002) and skin cancer (Dinkova-Kostova, et al., 2006). Finally, the Nrf2 pathway plays an important role in the ITC-induced detoxification process by targeting phase II detoxifying enzymes, among other proteins (Hu, et al., 2006).

On another note, it is well-established that ITCs exert their cytotoxic effects by inducing cell cycle arrest and apoptosis as documented in various *in vivo* and *in vitro* studies (Bhattacharya, et al., 2010; Boreddy, et al., 2011a; Cho, et al., 2016; Srivastava, et al., 2003; Chen, et al., 2012; Cheng, et al., 2016; Parnaud, et al., 2004; Stan, et al., 2014; Tsai, et al., 2012; Xiao, et al., 2006, Mantso, et al., 2016). For example, AITC can induce the ERK pathway resulting in the activation of the intrinsic apoptotic pathway, growth arrest in G2/M phase, mitochondrial depolarization and deregulation of mitochondrial-associated proteins (Tsai, et al., 2012). In line with these observations, PEITC also effectively inhibits squamous carcinoma growth through cell cycle growth arrest and apoptosis, stimulation of mitochondria-dependent pathway(s), ROS production and Ca2+ accumulation (Chen, et al., 2012). Overall, these and other studies support that ITCs-induced anti-proliferative effect is mediated by i) various signalling cascades including PI3K/AKT, MAPKKs and mTOR (Cheung, et al., 2008; Mondal, et al., 2016; Tsai, et al., 2012; Xu, et al., 2006a), ii) increased generation of ROS (de Oliveira, et al., 2014; Lee & Lee, 2011; Wu, et al., 2011), iii) inhibition of heat-shock proteins (Sarkar, et al., 2012) and iv) mitochondrial dysfunction (Chen, et al., 2012; Rudolf, et al., 2009; Sehrawat, et al., 2016). All of these pathways modulate the expression of genes that are important regulators of cell cycle control and apoptotic cell death.

ITCs can also modulate the metastatic and angiogenic processes by regulating the levels of expression of various metalloproteinases (MMPs), plasminogen activators (PAs) and pro-angiogenic factors like the vascular endothelial growth factor (VEGF) (Aras, et al., 2013; Boreddy, et al., 2011b; Gupta, et al., 2013; Thejass & Kuttan, 2007a). In addition, various signalling cascades also play an essential role in the regulation of the above-mentioned proteins (Milkiewicz, et al., 2011; Sehrawat, et al., 2012; Wang, et al., 2015). For example, inactivation of the MAPK pathway contributes to the anti-metastatic potential of AITC by down-regulating MMPs -2 and -9 in human colorectal adenocarcinoma (HT-29) cells (Lai, et al., 2014). Moreover, treatment of these cells with BITC decreased cell growth and altered cell metastatic potential by reduction in the expression of MMPs -2 and -9 as well as urokinase-type plasminogen activator (u-PA) both of which are mediated by the PKC and/or MAPK pathways (Lai, et al., 2010). Furthermore, BITC’s-induced anti-angiogenic effect was also shown to be accompanied by changes in the expression of several micro-RNAs including up-regulation of miR-144, miR-122 in addition to down-regulation of miR-181b, miR-9 thus inhibiting the adhesion and invasion of human glioma (U87MG) cells (Zhu, et al., 2014).

Finally, growing evidence also supports the involvement of ITCs in regulating the epigenetic response by interfering with all the components of the epigenome including histone deacetylases (HDACs), DNA methyltransferases (DNMTs) and mi-RNAs. ITCs have been documented to act as potent inhibitors of HDACs thereby resulting in changes in the carcinogenic activity of various xenobiotics through Nrf2-mediated induction of phase II detoxification enzymes, induction of cell cycle growth arrest and apoptosis (Batra, et al., 2010; Rajendran, et al., 2013; Su, et al., 2014; Wang, et al., 2008; Yuanfeng, et al., 2015). Similarly, ITCs also exert inhibitory effects on DNMTs suggesting that they can act as modulatory epigenetic agents capable of inhibiting both DNA hyper-methylation and histone de-acetylation (Hsu, et al., 2011; Wong, et al., 2014; Meeran, et al., 2010; Su, et al., 2014; Zhang, et al., 2013). This is best-illustrated in the case of the Ras-association domain family 1 isoform A (*RASSF1A*) gene which was shown to be reactivated after treatment with PEITC (through changes in the activity of both DNMTs and HDACs) leading to apoptotic induction in LNCaP cells (Boyanapalli, et al., 2016). Another significant aspect of ITCs interaction with the epigenome is their modulatory effect on levels of mi-RNAs in a wide range of malignancies including colon (Slaby, et al., 2013), osteosarcoma (Yan, et al., 2012), bladder (Shan, et al., 2013) and glioblastoma (Lan, et al., 2015).

# **ITCs in skin cancer chemoprevention**

Evidence supports the protective effect of ITCs against both UV- and chemically-induced skin carcinogenesis (Dinkova-Kostova, et al., 2010; Dinkova-Kostova, et al., 2007; Dinkova-Kostova, et al., 2006; Talalay, et al., 2007; Gills, et al., 2006; Xu, et al., 2006). More specifically, topical treatment with SFN in mouse skin enhances synthesis of glutathione (GSH) and glutathione S-transferase 4 (GST4) while it blocks chemically-induced skin mutagenesis (Abel, et al., 2013) by involving Nrf2-dependent mechanism(s) (Saw, et al., 2011; Xu, et al., 2006). It is noteworthy that SFN’s mode of action was shown to be different in normal epidermal keratinocytes compared to skin cancer cells. For instance, although SFN induces apoptosis in cancer cells it only slows the proliferation of normal keratinocytes, an effect which appears to be mediated by p53 (Chew, et al., 2012).

On another note, a large number of studies support a protective role of ITCs against the initiation, progression and metastatic stages of malignant melanoma by mediating various signal transduction pathways, generation of oxidative stress and mitochondrial disruption (Hamsa, et al., 2011; Huang, et al., 2012; Huang, et al., 2014; Rudolf, et al., 2014). Moreover, treatment of human malignant melanoma (A375) cells with SFN, BITC and PEITC exerted a cytotoxic effect via multiple apoptotic pathways (e.g. intrinsic, extrinsic and endoplasmic reticulum-based) as shown by increased expression and activity levels of various relevant caspases (Mantso, et al., 2016). In addition, ITCs have also shown to induce an anti-angiogenic effect that appears to be mediated by reduced levels of TNFα, NO and VEGF (Thejass & Kuttan, 2007; Thejass & Kuttan, 2007a). Finally, in support to these observations, a number of *in vivo* studies have documented an anti-melanoma effect during which intraperitoneal injection of ITCs had significantly decreased the size and weight of tumours in A375.S2 xenograft rodent models (Sahu, 2015; Thejass & Kuttan, 2007; Thejass & Kuttan, 2007b; Ni, et al., 2014; Ni, et al., 2013).

# **Overview of epigenetic mechanisms and their role in cancer development**

The term “epigenetics” refers to heritable and reversible changes in gene expression patterns that are independent from the DNA sequence itself (Probst, et al., 2009). These changes are established early in life and contribute to the differentiation of cells via modifications in DNA and histone proteins (Margueron & Reinberg, 2010). In addition, the epigenetic machinery also plays an important role in many physiological processes including genomic imprinting (Ferguson-Smith & Surani, 2001; Li, et al., 1993; Reik & Walter, 2001), X chromosome inactivation (Avner & Heard, 2001; Panning & Jaenisch, 1998) and development of the embryo and the placenta, (Hemberger, 2007; Maltepe, et al., 2010; Santos, et al., 2002). Deficiency to maintain the normal epigenetic state of cells results in a deregulated gene expression profile involved in signalling cascades leading to disease development including carcinogenesis (Egger, et al., 2004; Ziech, et al., 2010; Anestopoulos, et al., 2015). Thus, an extensive deregulation of normal epigenetic marks could potentially be associated with cancer initiation and progression (Sandoval & Esteller, 2012; Franco et al., 2008; Ziech et al., 2011).

The most important epigenetic mechanisms include DNA methylation, histone modifications and non-coding RNAs (Golbabapour, et al., 2011; Bonasio, et al., 2010). These post-translational modifications act in a coordinative and complex manner causing chromatin conformational changes that, in turn, regulate the genetic information accessed by transcription factors (Golbabapour, et al., 2011). Numeral evidence shows that cancer cells accumulate various gene mutations as well as epigenetic alterations both of which can contribute to tumour development and progression. Finally, given that epigenetic alterations are reversible modifications they can, in principle, act as potential targets for therapeutic intervention (Brien, et al., 2016; Panayiotidis, 2014).

# **DNA methylation and cancer development**

The addition of methyl groups in cytosine residues can occur in CpG dinucleotide sequences, dispersed across the genome, leading to the formation of 5-methylcytosine (5mC) (Kulis & Esteller, 2010; Tsai & Baylin, 2011). Such DNA methylation is catalysed by a class of enzymes known as DNA methyltransferases (DNMTs) the most important of which include DNMT1, DNMT3A and DNMT3B. More specifically, DNMTs 3A and 3B show a preference in catalysing the addition of methyl groups on non-methylated cytokines as opposed to DNMT1 which recognizes hemi-methylated DNA. In addition, DNMTs are involved in chromatin conformational changes by mediating the recruitment of methyl binding domain proteins (MBDs), histone modifying enzymes and other effector proteins and enzymes all of which can result in inducing changes in gene expression patterns (Fuks, et al., 2003; Klose & Bird, 2006).

Malignant cells have an altered developmental program in comparison to their normal counterparts thus reflecting the importance of the epigenetic machinery during cancer development. The first reports on the epigenetic involvement in tumorigenesis came from observations of altered DNA methylation patterns in various human cancers (Feinberg & Vogelstein, 1983). In general, cancer is characterized by global hypo-methylation together with site-specific hyper-methylation (Kulis & Esteller, 2010; Sharma, et al., 2010). To this end, genome-wide hypo-methylation can lead to the activation of oncogenes while promoter-specific hyper-methylation results in a compressed chromatin conformation and consequently transcriptional inactivation of tumour suppressor genes (Gokul & Khosla, 2013). Furthermore, DNA hypo-methylation enhances genomic and chromosomal instability through aberrant activation of various proto-oncogenes and translocation of transposons respectively (Berdasco & Esteller, 2010; Eden, et al., 2003; Sharma, et al., 2010). In addition, aberrant methylation of tumour suppressor genes contributes to oncogenesis through their suppressed expression. The first tumour suppressor gene to be reported as being inactivated due to promoter-specific hyper-methylation was the Retinoblastoma (RB) gene, an epigenetic event strongly associated with the occurrence of both sporadic and hereditary types of retinoblastoma (Greger, et al., 1989). Since then, a wide variety of genes have been found to be epigenetically silenced including those important for the maintenance of cell homeostasis and cell cycle regulation (Moison, et al., 2014). Finally, hyper-methylation can modulate gene transcription by mediating changes in the organization of chromatin through the recruitment of methylated-binding proteins and HDACs to the methylated sites thus blocking the access of transcription factors and consequently inducing the formation of repressive chromatin structures (Costello & Plass, 2001; Gokul & Khosla, 2013).

# **Histone modifications and cancer development**

Chromatin is characterized by multiple levels of regulation where various histone modifications mediate unique cellular responses (Berger, 2007; Martin & Zhang, 2005). More specifically, histone proteins can undergo various modifications, in their N-terminal, which directly affect the state of chromatin compression and include those of methylation, acetylation, phosphorylation, ubiquitination, poly(ADP-ribosylation) and symoylation (Dawson & Kouzarides, 2012; Berger, 2007; Rice & Allis, 2001). Specifically, histone acetylation results in gene activation whereas histone methylation can lead to either activation or repression of genes according to the site of modification (Yan & Boyd, 2006). The enzymes which catalyze histone acetylation are called histone acetyltransferases (HATs) while those catalyzing histone methylation are known as histone methyltransferases (HMTs) (Wang, et al., 2009). Finally, the spacing of nucleosome can be regulated by ATP-dependent chromatin regulators which use ATP hydrolysis to induce alterations in nucleosome positioning or alternatively may facilitate nucleosome exchange for the incorporation of histone variants (Kim, et al., 2009; Li, et al., 2007).

Overall, modifications in histone proteins are dynamic and the deregulation of the pattern of histone marks is considered as an important event during carcinogenesis (Sawan & Herceg, 2010). These modifications are co-ordinately regulated and reversed by opposing enzymes and thus, an imbalance in their function disrupt transcriptional activity consequently leading to inappropriate gene expression (Hassler & Egger, 2012). More specifically, global loss of acetylation on lysine 16 along with the loss of tri-methylation at lysine 20 of histone H4 (H4K20me3) were among the first deregulated marks to be reported in various cancers (Füllgrabe, et al., 2011). Furthermore, modifications in the methylation pattern of histone 3 at lysines 4 (H3K4), 9 (H3K9) and 27 (H3K27) have been shown to occur during carcinogenesis (Chakravarthi, et al., 2016).

Finally, HDACs were shown to be over-expressed in various cancers in addition to HMTs which were also shown to be deregulated in various tumours (Kanwal & Gupta, 2012; Albert & Helin, 2010). For example, enhancer of zeste homolog 2 (EZH2; which catalyses the methylation of H3K27) is over-expressed in various cancers and as such, methylation levels of H3K27 are associated with gene inactivation and often represent a common epigenetic marker in cancer (McCabe, et al., 2012; Anestopoulos, et al., 2016).

# **mi-RNAs and cancer development**

MicroRNAs (miRNAs) are functional RNA molecules, about 21-26 nucleotides in length, transcribed from DNA as non-coding primary miRNA (pri-miRNA) transcripts. The pri-miRNAs are processed into precursor miRNA (pre-miRNA) and finally into the mature and functional miRNA under the enzymatic activity of Drosha and Dicer respectively. They play a critical role in regulating gene expression by binding to the 3' untranslated region (UTR) of their target mRNAs and subsequently either suppress their translation or cleave their targets (Shukla, et al., 2011; Valencia-Sanchez, et al., 2006). In general, it is known that their localization, regulation, processing and control are all implicated in the carcinogenic process (Farazi, et al., 2011; Ohtsuka, et al., 2015).

mi-RNAs are important regulators of the transcriptional activity of genes involved in malignant transformation (Malumbres, 2013). Evidence from numerous studies examining the differential expression of mi-RNAs in cancer cells have revealed various alterations in their expression profile (Lu, et al., 2005; Volinia, et al., 2006). For instance, oncogenic mi-RNAs have been shown to be over-expressed while tumour suppressor ones are silenced. In addition, others have a dual role in tumorigenesis by acting both as tumour suppressors as well as oncogenes according to their target genes (Jansson & Lund, 2012; Li, et al., 2010). Interestingly, mi-RNA expression seems to be deregulated through interaction with other components of the epigenetic machinery, especially DNA methylation and histone modifications (Baer, et al., 2013; Malumbres, 2013).

# **Role of epigenetics in skin cancer**

# **Methylation and skin cancer**

The involvement of the epigenetic machinery in epidermal carcinogenesis has been extensively studied during the last years with most studies being focused on melanoma (Penta, et al., 2018). Changes in DNA methylation patterns are considered as a hallmark in epidermal carcinogenesis and are generally associated with the initiation, progression and metastasis of the disease (Greenberg, et al., 2014). Reduction in genomic 5mC content and hyper-methylation of tumour-related genes are usually observed in early as well as advanced stages of skin cancer (Saha, et al., 2013). For example, in SCC, the promoter region of tumour suppressor genes like *MLT-1* (Mucosa-associated lymphoid tissue lymphoma translocation protein 1), *Snail* (Zinc finger protein SNAI1) and *MGMT* (O-6-methylguanine-DNA methyltransferase) are hyper-methylated and therefore silenced during the early and late stages of the disease (Fraga, et al., 2004; Murao, et al., 2006; Wu, et al., 2014). Promoter hyper-methylation appears to be the most common mechanism for silencing both *p16INK4a* and *p14ARF* cell cycle regulators which is an important event in SCC and BCC pathogenesis (Brown, et al., 2004; D'Arcangelo, et al., 2017; J. Wu, et al., 2014). Moreover, increased DNMTs’ activity was reported to accompany the high methylation levels observed in SCC tumours when compared to normal skin (Nandakumar, et al., 2011). In general, increased activation of DNMTs seems to play an essential role in the development of NMSC with DNMT3A being primarily up-regulated in BCCs while DNMT3B is usually up-regulated in SCCs (D'Arcangelo, et al., 2017).In melanoma, promoter-specific hyper-methylation has been reported to mediate the expression of several genes involved in the malignant transformation and progression of the disease (Tanemura, et al., 2009) (Table 1). One of the most important genes implicated in melanoma development is *CDKN2A*, which has been reported to be hyper-methylated in about 19% of melanoma patients. Its methylation has been associated with increased tumour proliferation and poor prognosis (Straume, et al., 2002). In addition, both *MGMT* (essential in DNA repair) and the estrogen receptor α (ER-α; a transcriptional activator) were also shown to be over-expressed in advanced stages of melanoma (Kohonen-Corish, et al., 2006; Mori, et al., 2006).

On another note, excessive loss of methylation is also a major characteristic of cancer development which is associated with transcriptional activation (Schinke, et al., 2010). For example, the over-expression of the melanoma antigen, MAGE, is associated with down-regulation of DNMT1 (Loriot, et al., 2006; Tellez, et al., 2009). Recently, an important role in malignant transformation has been proposed for 5-hydroxy-methylcytosine (5hmC) which is the product from the oxidation of 5mC by the Ten-Eleven Translocation (TET) family proteins during the active de-methylation process (Fu, et al., 2017). Reduced levels of 5hmC have been identified in melanoma samples possibly suggesting an important diagnostic and prognostic value. Although the exact mechanism is not yet fully understood, it has been proposed that decreased expression of isocitrate dehydrogenase 2 (IDH2) and TET proteins might contribute to the observed loss of 5hmC in melanoma pathogenesis (Lian, et al., 2012).

# **Histone modifications and skin cancer**

Modifications on the histone epigenetic landscape have been observed and studied in the context of malignant melanoma development (Kamalika Saha, et al., 2013). In general, genome-wide hypo-acetylation is the most common observed modification in melanoma resulting in the repression of tumour-associated gene expression (Sarkar, et al., 2015; van den Hurk, et al., 2012). For example, decreased acetylation of *CDKN1A* is linked to up-regulation of *p21Cip1*cyclin-dependent kinase inhibitor. Also, during melanogenesis, aberrant expression and/or activity levels of both HATs and HDACs lead to down-regulation of pro-apoptotic proteins Bax, Bak, Bim, Caspases 8/9, TNFRSF10A and TNFRSF10B while up-regulate anti-apoptotic proteins such as Bcl-2 and Bcl-xl. This imbalance in pro- and anti-apoptotic signals promotes malignant cell survival (Penta, et al., 2018; Sigalotti, et al., 2010; Boyle, et al., 2005; Facchetti, et al., 2004). In addition to histone acetylation, the methylation status of these proteins has also been implicated in malignant melanoma transformation. For instance, enhanced expression of *EZH2* down-regulates the expression of genes involved in the inhibition of cell cycle as well as tumour invasiveness thus reflecting the role of *EZH2* in the metastatic potential of the disease (Zingg, et al., 2015). A characteristic example is the inactivation of cyclin dependent kinase inhibitor 1A (*CDKN1A*) during which decreased activity of *p21Cip1*is associated with increased levels of tri-methylated lysine 4 at histone 3 (H3K4me3) and consequently enhanced cell survival (Fan, et al., 2011). Moreover, growing evidence indicates that SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodelling complexes have tumour-suppressive functions, in melanoma, where their decreased activity levels have been observed in primary and metastatic stages of the disease (Becker, et al., 2009). In SCC, silencing of *p16INK4a* and *RASSF1A* genes was associated with reduced acetylation on H3 and H4 and recruitment of methyl CpG binding protein 2 (MeCP2) and Methyl-CpG-binding domain protein 1 (MBD1) chromatin remodelling proteins thus resulting in a repressed chromatin structure (Nandakumar, et al., 2011). In this context, only currently, there has been proposed a role for Sirtuin 2 (Sirt-2) deacetylase in tumorigenesis during which its depletion leads to increased acetylation of lysine 16 on histone H4 (H4K16Ac) with subsequent deregulation of cell cycle and thus promotion of malignant transformation (Serrano, et al., 2013).

# **mi-RNAs and skin cancer**

The involvement of non-coding RNAs in skin tumorigenesis is reflected by the aberrant expression of Drosha and Dicer in NMSC (Sand, et al., 2010) as well as a deregulated cell proliferation and other cellular cascades (e.g. MAPK/ERK, PI3K-Akt, etc.) in BCC (Konicke, et al., 2018) and SCC (Sand, et al., 2012). Specifically, an aberrant expression profile of mir-21 and mir-183 were shown to be associated with both BCC (Heffelfinger, et al., 2012) and SCC (Darido, et al., 2011). In addition, down-regulation of miR-124 and miR-214 plays an important role in SCC as their low expression is accompanied with an increased expression of ERK1/2 protein leading to abnormal proliferation (Yamane, et al., 2013).

In melanoma, mir-221 mediates cell cycle de-regulation while mir-29c impacts the DNA methylation status of several tumour suppressor genes (Nguyen, et al., 2011; Kanemaru, et al., 2011). In addition, mir-137 (Bemis, et al., 2008), mir-148 (Haflidadottir, et al., 2010) and mir-182 (Segura, et al., 2009) have all been shown to interact with microphthalmia-associated transcription factor (*MITF*) and thus modulating genes like forkhead box O3 (*FOXO3*) known to be associated with melanoma’s metastatic potential (Segura, et al., 2009). To conclude, a large number of important mi-RNAs has been identified to contribute to skin carcinogenesis by means of being up- (Table 2) and/or down-regulated (Table 3).

# **The role of ITCs in the epigenetic regulation of skin cancer: The case of SFN**

The anti-cancer effect of ITCs against skin neoplastic transformation has been proposed to be associated with the epigenetic reprogramming of key target genes involved in cellular protection. More specifically, the effect of SFN on the epigenetic regulation of skin cancer cells has been recently focused on the function of the PcG proteins (e.g. Bmi1 and EZH2) by means of blocking tumour progression through their inhibition thus leading to decreased levels of H3K27me3. Such epigenetic modulation has been shown to cause alterations in the expression of proteins important in cell cycle and apoptosis thus suppressing cancer cell survival (Balasubramanian, et al., 2011). Furthermore, in SCC, treatment with SFN inhibits cancer progression and metastasis *in vivo* via reduction in arginine methylation at H3. Decreased levels of di-methylated arginine 3 at histone 4 (H4R3me2) are mediated by SFN-induced proteosomal degradation of arginine N-methyltransferase 5 (PRMT5) and WD Repeat Domain 77 (MEP50) both of which are responsible for arginine methylation at H3 and H4 respectively (Saha, et al., 2017). Moreover, SFN has been shown to induce Nrf2-dependent expression of detoxification enzymes HO-1, NQO1 and UGT1A1 thus suppressing TPA-induced malignant transformation. Such increased Nrf2 expression was attributed to promoter hypo-methylation through down-regulation of DNMTs and inhibition of overall HDAC activity (Su, et al., 2014).

On another note, a limited number of studies have shown that ITCs act as epigenetic modulatory compounds to protect against melanoma development. To this end, exposure to SFN inhibits growth and proliferation of B16 and S91 murine melanoma cells whereas intraperitoneal injection of SFN-encapsulated microspheres enhanced its anti-cancer activity in melanoma tumour-bearing C57BL/6 mice through down-regulation of de-acetylation enzymes (Do, et al., 2010). In another study, SFN decreased melanoma cancer stem (MCS) cell survival, metastasis and invasion through inactivation of EZH2, a protein shown to be over-expressed in these cells *in vitro* (Fisher, et al., 2016). In line with these observations, oral administration of SFN in mice inoculated with A375 melanoma-derived mesenchymal stem (MCS) cells inhibited tumour growth, an effect which was associated with reduced expression levels of EZH2, H3K27me3 and MMP together with increased expression of metalloproteinase inhibitor 3 (TIMP3) and enhanced apoptosis (Fisher, et al., 2016).

# **Concluding remarks**

ITCs are an important class of bio-active dietary agents considered to be of great value in various industries (e.g. food, nutraceutical, cosmetic, pharmaceutical, etc.) due to their wide range of biological properties (e.g. anti-bacterial, anti-inflammatory, anti-aging, anti-cancer, etc.). In the context of their anti-cancer activity, ITCs have been shown to interfere with many cellular pathways (e.g. growth, proliferation, apoptosis, etc.) which are usually found to be deregulated in cancer cells and thus exert their cytotoxicity.

Epigenetic modulations play a central role in both physiological and pathophysiological processes, including carcinogenesis. The most common epigenetic alterations, associated with disease pathophysiology, include alterations in DNA methylation patterns, histone modifications and modulation of mi-RNA expression that lead to the silencing and/or activation of gene-targets through changes in chromatin conformations. For instance, growing evidence support that ITCs interact with the epigenetic machinery to modulate the transcriptional activity of tumour-related genes. As such, their epigenetic modulatory effect poses a great interest to the pharmaceutical industry due to the reversible nature of the epigenetic modifications and the potential of ITCs to develop into more effective therapeutic strategies. To this end, several epigenetic alterations have been reported to play an essential role in the multi-stage process of skin tumorigenesis. Over the last decades, emerging evidence support that ITCs can act on the epigenome and restore normal epigenetic marks in skin cancer cells. Although the current evidence is rather limited, the overall data strongly support the potential of these dietary agents to act as epigenetic modulatory compounds thus contributing to a better understanding of their chemo-prevention particularly in the context of forming new therapeutic strategies in order to deliver a more effective clinical management in these patients.

# **Conflict of interest statement**

The authors declare that there is no conflict of interest.

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# **References**

Abdull, R., Ahmad, F., & Noor, N.M. (2013). Cruciferous vegetables: dietary phytochemicals for cancer prevention. *Asian Pac J Cancer Prev, 14*, 1565-1570.

Abel, E.L., Boulware, S., Fields, T., McIvor, E., Powell, K.L., DiGiovanni, J., Vasquez, K.M., & MacLeod, M.C. (2013). Sulforaphane induces phase II detoxication enzymes in mouse skin and prevents mutagenesis induced by a mustard gas analog. *Toxicol Appl Pharmacol, 266*, 439-442.

Albert, M., & Helin, K. (2010). Histone methyltransferases in cancer. *Semin Cell Dev Biol, 21*, 209-220.

Andréasson, E., & Jørgensen, L.B. (2003). Chapter four localization of plant myrosinases and glucosinolates. *Recent Adv Phytochem, 37*, 79-99.

Andréasson, E., Jørgensen, L.B., Höglund, A-S., Rask, L., & Meijer, J. (2001). Different myrosinase and idioblast distribution in Arabidopsis and Brassica napus. *Plant Physiol, 127*, 1750-1763.

Anestopoulos, I., Sfakianos, A.P., Franco, R., Chlichlia, K., Panayiotidis, M.I., Kroll, D.J., Pappa, A. (2016). A novel role of silibinin as a putative epigenetic modulator in human prostate carcinoma. *Molecules, 22(1), E62.*

Anestopoulos, I., Voulgaridou, G-P., Georgakilas, A.G., Franco, R., Pappa, A., Panayiotidis, M.I. (2015). Epigenetic therapy as a novel approach in hepatocellular carcinoma. *Pharmacol Ther, 145, 103-119.*

Angelino, D., & Jeffery, E. (2014). Glucosinolate hydrolysis and bioavailability of resulting isothiocyanates: focus on glucoraphanin. *J Funct Foods, 7*, 67-76.

Aras, U., Gandhi, Y.A., Masso‐Welch, P.A., & Morris, M.E. (2013). Chemopreventive and anti‐angiogenic effects of dietary phenethyl isothiocyanate in an N‐methyl nitrosourea‐induced breast cancer animal model. *Biopharm Drug Dispos, 34*, 98-106.

Armstrong, B.K., & Kricker, A. (2001). The epidemiology of UV induced skin cancer. *J Photochem Photobiol B, 63*, 8-18.

Athar, M., Li, C., Kim, A.L., Spiegelman, V.S., & Bickers, D.R. (2014). Sonic hedgehog signaling in basal cell nevus syndrome. *Cancer Res, 74*, 4967-4975.

Avner, P., & Heard, E. (2001). X-chromosome inactivation: counting, choice and initiation. *Nat Rev Genet, 2*, 59-67.

Baer, C., Claus, R., & Plass, C. (2013). Genome-wide epigenetic regulation of miRNAs in cancer. *Cancer Res, 73*, 473-477.

Balasubramanian, S., Chew, Y.C., & Eckert, R.L. (2011). Sulforaphane suppresses polycomb group protein level via a proteasome-dependent mechanism in skin cancer cells. *Mol Pharmacol, 80*, 870-878.

Barba, F.J., Nikmaram, N., Roohinejad, S., Khelfa, A., Zhu, Z., & Koubaa, M. (2016). Bioavailability of glucosinolates and their breakdown products: Impact of processing. *Front Nutr, 3, 24*.

Basten, G.P., Bao, Y., & Williamson, G. (2002). Sulforaphane and its glutathione conjugate but not sulforaphane nitrile induce UDP-glucuronosyl transferase (UGT1A1) and glutathione transferase (GSTA1) in cultured cells. *Carcinogenesis, 23*, 1399-1404.

Batra, S., Sahu, R.P., Kandala, P.K., & Srivastava, S.K. (2010). Benzyl isothiocyanate–mediated inhibition of histone deacetylase leads to NF-κB turnoff in human pancreatic carcinoma cells. *Mol Cancer Ther, 9*, 1596-1608.

Baxter, J.M., Patel, A.N., & Varma, S. (2012). Facial basal cell carcinoma. *BMJ, 345*, e5342.

Becker, T.M., Haferkamp, S., Dijkstra, M.K., Scurr, L.L., Frausto, M., Diefenbach, E., Scolyer, R.A., Reisman, D.N., Mann, G.J., Kefford, R.F., & Rizos, H. (2009). The chromatin remodelling factor BRG1 is a novel binding partner of the tumor suppressor p16INK4a. *Mol Cancer, 8*, 4.

Bemis, L.T., Chen, R., Amato, C.M., Classen, E.H., Robinson, S.E., Coffey, D.G., Erickson, P.F., Shellman, Y.G., & Robinson, W.A. (2008). MicroRNA-137 targets microphthalmia-associated transcription factor in melanoma cell lines. *Cancer Res, 68*, 1362-1368.

Berdasco, M., & Esteller, M. (2010). Aberrant Epigenetic Landscape in Cancer: How Cellular Identity Goes Awry. *Dev Cell, 19*, 698-711.

Berger, S.L. (2007). The complex language of chromatin regulation during transcription. *Nature, 447*, 407-412.

Bhattacharya, A., Li, Y., Wade, K.L., Paonessa, J.D., Fahey, J.W., & Zhang, Y. (2010). Allyl isothiocyanate-rich mustard seed powder inhibits bladder cancer growth and muscle invasion. *Carcinogenesis, 31*, 2105-2110.

Bonasio, R., Tu, S., & Reinberg, D. (2010). Molecular signals of epigenetic states. *Science, 330*, 612-616.

Boreddy, S.R., Pramanik, K.C., & Srivastava, S.K. (2011a). Pancreatic tumor suppression by benzyl isothiocyanate is associated with inhibition of PI3K/AKT/FOXO pathway. *Clin Cancer Res, 17*, 1784-1795.

Boreddy, S.R., Sahu, R.P., & Srivastava, S.K. (2011b). Benzyl isothiocyanate suppresses pancreatic tumor angiogenesis and invasion by inhibiting HIF-α/VEGF/Rho-GTPases: pivotal role of STAT-3. *PLoS One, 6*, e25799.

Bosserhoff, A.K. (2006). Novel biomarkers in malignant melanoma. *Clin Chim Acta, 367*, 28-35.

Boyanapalli, S.S., Li, W., Fuentes, F., Guo, Y., Ramirez, C.N., Gonzalez, X-P., Pung, D., & Kong, A-N.T. (2016). Epigenetic reactivation of RASSF1A by phenethyl isothiocyanate (PEITC) and promotion of apoptosis in LNCaP cells. *Pharmacol Res, 114*, 175-184.

Boyle, G.M., Martyn, A.C., & Parsons, P.G. (2005). Histone deacetylase inhibitors and malignant melanoma. *Pigment Cell Res, 18*, 160-166.

Brash, D.E. (2015). UV Signature Mutations. *Photochemistry and Photobiology, 91*, 15-26.

Brien, G.L., Valerio, D.G., & Armstrong, S.A. (2016). Exploiting the epigenome to control cancer-promoting gene-expression programs. *Cancer Cell, 29*, 464-476.

Brinkhuizen, T., van den Hurk, K., Winnepenninckx, V.J., de Hoon, J.P., van Marion, A.M., Veeck, J., van Engeland, M., & van Steensel, M.A. (2012). Epigenetic changes in basal cell carcinoma affect SHH and WNT signaling components. *PLoS One, 7*, e51710.

Brown, V.L., Harwood, C.A., Crook, T., Cronin, J.G., Kelsell, D.P., & Proby, C.M. (2004). p16INK4a and p14ARF Tumor suppressor genes are commonly inactivated in cutaneous squamous cell carcinoma. *J Invest Dermatol, 122*, 1284-1292.

Bustos, M.A., Ono, S., Marzese, D.M., Oyama, T., Iida, Y., Cheung, G., Nelson, N., Hsu, S. C., Yu, Q., & Hoon, D.S.B. (2017). MiR-200a regulates CDK4/6 inhibitor effect by targeting CDK6 in metastatic melanoma. *J Invest Dermatol, 137*, 1955-1964.

Chakravarthi, B.V.S.K., Nepal, S., & Varambally, S. (2016). Genomic and epigenomic alterations in cancer. *Am J Pathol, 186*, 1724-1735.

Chang, N-B., Feng, R., Gao, Z., & Gao, W. (2010). Skin cancer incidence is highly associated with ultraviolet-B radiation history. *Int J Hyg Environ Health, 213*, 359-368.

Chen, P-Y., Lin, K-C., Lin, J-P., Tang, N-Y., Yang, J-S., Lu, K-W., & Chung, J-G. (2012). Phenethyl Isothiocyanate (PEITC) inhibits the growth of human oral squamous carcinoma HSC-3 cells through G0/G1 phase arrest and mitochondria-mediated apoptotic cell death. *Evid Based Complement Alternat Med, 2012, 718320*.

Cheng, E., Trombetta, S.E., Kovacs, D., Beech, R.D., Ariyan, S., Reyes-Mugica, M., McNiff, J.M., Narayan, D., Kluger, H.M., Picardo, M., & Halaban, R. (2006). Rab33A: characterization, expression, and suppression by epigenetic modification. *J Invest Dermatol, 126*, 2257-2271.

Cheng, Y-M., Tsai, C-C., & Hsu, Y-C. (2016). Sulforaphane, a dietary isothiocyanate, induces G2/M arrest in cervical cancer cells through CyclinB1 downregulation and GADD45β /CDC2 association. *Int J Mol Sci, 17*, 1530.

Cheung, K.L., Khor, T.O., Yu, S., & Kong, A-N.T. (2008). PEITC induces G1 cell cycle arrest on HT-29 cells through the activation of p38 MAPK signaling pathway. *AAPS J, 10*, 277-281.

Cheung, K.L., & Kong, A-N. (2010). Molecular targets of dietary phenethyl isothiocyanate and sulforaphane for cancer chemoprevention. *AAPS J, 12*, 87-97.

Chew, Y.C., Adhikary, G., Wilson, G.M., Xu, W., & Eckert, R.L. (2012). Sulforaphane induction of p21Cip1 cyclin-dependent kinase inhibitor expression requires p53 and Sp1 transcription factors and is p53-dependent. *J Biol Chem, 287*, 16168-16178.

Cho, H.J., Lim, D.Y., Kwon, G.T., Kim, J.H., Huang, Z., Song, H., Oh, Y.S., Kang, Y.H., Lee, K.W., Dong, Z., & Park, J.H. (2016). Benzyl isothiocyanate inhibits prostate cancer development in the transgenic adenocarcinoma mouse prostate (TRAMP) model which is associated with the induction of cell cycle G1 arrest. *Int J Mol Sci, 17*, 264.

Chou, Y.C., Chang, M.Y., Wang, M.J., Yu, F.S., Liu, H.C., Harnod, T., Hung, C.H., Lee, H.T., & Chung, J.G. (2015). PEITC inhibits human brain glioblastoma GBM 8401 cell migration and invasion through the inhibition of uPA, Rho A, and Ras with inhibition of MMP-2, -7 and -9 gene expression. *Oncol Rep, 34*, 2489-2496.

Costello, J.F., & Plass, C. (2001). Methylation matters. *J Med Gen, 38*, 285-303.

Crichlow, G.V., Fan, C., Keeler, C., Hodsdon, M., & Lolis, E.J. (2012). Structural interactions dictate the kinetics of macrophage migration inhibitory factor inhibition by different cancer-preventive isothiocyanates. *Biochemistry, 51*, 7506-7514.

D'Arcangelo, D., Tinaburri, L., & Dellambra, E. (2017). The Role of p16(INK4a) pathway in human epidermal stem cell self-renewal, aging and cancer. *Int J Mol Sci, 18, E1591*.

Dahl, C., & Guldberg, P. (2007). The genome and epigenome of malignant melanoma. *APMIS, 115*, 1161-1176.

Darido, C., Georgy, S.R., Wilanowski, T., Dworkin, S., Auden, A., Zhao, Q., Rank, G., Srivastava, S., Finlay, M.J., Papenfuss, A.T., Pandolfi, P.P., Pearson, R.B., & Jane, S.M. (2011). Targeting of the tumor suppressor GRHL3 by a miR-21-dependent proto-oncogenic network results in PTEN loss and tumorigenesis. *Cancer Cell, 20,* 635-648.

Darr, O.A., Colacino, J.A., Tang, A.L., McHugh, J.B., Bellile, E.L., Bradford, C.R., Prince, M.P., Chepeha, D.B., Rozek, L.S., & Moyer, J.S. (2015). Epigenetic alterations in metastatic cutaneous carcinoma. *Head Neck, 37,* 994-1001*.*

Dawson, M.A., & Kouzarides, T. (2012). Cancer epigenetics: from mechanism to therapy. *Cell, 150*, 12-27.

de Oliveira, J.M.P.F., Costa, M., Pedrosa, T., Pinto, P., Remédios, C., Oliveira, H., Pimentel, F., Almeida, L., & Santos, C. (2014). Sulforaphane induces oxidative stress and death by p53-independent mechanism: implication of impaired glutathione recycling. *PLoS One, 9*, e92980.

del Carmen Martinez-Ballesta, M., & Carvajal, M. (2015). Myrosinase in Brassicaceae: the most important issue for glucosinolate turnover and food quality. *Phytochem Rev, 14*, 1045-1051.

Del Prete, A., Allavena, P., Santoro, G., Fumarulo, R., Corsi, M.M., & Mantovani, A. (2011). Molecular pathways in cancer-related inflammation. *Biochem Med (Zagreb), 21*, 264-275.

Devine, C., Srinivasan, B., Sayan, A., & Ilankovan, V. (2018). Epidemiology of basal cell carcinoma: a 10-year comparative study. *Br J Oral Maxillofac Surg, 56,* 101-106.

Diepgen, T., & Mahler, V. (2002). The epidemiology of skin cancer. *Br J Dermatol, 146*, 1-6.

Dinkova-Kostova, A.T., Fahey, J.W., Benedict, A.L., Jenkins, S.N., Ye, L., Wehage, S.L., & Talalay, P. (2010). Dietary glucoraphanin-rich broccoli sprout extracts protect against UV radiation-induced skin carcinogenesis in SKH-1 hairless mice. *Photochem Photobiol Sci, 9*, 597-600.

Dinkova-Kostova, A.T., Fahey, J.W., Wade, K.L., Jenkins, S.N., Shapiro, T.A., Fuchs, E.J., Kerns, M.L., & Talalay, P. (2007). Induction of the phase 2 response in mouse and human skin by sulforaphane-containing broccoli sprout extracts. *Cancer Epidemiol Biomarkers Prev, 16*, 847-851.

Dinkova-Kostova, A.T., Jenkins, S.N., Fahey, J.W., Ye, L., Wehage, S.L., Liby, K.T., Stephenson, K.K., Wade, K.L., & Talalay, P. (2006). Protection against UV-light-induced skin carcinogenesis in SKH-1 high-risk mice by sulforaphane-containing broccoli sprout extracts. *Cancer Lett, 240*, 243-252.

Dinkova-Kostova, A.T., & Kostov, R.V. (2012). Glucosinolates and isothiocyanates in health and disease. *Trends Mol Med, 18*, 337-347.

Do, D., Pai, S., Rizvi, S.A., & D'Souza, M.J. (2010). Development of sulforaphane-encapsulated microspheres for cancer epigenetic therapy. *Int J Pharm, 386*, 114-121.

Drobnica, L., Zemanova, M., Nemec, P., Antoš, K., Kristian, P., Štullerová, A., & Knoppova, V. (1967). Antifungal activity of isothiocyanates and related compounds I. Naturally occurring isothiocyanates and their analogues. *Appl Microbiol, 15*, 701-709.

Dufour, V., Stahl, M., & Baysse, C. (2015). The antibacterial properties of isothiocyanates. *Microbiology, 161*, 229-243.

Dziunycz, P., Iotzova-Weiss, G., Eloranta, J.J., Läuchli, S., Hafner, J., French, L.E., & Hofbauer, G.F.L. (2010). Squamous cell carcinoma of the skin shows a distinct microRNA profile modulated by UV radiation. *J Invest Dermatol, 130*, 2686-2689.

Eden, A., Gaudet, F., Waghmare, A., & Jaenisch, R. (2003). Chromosomal instability and tumors promoted by DNA hypomethylation. *Science, 300*, 455-455.

Egger, G., Liang, G., Aparicio, A., & Jones, P.A. (2004). Epigenetics in human disease and prospects for epigenetic therapy. *Nature, 429*, 457-463.

Emmert, S., Schön, M.P., & Haenssle, H.A. (2014). Molecular biology of basal and squamous cell carcinomas. In *Sunlight, Vitamin D and Skin Cancer* (pp. 234-252): Springer.

Erb, P., Ji, J., Kump, E., Mielgo, A., & Wernli, M. (2008). Apoptosis and pathogenesis of melanoma and nonmelanoma skin cancer. *Adv Exp Med Biol, 624*, 283-295.

Ernst, I.M., Wagner, A. E., Schuemann, C., Storm, N., Höppner, W., Döring, F., Stocker, A., & Rimbach, G. (2011). Allyl-, butyl-and phenylethyl-isothiocyanate activate Nrf2 in cultured fibroblasts. *Pharmacol Res, 63*, 233-240.

Facchetti, F., Previdi, S., Ballarini, M., Minucci, S., Perego, P., & Porta, C.A.M.L. (2004). Modulation of pro- and anti-apoptotic factors in human melanoma cells exposed to histone deacetylase inhibitors. *Apoptosis, 9*, 573-582.

Fahey, J. W., Zhang, Y., & Talalay, P. (1997). Broccoli sprouts: an exceptionally rich source of inducers of enzymes that protect against chemical carcinogens. *Proc Natl Acad Sci U S A, 94*, 10367-10372.

Fahey, J.W., Wehage, S.L., Holtzclaw, W.D., Kensler, T.W., Egner, P.A., Shapiro, T.A., Talaly, P. (2012). Protection of humans by plant glucosinolates: Efficiency of conversion of glucosinolates to isothiocyanates by the gastrointestinal microflora. *Cancer Prev Res (Phila), 5(4).* 603-611.

Fan, T., Jiang, S., Chung, N., Alikhan, A., Ni, C., Lee, C-C.R., & Hornyak, T.J. (2011). EZH2-dependent suppression of a cellular senescence phenotype in melanoma cells by inhibition of p21/<em>CDKN1A</em> expression. *Mol Cancer Res, 9*, 418-429.

Farazi, T.A., Spitzer, J.I., Morozov, P., & Tuschl, T. (2011). miRNAs in human cancer. *J Pathol, 223*, 102-115.

Feinberg, A.P., & Vogelstein, B. (1983). Hypomethylation distinguishes genes of some human cancers from their normal counterparts. *Nature, 301*, 89-92.

Ferguson-Smith, A.C., & Surani, M.A. (2001). Imprinting and the epigenetic asymmetry between parental genomes. *Science, 293*, 1086-1089.

Fisher, M.L., Adhikary, G., Grun, D., Kaetzel, D.M., & Eckert, R.L. (2016). The Ezh2 polycomb group protein drives an aggressive phenotype in melanoma cancer stem cells and is a target of diet derived sulforaphane. *Mol Carcinog, 55*, 2024-2036.

Fitsiou, E., Anestopoulos, I., Chlichlia, K., Galanis, A., Kourkoutas, I., Panayiotidis, M.I., & Pappa, A. (2016a). Antioxidant and antiproliferative properties of the essential oils of Satureja thymbra and Satureja parnassica and their major constituents. *Anticancer Res, 36*, 5757-5763.

Fitsiou, E., Mitropoulou, G., Spyridopoulou, K., Tripiti-Kourpeti, A., Vamvakias, M., Bardouki, H., Panayiotidis, M.I., Galanis, A., Kourkoutas, Y., Chlichlia, A., & Pappa, A. (2016b). Phytochemical profile and evaluation of the biological activities of essential oils derived from the Greek aromatic plant species Ocinum basilicum, Mentha spicata, Pimpinella anisum and Fortunella margarita. *Molecules, 21,* E1069.

Fitsiou, E., Mitropoulou, G., Spyridopoulou, K., Vamvakias, M., Bardouki, H., Galanis, A., Chlichlia, K., Kourkoutas, Y., Panayiotidis, M.I., & Pappa, A. (2018). Chemical composition and evaluation of the biological properties of the essential oil of the dietary phytochemical Lippia citriodora. *Molecules, 23,* E123*.*

Fraga, M.F., Herranz, M., Espada, J., Ballestar, E., Paz, M. F., Ropero, S., Erkek, E., Bozdogan, O., Peinado, H., & Niveleau, A. (2004). A mouse skin multistage carcinogenesis model reflects the aberrant DNA methylation patterns of human tumors. *Cancer Res, 64*, 5527-5534.

Franco, R., Schoneveld, O,. Georgakilas, A.G., Panayiotidis, M.I. (2008). Oxidative Stress, DNA methylation and carcinogenesis. *Cancer Lett, 266(1), 6-11.*

Freije, A., Molinuevo, R., Ceballos, L., Cagigas, M., Alonso-Lecue, P., Rodriguez, R., Menendez, P., Aberdam, D., De Diego, E., & Gandarillas, A. (2014). Inactivation of p53 in human keratinocytes leads to squamous differentiation and shedding via replication stress and mitotic slippage. *Cell Rep, 9*, 1349-1360.

Freitas, E., Aires, A., Rosa, E., & Saavedra, M.J. (2013). Antibacterial activity and synergistic effect between watercress extracts, 2‐phenylethyl isothiocyanate and antibiotics against 11 isolates of Escherichia coli from clinical and animal source. *Lett Appl Microbiol, 57*, 266-273.

Fu, S., Wu, H., Zhang, H., Lian, C.G., & Lu, Q. (2017). DNA methylation/hydroxymethylation in melanoma. *Oncotarget, 8*, 78163-78173.

Fuks, F., Hurd, P.J., Deplus, R., & Kouzarides, T. (2003). The DNA methyltransferases associate with HP1 and the SUV39H1 histone methyltransferase. *Nucleic Acids Res, 31*, 2305-2312.

Füllgrabe, J., Kavanagh, E., & Joseph, B. (2011). Histone onco-modifications. *Oncogene, 30*, 3391.

Furuta, J., Nobeyama, Y., Umebayashi, Y., Otsuka, F., Kikuchi, K., & Ushijima, T. (2006). Silencing of Peroxiredoxin 2 and aberrant methylation of 33 CpG islands in putative promoter regions in human malignant melanomas. *Cancer Res, 66*, 6080-6086.

Gao, L., van den Hurk, K., Moerkerk, P.T.M., Goeman, J.J., Beck, S., Gruis, N.A., van den Oord, J.J., Winnepenninckx, V.J., van Engeland, M., & van Doorn, R. (2014). Promoter CpG island hypermethylation in dysplastic nevus and melanoma: CLDN11 as an epigenetic biomarker for malignancy. *J Invest Dermatol, 134*, 2957-2966.

Gao, S.S., Chen, X.Y., Zhu, R.Z., Choi, B.M., & Kim, B.R. (2010). Sulforaphane induces glutathione S‐transferase isozymes which detoxify aflatoxin B1‐8, 9‐epoxide in AML 12 cells. *Biofactors, 36*, 289-296.

Gills, J.J., Jeffery, E.H., Matusheski, N.V., Moon, R.C., Lantvit, D.D., & Pezzuto, J.M. (2006). Sulforaphane prevents mouse skin tumorigenesis during the stage of promotion. *Cancer Lett, 236*, 72-79.

Gokul, G., & Khosla, S. (2013). DNA Methylation and Cancer. In T. K. Kundu (Ed.), *Epigenetics: Development and Disease* (pp. 597-625). Dordrecht: Springer Netherlands.

Golbabapour, S., Abdulla, M.A., & Hajrezaei, M. (2011). A concise review on epigenetic regulation: insight into molecular mechanisms. *Int J Mol Sci, 12*, 8661-8694.

Goldberg, M., Rummelt, C., Laerm, A., Helmbold, P., Holbach, L.M., & Ballhausen, W.G. (2006). Epigenetic silencing contributes to frequent loss of the fragile histidine triad tumour suppressor in basal cell carcinomas. *Br J Dermatol, 155*, 1154-1158.

Gordon, R. (2013). Skin Cancer: An overview of epidemiology and risk factors. *Semin Oncol Nurs, 29*, 160-169.

Goto, N., Bazar, G., Kovacs, Z., Kunisada, M., Morita, H., Kizaki, S., Sugiyama, H., Tsenkova, R., & Nishigori, C. (2015). Detection of UV-induced cyclobutane pyrimidine dimers by near-infrared spectroscopy and aquaphotomics. *Sci Rep, 5*, 11808.

Greaney, A.J., Maier, N.K., Leppla, S.H., & Moayeri, M. (2016). Sulforaphane inhibits multiple inflammasomes through an Nrf2-independent mechanism. *J Leukoc Biol, 99*, 189-199.

Greenberg, E.S., Chong, K.K., Huynh, K.T., Tanaka, R., & Hoon, D.S. (2014). Epigenetic biomarkers in skin cancer. *Cancer Lett, 342*, 170-177.

Greger, V., Passarge, E., Hopping, W., Messmer, E., & Horsthemke, B. (1989). Epigenetic changes may contribute to the formation and spontaneous regression of retinoblastoma. *Hum Genet, 83*, 155-158.

Greinert, R. (2009). Skin cancer: new markers for better prevention. *Pathobiology, 76*, 64-81.

Grignol, V., Fairchild, E.T., Zimmerer, J.M., Lesinski, G.B., Walker, M.J., Magro, C.M., Kacher, J.E., Karpa, V.I., Clark, J., Nuovo, G., Lehman, A., Volinia, S., Agnese, D.M., Croce, C.M., & Carson, W.E., 3rd. (2011). miR-21 and miR-155 are associated with mitotic activity and lesion depth of borderline melanocytic lesions. *Br J Cancer, 105*, 1023-1029.

Grubb, C.D., & Abel, S. (2006). Glucosinolate metabolism and its control. *Trends Plant Sci, 11*, 89-100.

Guan, X., Sagara, J., Yokoyama, T., Koganehira, Y., Oguchi, M., Saida, T., & Taniguchi, S. (2003). ASC/TMS1, a caspase-1 activating adaptor, is downregulated by aberrant methylation in human melanoma. *Int J Cancer, 107*, 202-208.

Gupta, P., Adkins, C., Lockman, P., & Srivastava, S.K. (2013). Metastasis of breast tumor cells to brain is suppressed by phenethyl isothiocyanate in a novel in vivo metastasis model. *PLoS One, 8*, e67278.

Haflidadottir, B.S., Bergsteinsdottir, K., Praetorius, C., & Steingrimsson, E. (2010). miR-148 regulates Mitf in melanoma cells. *PLoS One, 5*, e11574.

Hallberg, A.R., Vorrink, S.U., Hudachek, D.R., Cramer-Morales, K., Milhem, M.M., Cornell, R.A., & Domann, F.E. (2014). Aberrant CpG methylation of the TFAP2A gene constitutes a mechanism for loss of TFAP2A expression in human metastatic melanoma. *Epigenetics, 9*, 1641-1647.

Halliday, G.M. (2005). Inflammation, gene mutation and photoimmunosuppression in response to UVR-induced oxidative damage contributes to photocarcinogenesis. *Mut Res, 571*, 107-120.

Hamsa, T.P., Thejass, P., & Kuttan, G. (2011). Induction of apoptosis by sulforaphane in highly metastatic B16F-10 melanoma cells. *Drug Chem Toxicol, 34*, 332-340.

Hanschen, F.S., Klopsch, R., Oliviero, T., Schreiner, M., Verkerk, R., Dekker, M. (2017). Optimizing isothiocyanate formation during enzymatic glucosinolate breakdown for adjusting pH value, temperature and dilution in Brassica vegetables and Arabidopsis thaliana. *Sci Rep, 7,* 40807.

Hassler, M.R., & Egger, G. (2012). Epigenomics of cancer-emerging new concepts. *Biochimie, 94*, 2219-2230.

Heffelfinger, C., Ouyang, Z., Engberg, A., Leffell, D.J., Hanlon, A.M., Gordon, P.B., Zheng, W., Zhao, H., Snyder, M.P., & Bale, A.E. (2012). Correlation of global microRNA expression with basal cell carcinoma subtype. *G3 (Bethesda), 2*, 279-286.

Hemberger, M. (2007). Epigenetic landscape required for placental development. *Cell Mol Life Sci, 64*, 2422-2436.

Higdon, J.V., Delage, B., Williams, D.E., & Dashwood, R.H. (2007). Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. *Pharmacol Res, 55*, 224-236.

Hocker, T.L., Singh, M.K., & Tsao, H. (2008). Melanoma genetics and therapeutic approaches in the 21st Century: Moving from the benchside to the bedside. *J Invest Dermatol, 128*, 2575-2595.

Hoon, D.S., Spugnardi, M., Kuo, C., Huang, S.K., Morton, D.L., & Taback, B. (2004). Profiling epigenetic inactivation of tumor suppressor genes in tumors and plasma from cutaneous melanoma patients. *Oncogene, 23*, 4014-4022.

Howarth, N.C., Saltzman, E., Roberts, S.B. (2001). Dietary fiber and weight regulation. *Nutr Rev, 59(5),* 129-139.

Hsu, A., Wong, C.P., Yu, Z., Williams, D.E., Dashwood, R.H., & Ho, E. (2011). Promoter de-methylation of cyclin D2 by sulforaphane in prostate cancer cells. *Clin Epigen, 3*, 3.

Hu, R., Xu, C., Shen, G., Jain, M.R., Khor, T.O., Gopalkrishnan, A., Lin, W., Reddy, B., Chan, J.Y., & Kong, A-N.T. (2006). Gene expression profiles induced by cancer chemopreventive isothiocyanate sulforaphane in the liver of C57BL/6J mice and C57BL/6J/Nrf2 (−/−) mice. *Cancer Lett, 243*, 170-192.

Huang, S-H., Wu, L-W., Huang, A-C., Yu, C-C., Lien, J-C., Huang, Y-P., Yang, J-S., Yang, J-H., Hsiao, Y-P., & Wood, W.G. (2012). Benzyl isothiocyanate (BITC) induces G2/M phase arrest and apoptosis in human melanoma A375.S2 cells through reactive oxygen species (ROS) and both mitochondria-dependent and death receptor-mediated multiple signaling pathways. *J Agri Food Chem, 60*, 665-675.

Huang, S., Hsu, M., Hsu, S., Yang, J., Huang, W., Huang, A., Hsiao, Y., Yu, C., & Chung, J. (2014). Phenethyl isothiocyanate triggers apoptosis in human malignant melanoma A375.S2 cells through reactive oxygen species and the mitochondria-dependent pathways. *Hum Exp Toxicol, 33*, 270-283.

Ichihashi, M., Ueda, M., Budiyanto, A., Bito, T., Oka, M., Fukunaga, M., Tsuru, K., & Horikawa, T. (2003). UV-induced skin damage. *Toxicology, 189*, 21-39.

Ippoushi, K., Ueda, A., Takeuchi, A. (2013). Corn oil and milk enhance the absorption of orally administered allyl isothiocyanate in rats. *Food Chem, 141(2),* 1192-1195

Ippoushi, K., Ueda, H., Takeuchi, A. (2014). Milk prevents the degradation of daikon (Raphanus sativus L.) isothiocyanate and enhances its absorption in rats. *Food Chem, 161,* 176-180.

Issa, A.Y., Volate, S.R., & Wargovich, M.J. (2006). The role of phytochemicals in inhibition of cancer and inflammation: New directions and perspectives. *J Food Compost Anal, 19*, 405-419.

Jakubíková, J., Sedlák, J., Mithen, R., & Bao, Y. (2005). Role of PI3K/Akt and MEK/ERK signaling pathways in sulforaphane-and erucin-induced phase II enzymes and MRP2 transcription, G 2/M arrest and cell death in Caco-2 cells. *Biochem Pharmacol, 69*, 1543-1552.

Jansson, M.D., & Lund, A.H. (2012). MicroRNA and cancer. *Mol Oncol, 6*, 590-610.

Johnson, G.S., Li, J., Beaver, L. M., Dashwood, W.M., Sun, D., Rajendran, P., Williams, D. E., Ho, E., & Dashwood, R.H. (2017). A functional pseudogene, NMRAL2P, is regulated by Nrf2 and serves as a coactivator of NQO1 in sulforaphane‐treated colon cancer cells. *Mol Nutr Food Res, 61*.

Johnson, I.T. (2007). Phytochemicals and cancer. *Proc Nutr Soc, 66*, 207-215.

Kaiser, S.J., Mutters, N.T., Blessing, B., & Günther, F. (2017). Natural isothiocyanates express antimicrobial activity against developing and mature biofilms of Pseudomonas aeruginosa. *Fitoterapia, 119*, 57-63.

Kanavy, H.E., & Gerstenblith, M.R. (2011). Ultraviolet radiation and melanoma. In *Seminars in cutaneous medicine and surgery* (Vol. 30, pp. 222-228): Frontline Medical Communications.

Kanemaru, H., Fukushima, S., Yamashita, J., Honda, N., Oyama, R., Kakimoto, A., Masuguchi, S., Ishihara, T., Inoue, Y., & Jinnin, M. (2011). The circulating microRNA-221 level in patients with malignant melanoma as a new tumor marker. *J Dermatol Sci, 61*, 187-193.

Kang, N.J., Shin, S.H., Lee, H.J., & Lee, K.W. (2011). Polyphenols as small molecular inhibitors of signaling cascades in carcinogenesis. *Pharmacol Ther, 130*, 310-324.

Kanwal, R., & Gupta, S. (2012). Epigenetic modifications in cancer. *Clin Genet, 81*, 303-311.

Kerr, C., Adhikary, G., Grun, D., George, N., & Eckert, R.L. (2018). Combination cisplatin and sulforaphane treatment reduces proliferation, invasion, and tumor formation in epidermal squamous cell carcinoma. *Mol Carcinog, 57*, 3-11.

Keum, Y-S., Jeong, W-S., & Kong, A.T. (2004). Chemoprevention by isothiocyanates and their underlying molecular signaling mechanisms. *Mutat Res, 555*, 191-202.

Keum, Y-S., Owuor, E.D., Kim, B-R., Hu, R., & Kong, A-N.T. (2003). Involvement of Nrf2 and JNK1 in the activation of antioxidant responsive element (ARE) by chemopreventive agent phenethyl isothiocyanate (PEITC). *Pharm Res, 20*, 1351-1356.

Khurana, N., Kim, H., Chandra, P.K., Talwar, S., Sharma, P., Abdel-Mageed, A.B., Sikka, S.C., & Mondal, D. (2017). Multimodal actions of the phytochemical sulforaphane suppress both AR and AR-V7 in 22Rv1 cells: Advocating a potent pharmaceutical combination against castration-resistant prostate cancer. *Oncol Rep, 38*, 2774-2786.

Kim, B.K., Kim, I., & Yoon, S.K. (2015). Identification of miR-199a-5p target genes in the skin keratinocyte and their expression in cutaneous squamous cell carcinoma. *J Dermatol Sci, 79*, 137-147.

Kim, J., Samaranayake, M., & Pradhan, S. (2009). Epigenetic mechanisms in mammals. *Cell Mol Life Sci, 66*, 596-612.

Kim, S-I., Jin, S-G., & Pfeifer, G.P. (2013). Formation of cyclobutane pyrimidine dimers at dipyrimidines containing 5-hydroxymethylcytosine. *Photochem Photobiolol Sci, 12*, 1409-1415.

Klose, R.J., & Bird, A.P. (2006). Genomic DNA methylation: the mark and its mediators. *Trends Biochem Sci, 31*, 89-97.

Ko, J.M., & Fisher, D.E. (2011). A new era: melanoma genetics and therapeutics. *J Pathol, 223*, 242-251.

Ko, M-O., Kim, M-B., & Lim, S-B. (2016). Relationship between chemical structure and antimicrobial activities of isothiocyanates from cruciferous vegetables against oral pathogens. *J Microbiol Biotechnol, 26*, 2036-2042.

Koga, Y., Pelizzola, M., Cheng, E., Krauthammer, M., Sznol, M., Ariyan, S., Narayan, D., Molinaro, A.M., Halaban, R., & Weissman, S.M. (2009). Genome-wide screen of promoter methylation identifies novel markers in melanoma. *Genome Res, 19*, 1462-1470.

Kohonen-Corish, M.R., Cooper, W.A., Saab, J., Thompson, J.F., Trent, R.J., & Millward, M.J. (2006). Promoter hypermethylation of the O(6)-methylguanine DNA methyltransferase gene and microsatellite instability in metastatic melanoma. *J Invest Dermatol, 126*, 167-171.

Konicke, K., López-Luna, A., Muñoz-Carrillo, J.L., Servín-González, L.S., Flores-de la Torre, A., Olasz, E., & Lazarova, Z. (2018). The microRNA landscape of cutaneous squamous cell carcinoma. *Drug Discov Today, 23,* 864-870.

Koroleva, O.A., Davies, A., Deeken, R., Thorpe, M.R., Tomos, A.D., & Hedrich, R. (2000). Identification of a new glucosinolate-rich cell type in Arabidopsis flower stalk. *Plant Physiol, 124*, 599-608.

Kroll, J., Rawel, H., Krock, R., Proll, J., Schnaak, W. (1994). Interactions of isothiocyanates with egg white proteins. *Mol. Nutr. Food Res, 38,* 53.

Kulis, M., & Esteller, M. (2010). DNA methylation and cancer. *Adv Genet, 70*, 27-56.

Kurepina, N., Kreiswirth, B.N., & Mustaev, A. (2013). Growth‐inhibitory activity of natural and synthetic isothiocyanates against representative human microbial pathogens. *J App Microbiol, 115*, 943-954.

Lai, K-C., Huang, A-C., Hsu, S-C., Kuo, C-L., Yang, J-S., Wu, S-H., & Chung, J-G. (2010). Benzyl isothiocyanate (BITC) inhibits migration and invasion of human colon cancer HT29 cells by inhibiting matrix metalloproteinase-2/-9 and urokinase plasminogen (uPA) through PKC and MAPK signaling pathway. *J Agri Food Chem, 58*, 2935-2942.

Lai, K-C., Lu, C-C., Tang, Y-J., Chiang, J-H., Kuo, D-H., Chen, F-A., Chen, I-L., & Yang, J-S. (2014). Allyl isothiocyanate inhibits cell metastasis through suppression of the MAPK pathways in epidermal growth factor‑stimulated HT29 human colorectal adenocarcinoma cells. *Oncol Rep, 31*, 189-196.

Lan, F., Pan, Q., Yu, H., & Yue, X. (2015). Sulforaphane enhances temozolomide-induced apoptosis because of down-regulation of miR-21 via Wnt/beta-catenin signaling in glioblastoma. *J Neurochem, 134*, 811-818.

Lee, Y-J., & Lee, S-H. (2011). Sulforaphane induces antioxidative and antiproliferative responses by generating reactive oxygen species in human bronchial epithelial BEAS-2B cells. *J Kor Med Sci, 26*, 1474-1482.

Lefort, K., Brooks, Y., Ostano, P., Cario-Andre, M., Calpini, V., Guinea-Viniegra, J., Albinger-Hegyi, A., Hoetzenecker, W., Kolfschoten, I., Wagner, E.F., Werner, S., & Dotto, G.P. (2013). A miR-34a-SIRT6 axis in the squamous cell differentiation network. *EMBO J, 32*, 2248-2263.

Li, A-N., Li, S., Zhang, Y-J., Xu, X-R., Chen, Y-M., & Li, H-B. (2014). Resources and biological activities of natural polyphenols. *Nutrients, 6*, 6020-6047.

Li, B., Carey, M., & Workman, J-L. (2007). The role of chromatin during transcription. *Cell, 128*, 707-719.

Li, E., Beard, C., & Jaenisch, R. (1993). Role for DNA methylation in genomic imprinting. *Nature, 366*, 362-365.

Li, M., Li, J., Ding, X., He, M., & Cheng, S-Y. (2010). microRNA and cancer. *AAPS J, 12*, 309-317.

Li, W., Guo, Y., Zhang, C., Wu, R., Yang, A. Y., Gaspar, J., & Kong, A-N.T. (2016). Dietary phytochemicals and cancer chemoprevention: a perspective on oxidative stress, inflammation, and epigenetics. *Chem Res Toxicol, 29*, 2071-2095.

Lian, C.G., Xu, Y., Ceol, C., Wu, F., Larson, A., Dresser, K., Xu, W., Tan, L., Hu, Y., Zhan, Q., Lee, C.W., Hu, D., Lian, B.Q., Kleffel, S., Yang, Y., Neiswender, J., Khorasani, A.J., Fang, R., Lezcano, C., Duncan, L.M., Scolyer, R.A., Thompson, J.F., Kakavand, H., Houvras, Y., Zon, L.I., Mihm, M.C., Kaiser, U.B., Schatton, T., Woda, B.A., Murphy, G.F., & Shi, Y.G. (2012). Loss of 5-Hydroxymethylcytosine is an epigenetic hallmark of melanoma. *Cell, 150*, 1135-1146.

Liang, J., Kang, X., Halifu, Y., Zeng, X., Jin, T., Zhang, M., Luo, D., Ding, Y., Zhou, Y., Yakeya, B., Abudu, D., & Pu, X. (2015). Secreted frizzled-related protein promoters are hypermethylated in cutaneous squamous carcinoma compared with normal epidermis. *BMC Cancer, 15*, 641.

Liu, S., Ren, S., Howell, P., Fodstad, O., & Riker, A.I. (2008). Identification of novel epigenetically modified genes in human melanoma via promoter methylation gene profiling. *Pigment Cell Melanoma Res, 21*, 545-558.

Liu, X., Takano, C., Shimizu, T., Yokobe, S., Abe-Kanoh, N., Zhu, B., Nakamura, T., Munemasa, S., Murata, Y., & Nakamura, Y. (2017). Inhibition of phosphatidylinositide 3-kinase ameliorates antiproliferation by benzyl isothiocyanate in human colon cancer cells. *Biochem Biophys Res Commun, 491*, 209-216.

Lodygin, D., Tarasov, V., Epanchintsev, A., Berking, C., Knyazeva, T., Korner, H., Knyazev, P., Diebold, J., & Hermeking, H. (2008). Inactivation of miR-34a by aberrant CpG methylation in multiple types of cancer. *Cell Cycle, 7*, 2591-2600.

Lodygin, D., Yazdi, A.S., Sander, C.A., Herzinger, T., & Hermeking, H. (2003). Analysis of 14-3-3σ expression in hyperproliferative skin diseases reveals selective loss associated with CpG-methylation in basal cell carcinoma. *Oncogene, 22*, 5519.

Loriot, A., De Plaen, E., Boon, T., & De Smet, C. (2006). Transient down-regulation of DNMT1 methyltransferase leads to activation and stable hypomethylation of MAGE-A1 in melanoma cells. *J Biol Chem, 281*, 10118-10126.

Lu, J., Getz, G., Miska, E.A., Alvarez-Saavedra, E., Lamb, J., Peck, D., Sweet-Cordero, A., Ebert, B.L., Mak, R.H., Ferrando, A.A., Downing, J.R., Jacks, T., Horvitz, H.R., & Golub, T.R. (2005). MicroRNA expression profiles classify human cancers. *Nature, 435*, 834.

Luciano, F.B., & Holley, R.A. (2009). Enzymatic inhibition by allyl isothiocyanate and factors affecting its antimicrobial action against Escherichia coli O157:H7. *Int J Food Microbiol, 131*, 240-245.

Luo, J.L., Tong, W.M., Yoon, J.H., Hergenhahn, M., Koomagi, R., Yang, Q., Galendo, D., Pfeifer, G.P., Wang, Z.Q., & Hollstein, M. (2001). UV-induced DNA damage and mutations in Hupki (human p53 knock-in) mice recapitulate p53 hotspot alterations in sun-exposed human skin. *Cancer Res, 61*, 8158-8163.

Madan, V., Lear, J.T., & Szeimies, R-M. (2010). Non-melanoma skin cancer. *Lancet, 375*, 673-685.

Maltepe, E., Bakardjiev, A.I., & Fisher, S.J. (2010). The placenta: transcriptional, epigenetic, and physiological integration during development. *J Clin Invest, 120*, 1016-1025.

Malumbres, M. (2013). miRNAs and cancer: An epigenetics view. *Mol Asp Med, 34*, 863-874.

Mantso, T., Sfakianos, A.P., Atkinson, A., Anestopoulos, I., Mitsiogianni, M., Botaitis, S., Perente, S., Simopoulos, C., Vasileiadis, S., Franco, R., Pappa, A., & Panayiotidis, M.I. (2016). Development of a novel experimental in vitro model of isothiocyanate-induced apoptosis in human malignant melanoma cells. *Anticancer Res, 36*, 6303-6309.

Manyes, L., Luciano, F.B., Mañes, J., & Meca, G. (2015). In vitro antifungal activity of allyl isothiocyanate (AITC) against Aspergillus parasiticus and Penicillium expansum and evaluation of the AITC estimated daily intake. *Food Chem Toxicol, 83*, 293-299.

Margueron, R., & Reinberg, D. (2010). Chromatin structure and the inheritance of epigenetic information. *Nat Rev Genet, 11*, 285-296.

Martin-Gorgojo, A., Llinares, M., Viros, A., Requena, C., Garcia-Casado, Z., Traves, V., Kumar, R., & Nagore, E. (2017). Cutaneous melanoma primary site is linked to nevus density. *Oncotarget, 8*, 98876-98886.

Martin, C., & Zhang, Y. (2005). The diverse functions of histone lysine methylation. *Nature Reviews Mol Cell Biol, 6*, 838-849.

Matusheski, N.V., Juvik, J.A., Jeffery, E.H. Heating decreases epithiospecifier protein activity and increases sulforaphane formation in broccoli. (2004). *Phytochemistry, 65(9),* 1273-1281.

Mazar, J., DeBlasio, D., Govindarajan, S.S., Zhang, S., & Perera, R.J. (2011). Epigenetic regulation of microRNA‐375 and its role in melanoma development in humans. *FEBS Lett, 585*, 2467-2476.

Mazar, J., DeYoung, K., Khaitan, D., Meister, E., Almodovar, A., Goydos, J., Ray, A., & Perera, R.J. (2010). The regulation of miRNA-211 expression and its role in melanoma cell invasiveness. *PLoS One, 5*, e13779.

McCabe, M.T., Graves, A.P., Ganji, G., Diaz, E., Halsey, W.S., Jiang, Y., Smitheman, K.N., Ott, H.M., Pappalardi, M.B., Allen, K.E., Chen, S.B., Della Pietra, A., Dul, E., Hughes, A.M., Gilbert, S.A., Thrall, S.H., Tummino, P.J., Kruger, R.G., Brandt, M., Schwartz, B., & Creasy, C.L. (2012). Mutation of A677 in histone methyltransferase EZH2 in human B-cell lymphoma promotes hypertrimethylation of histone H3 on lysine 27 (H3K27). *Proc Natl Acad Sci USA, 109*, 2989-2994.

McWalter, G.K., Higgins, L.G., McLellan, L.I., Henderson, C.J., Song, L., Thornalley, P.J., Itoh, K., Yamamoto, M., & Hayes, J.D. (2004). Transcription factor Nrf2 is essential for induction of NAD (P) H: quinone oxidoreductase 1, glutathione S-transferases, and glutamate cysteine ligase by broccoli seeds and isothiocyanates. *J Nutr, 134*, 3499S-3506S.

Meeran, S.M., Patel, S.N., & Tollefsbol, T.O. (2010). Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines. *PLoS One, 5*, e11457.

Meeran, S.M., Punathil, T., & Katiyar, S.K. (2008). IL-12 Deficiency exacerbates inflammatory responses in UV-irradiated skin and skin tumors. *J Invest Dermatol, 128*, 2716-2727.

Meier, K., Drexler, S.K., Eberle, F.C., Lefort, K., & Yazdi, A.S. (2016). Silencing of ASC in cutaneous squamous cell carcinoma. *PLoS One, 11*, e0164742.

Milkiewicz, M., Roudier, E., Doyle, J.L., Trifonova, A., Birot, O., & Haas, T.L. (2011). Identification of a mechanism underlying regulation of the anti-angiogenic forkhead transcription factor FoxO1 in cultured endothelial cells and ischemic muscle. *Am J Pathol, 178*, 935-944.

Mirmohammadsadegh, A., Marini, A., Nambiar, S., Hassan, M., Tannapfel, A., Ruzicka, T., & Hengge, U.R. (2006). Epigenetic silencing of the PTEN gene in melanoma. *Cancer Res, 66*, 6546-6552.

Moan, J., Grigalavicius, M., Baturaite, Z., Dahlback, A., & Juzeniene, A. (2015). The relationship between UV exposure and incidence of skin cancer. *Photodermatol, Photoimmunol Photomed, 31*, 26-35.

Moison, C., Guieysse-Peugeot, A-L., & Arimondo, P.B. (2014). DNA methylation in cancer.

Mondal, A., Biswas, R., Rhee, Y-H., Kim, J., & Ahn, J-C. (2016). Sulforaphene promotes Bax/Bcl2, MAPK-dependent human gastric cancer AGS cells apoptosis and inhibits migration via EGFR, p-ERK1/2 down-regulation. *Gen Physiol Biophys, 35*, 25-34.

Mori, T., Martinez, S.R., O'Day, S.J., Morton, D.L., Umetani, N., Kitago, M., Tanemura, A., Nguyen, S.L., Tran, A.N., & Wang, H-J. (2006). Estrogen receptor-α methylation predicts melanoma progression. *Cancer Res, 66*, 6692-6698.

Munday, C.M. (2002). Selective induction of phase II enzymes in the urinary bladder of rats by allyl isothiocyanate, a compound derived from Brassica vegetables. *Nutr Cancer, 44*, 52-59.

Murao, K., Kubo, Y., Ohtani, N., Hara, E., & Arase, S. (2006). Epigenetic abnormalities in cutaneous squamous cell carcinomas: frequent inactivation of the RB1/p16 and p53 pathways. *Br J Dermatol, 155*, 999-1005.

Murillo, G., & Mehta, R.G. (2001). Cruciferous vegetables and cancer prevention. *Nutr Cancer, 41*, 17-28.

Muthusamy, V., Duraisamy, S., Bradbury, C.M., Hobbs, C., Curley, D.P., Nelson, B., & Bosenberg, M. (2006). Epigenetic silencing of novel tumor suppressors in malignant melanoma. *Cancer Res, 66*, 11187-11193.

Nandakumar, V., Vaid, M., Tollefsbol, T.O., & Katiyar, S.K. (2011). Aberrant DNA hypermethylation patterns lead to transcriptional silencing of tumor suppressor genes in UVB-exposed skin and UVB-induced skin tumors of mice. *Carcinogenesis, 32*, 597-604.

Narayanan, D.L., Saladi, R.N., & Fox, J.L. (2010). Ultraviolet radiation and skin cancer. *Int J Dermatol, 49*, 978-986.

Nguyen, T., Kuo, C., Nicholl, M.B., Sim, M.S., Turner, R.R., Morton, D.L., & Hoon, D.S. (2011). Downregulation of microRNA-29c is associated with hypermethylation of tumor-related genes and disease outcome in cutaneous melanoma. *Epigenetics, 6*, 388-394.

Nguyen, T.H., & Ho, D.Q-D. (2002). Nonmelanoma skin cancer. *Curr Treat Opt Oncol, 3*, 193-203.

Ni, W-Y., Hsiao, Y-P., Hsu, S-C., Hsueh, S-C., Chang, C-H., Ji, B-C., Yang, J-S., Lu, H-F., & Chung, J-G. (2013). Oral administration of benzyl-isothiocyanate inhibits in vivo growth of subcutaneous xenograft tumors of human malignant melanoma A375.S2 cells. *In Vivo, 27*, 623-626.

Ni, W.Y., Lu, H.F., Hsu, S.C., Hsiao, Y.P., Liu, K.C., Liu, J.Y., Ji, B.C., Hsueh, S.C., Hung, F.M., Shang, H.S., & Chung, J.G. (2014). Phenethyl isothiocyanate inhibits in vivo growth of subcutaneous xenograft tumors of human malignant melanoma A375.S2 cells. *In Vivo, 28*, 891-894.

Nobeyama, Y., & Nakagawa, H. (2017a). Silencing of interferon regulatory factor gene 6 in melanoma. *PLoS One, 12*, e0184444.

Nobeyama, Y., & Nakagawa, H. (2017b). Silencing of metallothionein 1A gene in melanoma. *J Dermatol Sci, 88*, 232-237.

Nobeyama, Y., Watanabe, Y., & Nakagawa, H. (2017). Silencing of G0/G1 switch gene 2 in cutaneous squamous cell carcinoma. *PLoS One, 12*, e0187047.

Nohynek, L.J., Alakomi, H-L., Kähkönen, M.P., Heinonen, M., Helander, I.M., Oksman-Caldentey, K-M., & Puupponen-Pimiä, R.H. (2006). Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens. *Nutr Cancer, 54*, 18-32.

Norval, M., & Halliday, G.M. (2011). The consequences of UV‐induced immunosuppression for human health. *Photochem Photobiol, 87*, 965-977.

Ohtsuka, M., Ling, H., Doki, Y., Mori, M., & Calin, G.A. (2015). MicroRNA processing and human cancer. *J Clin Med, 4*, 1651-1667.

Oliviero, T., Lamers, S., Capuano, E., Dekker, M., Verkerk, R. (2018). Bioavailability of isothiocyanates from broccoli sprouts in protein, lipid, and fiber gels. *Mol Nutr Food Res, e1700837*

Panayiotidis, M.I. (2014). Cancer epigenetics as biomarkers of clinical significance. *Cancer Lett, 342(2), 168-69.*

Panning, B., & Jaenisch, R. (1998). RNA and the epigenetic regulation of X chromosome inactivation. *Cell, 93*, 305-308.

Pappa, G., Lichtenberg, M., Iori, R., Barillari, J., Bartsch, H., & Gerhäuser, C. (2006). Comparison of growth inhibition profiles and mechanisms of apoptosis induction in human colon cancer cell lines by isothiocyanates and indoles from Brassicaceae. *Mutat Res, 599*, 76-87.

Park, H-W., Choi, K-D., & Shin, I-S. (2013). Antimicrobial activity of isothiocyanates (ITCs) extracted from horseradish (Armoracia rusticana) root against oral microorganisms. *Biocontrol Sci, 18*, 163-168.

Parnaud, G., Li, P., Cassar, G., Rouimi, P., Tulliez, J., Combaret, L., & Gamet-Payrastre, L. (2004). Mechanism of sulforaphane-induced cell cycle arrest and apoptosis in human colon cancer cells. *Nutr Cancer, 48*, 198-206.

Peng, J., Liu, H., & Liu, C. (2017). miR-155 promotes uveal melanoma cell proliferation and invasion by regulating NDFIP1 expression. *Technol Cancer Res Treat, 16*, 1160-1167.

Penta, D., Somashekar, B.S., & Meeran, S.M. (2018). Epigenetics of skin cancer: Interventions by selected bioactive phytochemicals. *Photodermatol Photoimmunol Photomed, 34*, 42-49.

Pfeifer, G.P., & Besaratinia, A. (2012). UV wavelength-dependent DNA damage and human non-melanoma and melanoma skin cancer. *Photochem Photobiol Sci, 11*, 90-97.

Pledgie-Tracy, A., Sobolewski, M.D., & Davidson, N.E. (2007). Sulforaphane induces cell type–specific apoptosis in human breast cancer cell lines. *Mol Cancer Ther, 6*, 1013-1021.

Polat, U. (2010). The effects on metabolism of glucosinolates and theirs hydrolysis products. *J Biol Environ Sci, 4,* 39-42.

Probst, A.V., Dunleavy, E., & Almouzni, G. (2009). Epigenetic inheritance during the cell cycle. *Nat Rev Mol Cell Biol, 10*, 192-206.

Qu, X., Pröll, M., Neuhoff, C., Zhang, R., Cinar, M. U., Hossain, M. M., Tesfaye, D., Grobe-Brinkhaus, C., Salilew-Wondim, D., & Tholen, E. (2015). Sulforaphane epigenetically regulates innate immune responses of porcine monocyte-derived dendritic cells induced with lipopolysaccharide. *PLoS One, 10*, e0121574.

Rajendran, P., Kidane, A.I., Yu, T-W., Dashwood, W-M., Bisson, W.H., Löhr, C.V., Ho, E., Williams, D.E., & Dashwood, R.H. (2013). HDAC turnover, CtIP acetylation and dysregulated DNA damage signaling in colon cancer cells treated with sulforaphane and related dietary isothiocyanates. *Epigenetics, 8*, 612-623.

Reik, W., & Walter, J. (2001). Genomic imprinting: parental influence on the genome. *Nat Rev Genet, 2*, 21-32.

Rice, J.C., & Allis, C.D. (2001). Histone methylation versus histone acetylation: new insights into epigenetic regulation. *Curr Opin Cell Biol, 13*, 263-273.

Rudolf, E., Andělová, H., & Červinka, M. (2009). Activation of several concurrent proapoptic pathways by sulforaphane in human colon cancer cells SW620. *Food Chem Toxicol, 47*, 2366-2373.

Rudolf, K., Cervinka, M., & Rudolf, E. (2014). Sulforaphane-induced apoptosis involves p53 and p38 in melanoma cells. *Apoptosis, 19*, 734-747.

Rungapamestry, V., Duncan, A.J., Fuller, Z., Ratcliffe, B. (2007). Effect of meal consumption and cooking duration on the fate of sulforaphane following consumption of broccoli by healthy human subjects. *Br J Nutr, 97(4),* 644-652.

Rünger, T.M. (2008). C→T Transition mutations are not solely UVB-signature mutations, because they are also generated by UVA. *J Inv Dermatol, 128*, 2138-2140.

Rupasinghe, H.P., Sekhon-Loodu, S., Mantso, T., & Panayiotidis, M.I. (2016). Phytochemicals in regulating fatty acid beta-oxidation: Potential underlying mechanisms and their involvement in obesity and weight loss. *Pharmacol Ther, 165*, 153-163.

Sage, E., Girard, P-M., & Francesconi, S. (2012). Unravelling UVA-induced mutagenesis. *Photochem Photobiol Sci, 11*, 74-80.

Saha, K., Fisher, M.L., Adhikary, G., Grun, D., & Eckert, R.L. (2017). Sulforaphane suppresses PRMT5/MEP50 function in epidermal squamous cell carcinoma leading to reduced tumor formation. *Carcinogenesis, 38*, 827-836.

Saha, K., Hornyak, T.J., & Eckert, R.L. (2013). Epigenetic cancer prevention mechanisms in skin cancer. *AAPS J, 15*, 1064-1071.

Sahu, R.P. (2015). Expression of the platelet-activating factor receptor enhances benzyl isothiocyanate-induced apoptosis in murine and human melanoma cells. *Mol Med Rep, 12*, 394-400.

Sahu, R.P., & Srivastava, S.K. (2009). The role of STAT-3 in the induction of apoptosis in pancreatic cancer cells by benzyl isothiocyanate. *J Natl Cancer Inst, 101*, 176-193.

Sand, M., Gambichler, T., Skrygan, M., Sand, D., Scola, N., Altmeyer, P., & Bechara, F.G. (2010). Expression levels of the microRNA processing enzymes Drosha and dicer in epithelial skin cancer. *Cancer Invest, 28*, 649-653.

Sand, M., Sand, D., Altmeyer, P., & Bechara, F.G. (2012). MicroRNA in non-melanoma skin cancer. *Cancer Biomark, 11*, 253-257.

Sand, M., Skrygan, M., Sand, D., Georgas, D., Hahn, S., Gambichler, T., Altmeyer, P., & Bechara, F. (2012). Expression of microRNAs in basal cell carcinoma. *Br J Dermatol, 167*, 847-855.

Sandoval, J., & Esteller, M. (2012). Cancer epigenomics: beyond genomics. *Curr Opin Genet Dev, 22*, 50-55.

Santos, F., Hendrich, B., Reik, W., & Dean, W. (2002). Dynamic reprogramming of DNA methylation in the early mouse embryo. *Dev Biol, 241*, 172-182.

Sarkar, D., Leung, E.Y., Baguley, B.C., Finlay, G.J., & Askarian-Amiri, M.E. (2015). Epigenetic regulation in human melanoma: past and future. *Epigenetics, 10*, 103-121.

Sarkar, R., Mukherjee, S., Biswas, J., & Roy, M. (2012). Sulphoraphane, a naturally occurring isothiocyanate induces apoptosis in breast cancer cells by targeting heat shock proteins. *Biochem Biophys Res Comm, 427*, 80-85.

Saw, C.L., Huang, M.T., Liu, Y., Khor, T.O., Conney, A.H., & Kong, A.N. (2011). Impact of Nrf2 on UVB‐induced skin inflammation/photoprotection and photoprotective effect of sulforaphane. *Mol Carcinog, 50*, 479-486.

Sawan, C., & Herceg, Z. (2010). 3 - Histone Modifications and Cancer. In Z. Herceg & T. Ushijima (Eds.), *Advances in Genetics* (Vol. 70, pp. 57-85): Academic Press.

Schinke, C., Mo, Y., Yu, Y., Amiri, K., Sosman, J., Greally, J., & Verma, A. (2010). Aberrant DNA methylation in malignant melanoma. *Melanoma Res, 20*, 253.

Schwarz, A., Noordegraaf, M., Maeda, A., Torii, K., Clausen, B.E., & Schwarz, T. (2010). Langerhans cells are required for UVR-induced immunosuppression. *J Invest Dermatol, 130*, 1419-1427.

Seebode, C., Lehmann, J., & Emmert, S. (2016). Photocarcinogenesis and skin cancer prevention strategies. *Anticancer Res, 36*, 1371-1378.

Segura, M.F., Hanniford, D., Menendez, S., Reavie, L., Zou, X., Alvarez-Diaz, S., Zakrzewski, J., Blochin, E., Rose, A., Bogunovic, D., Polsky, D., Wei, J., Lee, P., Belitskaya-Levy, I., Bhardwaj, N., Osman, I., & Hernando, E. (2009). Aberrant miR-182 expression promotes melanoma metastasis by repressing FOXO3 and microphthalmia-associated transcription factor. *Proc Natl Acad Sci USA, 106*, 1814-1819.

Sehrawat, A., Croix, C.S., Baty, C.J., Watkins, S., Tailor, D., Singh, R.P., & Singh, S.V. (2016). Inhibition of mitochondrial fusion is an early and critical event in breast cancer cell apoptosis by dietary chemopreventative benzyl isothiocyanate. *Mitochondrion, 30*, 67-77.

Sehrawat, A., Kim, S.-H., Vogt, A., & Singh, S.V. (2012). Suppression of FOXQ1 in benzyl isothiocyanate-mediated inhibition of epithelial–mesenchymal transition in human breast cancer cells. *Carcinogenesis, 34*, 864-873.

Serrano, L., Martínez-Redondo, P., Marazuela-Duque, A., Vazquez, B. N., Dooley, S.J., Voigt, P., Beck, D.B., Kane-Goldsmith, N., Tong, Q., & Rabanal, R.M. (2013). The tumor suppressor Sirt2 regulates cell cycle progression and genome stability by modulating the mitotic deposition of H4K20 methylation. *Genes Dev, 27*, 639-653.

Shan, Y., Lin, N., Yang, X., Tan, J., Zhao, R., Dong, S., & Wang, S. (2012). Sulphoraphane inhibited the expressions of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 through MyD88-dependent toll-like receptor-4 pathway in cultured endothelial cells. *Nutr Metab Cardiovasc Dis, 22*, 215-222.

Shan, Y., Zhang, L., Bao, Y., Li, B., He, C., Gao, M., Feng, X., Xu, W., Zhang, X., & Wang, S. (2013). Epithelial-mesenchymal transition, a novel target of sulforaphane via COX-2/MMP2, 9/Snail, ZEB1 and miR-200c/ZEB1 pathways in human bladder cancer cells. *J Nutr Biochem, 24*, 1062-1069.

Sharma, S., Kelly, T.K., & Jones, P.A. (2010). Epigenetics in cancer. *Carcinogenesis, 31*, 27-36.

Shtivelman, E., Davies, M. Q., Hwu, P., Yang, J., Lotem, M., Oren, M., Flaherty, K.T., & Fisher, D.E. (2014). Pathways and therapeutic targets in melanoma. *Oncotarget, 5*, 1701-1752.

Shukla, G.C., Singh, J., & Barik, S. (2011). MicroRNAs: Processing, maturation, target recognition and regulatory functions. *Mol Cell Pharmacol, 3*, 83-92.

Sigalotti, L., Covre, A., Fratta, E., Parisi, G., Colizzi, F., Rizzo, A., Danielli, R., Nicolay, H. J., Coral, S., & Maio, M. (2010). Epigenetics of human cutaneous melanoma: setting the stage for new therapeutic strategies. *J Trans Med, 8*, 56.

Slaby, O., Sachlova, M., Brezkova, V., Hezova, R., Kovarikova, A., Bischofová, S., Sevcikova, S., Bienertova-Vasku, J., Vasku, A., & Svoboda, M. (2013). Identification of microRNAs regulated by isothiocyanates and association of polymorphisms inside their target sites with risk of sporadic colorectal cancer. *Nutr Cancer, 65*, 247-254.

Spencer, E.S., Dale, E.J., Gommans, A.L., Rutledge, M.T., Vo, C.T., Nakatani, Y., Gamble, A.B., Smith, R.A.J., Wilbanks, S.M., Hampton, M.B., & Tyndall, J.D.A. (2015). Multiple binding modes of isothiocyanates that inhibit macrophage migration inhibitory factor. *Eur J Med Chem, 93*, 501-510.

Spugnardi, M., Tommasi, S., Dammann, R., Pfeifer, G.P., & Hoon, D.S. (2003). Epigenetic inactivation of RAS association domain family protein 1 (RASSF1A) in malignant cutaneous melanoma. *Cancer Res, 63*, 1639-1643.

Spyridopoulou, K., Tripiti-Kourpeti, A., Lampri, E., Fitsiou, E., Vasileiadis, S., Vamvakias, M., Bardouki, H., Goussia, A., Malamou-Mitsi, V., Panayiotidis, M.I., Galanis, A., Pappa, A., & Chlichlia, K. (2017). Dietary mastic oil from Pistacia lentiscus var. chia suppresses tumour growth in experimental colon cancer models. *Sci Rep, 7, 3782.*

Srivastava, S.K., Xiao, D., Lew, K.L., Hershberger, P., Kokkinakis, D.M., Johnson, C.S., Trump, D.L., & Singh, S.V. (2003). Allyl isothiocyanate, a constituent of cruciferous vegetables, inhibits growth of PC-3 human prostate cancer xenografts in vivo. *Carcinogenesis, 24*, 1665-1670.

Stan, S.D., Singh, S.V., Whitcomb, D.C., & Brand, R.E. (2014). Phenethyl isothiocyanate inhibits proliferation and induces apoptosis in pancreatic cancer cells in vitro and in a MIAPaca2 xenograft animal model. *Nutr Cancer, 66*, 747-755.

Straume, O., Smeds, J., Kumar, R., Hemminki, K., & Akslen, L.A. (2002). Significant impact of promoter hypermethylation and the 540 C>T polymorphism of CDKN2A in cutaneous melanoma of the vertical growth phase. *Am J Pathol, 161*, 229-237.

Su, Z-Y., Zhang, C., Lee, J.H., Shu, L., Wu, T-Y., Khor, T.O., Conney, A.H., Lu, Y-P., & Kong, A-N.T. (2014). Requirement and epigenetics reprogramming of Nrf2 in suppression of tumor promoter TPA-induced mouse skin cell transformation by sulforaphane. *Cancer Prev Res (Phila), 7*, 319-329.

Supic, G., Jagodic, M., & Magic, Z. (2013). Epigenetics: a new link between nutrition and cancer. *Nutr Cancer, 65*, 781-792.

Surh, Y-J., & Na, H-K. (2008). NF-κB and Nrf2 as prime molecular targets for chemoprevention and cytoprotection with anti-inflammatory and antioxidant phytochemicals. *Genes Nutr, 2*, 313-317.

Talalay, P., & Fahey, J.W. (2001). Phytochemicals from cruciferous plants protect against cancer by modulating carcinogen metabolism. *J Nutr, 131*, 3027S-3033S.

Talalay, P., Fahey, J.W., Healy, Z.R., Wehage, S.L., Benedict, A.L., Min, C., & Dinkova-Kostova, A.T. (2007). Sulforaphane mobilizes cellular defenses that protect skin against damage by UV radiation. *Proc Natl Acad Sci USA, 104*, 17500-17505.

Talalay, P., & Zhang, Y. (1996). Chemoprotection against cancer by isothiocyanates and glucosinolates. In: Portland Press Limited.

Tan, X-L., Shi, M., Tang, H., Han, W., & Spivack, S.D. (2010). Candidate dietary phytochemicals modulate expression of phase II enzymes GSTP1 and NQO1 in human lung cells. *J Nutr, 140*, 1404-1410.

Tanemura, A., Terando, A.M., Sim, M.S., van Hoesel, A.Q., de Maat, M.F., Morton, D.L., & Hoon, D.S. (2009). CpG island methylator phenotype predicts progression of malignant melanoma. *Clin Cancer Res, 15*, 1801-1807.

Telang, U., & Morris, M.E. (2010). Effect of orally administered phenethyl isothiocyanate on hepatic gene expression in rats. *Molecular Nutrition & Food Research, 54*, 1802-1806.

Tellez, C.S., Shen, L., Estécio, M.R., Jelinek, J., Gershenwald, J.E., & Issa, J-P.J. (2009). CpG island methylation profiling in human melanoma cell lines. *Melanoma Res, 19*, 146-155.

Thejass, P., & Kuttan, G. (2007). Allyl isothiocyanate (AITC) and phenyl isothiocyanate (PITC) inhibit tumour-specific angiogenesis by downregulating nitric oxide (NO) and tumour necrosis factor-α (TNF-α) production. *Nitric Oxide, 16*, 247-257.

Thejass, P., & Kuttan, G. (2007a). Inhibition of endothelial cell differentiation and proinflammatory cytokine production during angiogenesis by allyl isothiocyanate and phenyl isothiocyanate. *Integr Cancer Ther, 6*, 389-399.

Thejass, P., & Kuttan, G. (2007b). Modulation of cell-mediated immune response in B16F-10 melanoma-induced metastatic tumor-bearing C57BL/6 mice by sulforaphane. *Immunopharmacol Immunotoxicol, 29*, 173-186.

Tierens, K.F-J., Thomma, B.P., Brouwer, M., Schmidt, J., Kistner, K., Porzel, A., Mauch-Mani, B., Cammue, B.P., & Broekaert, W.F. (2001). Study of the role of antimicrobial glucosinolate-derived isothiocyanates in resistance of Arabidopsis to microbial pathogens. *Plant Physiol, 125*, 1688-1699.

Ting, W., Schultz, K., Cac, N.N., Peterson, M., & Walling, H.W. (2007). Tanning bed exposure increases the risk of malignant melanoma. *Int J Dermatol, 46*, 1253-1257.

Tsai, H-C., & Baylin, S.B. (2011). Cancer epigenetics: linking basic biology to clinical medicine. *Cell Res, 21*, 502-517.

Tsai, S-C., Huang, W-W., Huang, W-C., Lu, C-C., Chiang, J-H., Peng, S-F., Chung, J-G., Lin, Y-H., Hsu, Y-M., & Amagaya, S. (2012). ERK-modulated intrinsic signaling and G2/M phase arrest contribute to the induction of apoptotic death by allyl isothiocyanate in MDA-MB-468 human breast adenocarcinoma cells. *Int J Oncol, 41*, 2065-2072.

Valencia-Sanchez, M.A., Liu, J., Hannon, G.J., & Parker, R. (2006). Control of translation and mRNA degradation by miRNAs and siRNAs. *Genes Dev, 20*, 515-524.

van den Hurk, K., Niessen, H.E.C., Veeck, J., van den Oord, J.J., van Steensel, M.A.M., zur Hausen, A., van Engeland, M., & Winnepenninckx, V.J.L. (2012). Genetics and epigenetics of cutaneous malignant melanoma: A concert out of tune. *Biochim Biophys Acta, 1826*, 89-102.

Venza, I., Visalli, M., Tripodo, B., De Grazia, G., Loddo, S., Teti, D., & Venza, M. (2010). FOXE1 is a target for aberrant methylation in cutaneous squamous cell carcinoma. *Br J Dermatol, 162*, 1093-1097.

Verkerk, R., Dekker, M. (2004). Glucosinolates and myrosinase activity in red cabbage (Brassica oleracea L. var. Capitata f. rubra DC.) after various microwave treatments. *J Agric Food Chem, 52(24),* 7318-7323.

Volinia, S., Calin, G.A., Liu, C-G., Ambs, S., Cimmino, A., Petrocca, F., Visone, R., Iorio, M., Roldo, C., & Ferracin, M. (2006). A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc Natl Acad Sci USA, 103*, 2257-2261.

von Weymarn, L.B., Chun, J.A., & Hollenberg, P.F. (2006). Effects of benzyl and phenethyl isothiocyanate on P450s 2A6 and 2A13: potential for chemoprevention in smokers. *Carcinogenesis, 27*, 782-790.

Wagner, A.E., Boesch‐Saadatmandi, C., Dose, J., Schultheiss, G., & Rimbach, G. (2012). Anti‐inflammatory potential of allyl‐isothiocyanate–role of Nrf2, NF‐κB and microRNA‐155. *J Cell Mol Med, 16*, 836-843.

Wagner, A.E., Terschluesen, A.M., & Rimbach, G. (2013). Health promoting effects of brassica-derived phytochemicals: from chemopreventive and anti-inflammatory activities to epigenetic regulation. *Oxid Med Cell Longev, 9,* 964539.

Walesch, S.K., Richter, A.M., Helmbold, P., & Dammann, R.H. (2015). Claudin11 promoter hypermethylation is frequent in malignant melanoma of the skin, but uncommon in nevus cell nevi. *Cancers, 7*, 1233-1243.

Wang, L., Tian, Z., Yang, Q., Li, H., Guan, H., Shi, B., Hou, P., & Ji, M. (2015). Sulforaphane inhibits thyroid cancer cell growth and invasiveness through the reactive oxygen species-dependent pathway. *Oncotarget, 6*, 25917-25931.

Wang, L.G., Liu, X. M., Fang, Y., Dai, W., Chiao, F.B., Puccio, G.M., Feng, J., Liu, D., & Chiao, J.W. (2008). De-repression of the p21 promoter in prostate cancer cells by an isothiocyanate via inhibition of HDACs and c-Myc. *Int J Oncol, 33*, 375-380.

Wang, S-H., Zhou, J-D., He, Q-Y., Yin, Z-Q., Cao, K., & Luo, C-Q. (2014). miR-199a inhibits the ability of proliferation and migration by regulating CD44-Ezrin signaling in cutaneous squamous cell carcinoma cells. *Int J Clin Exper Pathol, 7*, 7131.

Wang, S., Cao, K.E., He, Q., Yin, Z., & Zhou, J. (2016). miR-199a-5p induces cell invasion by suppressing E-cadherin expression in cutaneous squamous cell carcinoma. *Oncol Lett, 12*, 97-101.

Wang, W., Wang, S., Howie, A.F., Beckett, G.J., Mithen, R., & Bao, Y. (2005). Sulforaphane, erucin, and iberin up-regulate thioredoxin reductase 1 expression in human MCF-7 cells. *J Agric Food Chem, 53*, 1417-1421.

Wang, Z., Zang, C., Cui, K., Schones, D.E., Barski, A., Peng, W., & Zhao, K. (2009). Genome-wide mapping of HATs and HDACs reveals distinct functions in active and inactive genes. *Cell, 138*, 1019-1031.

Welsh, M.M., Karagas, M.R., Kuriger, J.K., Houseman, A., Spencer, S.K., Perry, A.E., & Nelson, H.H. (2011). Genetic determinants of UV-susceptibility in non-melanoma skin cancer. *PLoS One, 6*, e20019.

Weng, C-J., & Yen, G-C. (2012). Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives. *Cancer Treat Rev, 38*, 76-87.

Wikonkal, N.M., & Brash, D.E. (1999). Ultraviolet radiation induced signature mutations in photocarcinogenesis. *J Investig Dermatol Symp Proc, 4*, 6-10.

Wong, C.P., Hsu, A., Buchanan, A., Palomera-Sanchez, Z., Beaver, L.M., Houseman, E.A., Williams, D.E., Dashwood, R.H., & Ho, E. (2014). Effects of sulforaphane and 3,3'-diindolylmethane on genome-wide promoter methylation in normal prostate epithelial cells and prostate cancer cells. *PLoS One, 9*, e86787.

Wu, C. L., Huang, A. C., Yang, J. S., Liao, C. L., Lu, H. F., Chou, S. T., Ma, C. Y., Hsia, T. C., Ko, Y. C., & Chung, J. G. (2011). Benzyl isothiocyanate (BITC) and phenethyl isothiocyanate (PEITC)‐mediated generation of reactive oxygen species causes cell cycle arrest and induces apoptosis via activation of caspase‐3, mitochondria dysfunction and nitric oxide (NO) in human osteogenic sarcoma U‐2 OS cells. *J Orthop Res, 29*, 1199-1209.

Wu, J., Zhang, J-R., & Qin, J. (2014). Clinical significance of methylation of E-cadherin and p14ARF gene promoters in skin squamous cell carcinoma tissues. *Int J Clin Exper Med, 7*, 1808.

Xiao, D., Powolny, A.A., & Singh, S.V. (2008). Benzyl isothiocyanate targets mitochondrial respiratory chain to trigger reactive oxygen species-dependent apoptosis in human breast cancer cells. *J Biol Chem, 283*, 30151-30163.

Xiao, D., Vogel, V., & Singh, S.V. (2006). Benzyl isothiocyanate–induced apoptosis in human breast cancer cells is initiated by reactive oxygen species and regulated by Bax and Bak. *Mol Cancer Ther, 5*, 2931-2945.

Xie, B., Nagalingam, A., Kuppusamy, P., Muniraj, N., Langford, P., Gyorffy, B., Saxena, N. K., & Sharma, D. (2017). Benzyl Isothiocyanate potentiates p53 signaling and antitumor effects against breast cancer through activation of p53-LKB1 and p73-LKB1 axes. *Sci Rep, 7*, 40070.

Xie, J. (2008). Molecular biology of basal and squamous cell carcinomas. In *Sunlight, Vitamin D and Skin Cancer* (pp. 241-251): Springer.

Xu, C., Huang, M.T., Shen, G., Yuan, X., Lin, W., Khor, T.O., Conney, A.H., & Kong, A.N. (2006). Inhibition of 7,12-dimethylbenz(a)anthracene-induced skin tumorigenesis in C57BL/6 mice by sulforaphane is mediated by nuclear factor E2-related factor 2. *Cancer Res, 66*, 8293-8296.

Xu, C., Shen, G., Yuan, X., Kim, J-H., Gopalkrishnan, A., Keum, Y-S., Nair, S., & Kong, A-N.T. (2006a). ERK and JNK signaling pathways are involved in the regulation of activator protein 1 and cell death elicited by three isothiocyanates in human prostate cancer PC-3 cells. *Carcinogenesis, 27*, 437-445.

Xu, C., Yuan, X., Pan, Z., Shen, G., Kim, J-H., Yu, S., Khor, T.O., Li, W., Ma, J., & Kong, A-N.T. (2006b). Mechanism of action of isothiocyanates: the induction of ARE-regulated genes is associated with activation of ERK and JNK and the phosphorylation and nuclear translocation of Nrf2. *Mol Cancer Therap, 5*, 1918-1926.

Yamane, K., Jinnin, M., Etoh, T., Kobayashi, Y., Shimozono, N., Fukushima, S., Masuguchi, S., Maruo, K., Inoue, Y., & Ishihara, T. (2013). Down-regulation of miR-124/-214 in cutaneous squamous cell carcinoma mediates abnormal cell proliferation via the induction of ERK. *J Mol Med (Berl), 91*, 69-81.

Yan, C., & Boyd, D.D. (2006). Histone H3 acetylation and H3 K4 methylation define distinct chromatin regions permissive for transgene expression. *Mol Cell Biol, 26*, 6357-6371.

Yan, K., Gao, J., Yang, T., Ma, Q., Qiu, X., Fan, Q., & Ma, B. (2012). MicroRNA-34a inhibits the proliferation and metastasis of osteosarcoma cells both in vitro and in vivo. *PLoS One, 7*, e33778.

Yang, Q., Proll, M. J., Salilew-Wondim, D., Zhang, R., Tesfaye, D., Fan, H., Cinar, M.U., Grosse-Brinkhaus, C., Tholen, E., Islam, M. A., Holker, M., Schellander, K., Uddin, M.J., & Neuhoff, C. (2016). LPS-induced expression of CD14 in the TRIF pathway is epigenetically regulated by sulforaphane in porcine pulmonary alveolar macrophages. *Innate Immun, 22*, 682-695.

Yu, S.H., Bordeaux, J.S., & Baron, E.D. (2014). The immune system and skin cancer. *Adv Exp Med Biol, 810*, 182-191.

Yuanfeng, W., Gongnian, X., Jianwei, M., Shiwang, L., Jun, H., & Lehe, M. (2015). Dietary sulforaphane inhibits histone deacetylase activity in B16 melanoma cells. *J Funct Foods, 18*, 182-189.

Zhang, C., Shu, L., Kim, H., Khor, T.O., Wu, R., Li, W., & Kong, A.N. (2016). Phenethyl isothiocyanate (PEITC) suppresses prostate cancer cell invasion epigenetically through regulating microRNA-194. *Mol Nutr Food Res, 60*, 1427-1436.

Zhang, C., Su, Z. Y., Khor, T.O., Shu, L., & Kong, A.N. (2013). Sulforaphane enhances Nrf2 expression in prostate cancer TRAMP C1 cells through epigenetic regulation. *Biochem Pharmacol, 85*, 1398-1404.

Zhang, Y., & Talalay, P. (1994). Anticarcinogenic activities of organic isothiocyanates: chemistry and mechanisms. *Cancer Res, 54*, 1976s-1981s.

Zhang, Y., Talalay, P., Cho, C.G., & Posner, G.H. (1992). A major inducer of anticarcinogenic protective enzymes from broccoli: Isolation and elucidation of structure. *Proc Natl Acad Sci USA, 89*, 2399-2403.

Zhu, Y., Zhang, L., Zhang, G-D., Wang, H-O., Liu, M-Y., Jiang, Y., Qi, L-S., Li, Q., & Yang, P. (2014). Potential mechanisms of benzyl isothiocyanate suppression of invasion and angiogenesis by the U87MG human glioma cell line. *Asian Pac J Cancer Prev, 15*, 8225-8228.

Ziech, D., Anestopoulos, I., Hanafi, R., Voulgaridou, G-P., Franco, R., Georgakilas, A.G., Pappa, A., & Panayiotidis, M.I. (2012). Pleiotrophic effects of natural products in ROS-induced carcinogenesis: The role of plant-derived natural products in oral cancer chemoprevention. *Cancer Lett, 327*, 16-25.

Ziech, D., Franco, R., Pappa, A., Panayiotidis, M.I. (2011). Reactive oxygen species (ROS)-induced genetic and epigenetic alterations in human carcinogenesis. *Mutat Res, 711, 167-173.*

Ziech, D., Franco, R., Pappa, A., Malamou-Mitsi, V., Georgakila, S., Georgakilas, A.G., Panayiotidis, M.I. (2010). The role of epigenetics in environmental and occupational carcinogenesis. *Chem Biol Interact, 188*, 340-349.

Ziegler, A., Leffell, D.J., Kunala, S., Sharma, H.W., Gailani, M., Simon, J.A., Halperin, A.J., Baden, H.P., Shapiro, P.E., Bale, A.E., & et al. (1993). Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. *Proc Natl Acad Sci USA, 90*, 4216-4220.

Zingg, D., Debbache, J., Schaefer, S.M., Tuncer, E., Frommel, S.C., Cheng, P., Arenas-Ramirez, N., Haeusel, J., Zhang, Y., Bonalli, M., McCabe, M.T., Creasy, C.L., Levesque, M.P., Boyman, O., Santoro, R., Shakhova, O., Dummer, R., & Sommer, L. (2015). The epigenetic modifier EZH2 controls melanoma growth and metastasis through silencing of distinct tumour suppressors. *Nat Commun, 6*, 6051.

Zou, Y., Jung, L-S., Lee, S.H., Kim, S., Cho, Y., & Ahn, J. (2013). Enhanced antimicrobial activity of nisin in combination with allyl isothiocyanate against Listeria monocytogenes, Staphylococcus aureus, Salmonella Typhimurium and Shigella boydii. *Int J Food Sci Technol, 48*, 324-333.

**Table 1:** Hyper-methylated genes in Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC) and Melanoma

|  |  |  |
| --- | --- | --- |
| Gene | Function | Reference |
| Squamous Cell Carcinoma (SCC) | | |
| *ASC* | Inflammasome activator, involved in cell proliferation | Meier, et al., 2016 |
| *ASCL2* | Developmental transcription factor | Darr, et al., 2015 |
| *DAPK1* | Mediator of apoptosis | Murao, et al., 2006 |
| *E-cadherin* | Involved in cell-cell adhesion of epithelial tissues, invasion & metastasis | Fraga, et al., 2004  Murao, et al., 2006  Wu, et al., 2014 |
| *FOXE1* | Regulator of embryogenesis, cell growth & differentiation | Venza, et al., 2010 |
| *FRZB* | Modulator of Wnt signalling | Darr, et al., 2015 |
| *G0S2* | Cell cycle regulator | Nobeyama, et al., 2017 |
| *MGMT* | DNA repair | Fraga, et al., 2004  Murao, et al., 2006 |
| *MLT-1* | Snail/Gfi-1 repressor family member | Fraga, et al., 2004 |
| *P14ARF* | Cyclin-dependent kinase inhibitor | Brown, et al., 2004  Murao, et al., 2006  Wu, et al., 2014 |
| *p16INK4a* | Cell cycle inhibitor | Brown, et al., 2004  Murao, et al., 2006 |
| *SFRP1 / 2 / 4 / 5* | Regulators of Wnt signalling | Liang, et al., 2015 |
| *Snail* | Transcriptional repressor | Fraga, et al., 2004 |
| *TFAP2C* | Developmental transcription factor | Darr, et al., 2015 |
| Basal Cell Carcinoma (BCC) | | |
| *14-3-3σ* | Cell cycle inhibitor | Lodygin, et al., 2003 |
| *APC* | Regulator of the canonical WNT pathway | Brinkhuizen, et al., 2012 |
| *FHIT* | Pro-apoptotic protein | Goldberg, et al., 2006 |
| *RASSF1A* | Regulator of mTOR activity | Brinkhuizen, et al., 2012 |
| *SFRP5* | Regulator of the canonical WNT pathway | Brinkhuizen, et al., 2012 |
| *SHH* | Regulator of Sonic Hedgehog pathway | Brinkhuizen, et al., 2012 |
| Melanoma | | |
| *APC* | Regulator of the canonical WNT pathway | Liu, et al., 2008 |
| *ASC/TMS1* | Caspase-1 activating adaptor | Guan, et al., 2003  Liu, et al., 2008 |
| *CDKN1B* | Cell cycle regulator | Liu, et al., 2008 |
| *CDKN2A* | Cell cycle regulator | Liu, et al., 2008  Straume, et al., 2002 |
| *CLDN11* | An integral membrane  protein & component of tight-junction strands | Gao, et al., 2014  Walesch, et al., 2015 |
| *COL1A2* | Involved in the maintenance of cellular & tissue integrity | Koga, et al., 2009 Muthusamy, et al., 2006 |
| *CYP1B1* | Member of the cytochrome P450 family of monooxygenases | Muthusamy, et al., 2006 |
| *DAPK1* | Mediator of apoptosis | Hoon, et al., 2004  Liu, et al., 2008 |
| *DDIT4L* | Inhibitor of cell growth | Furuta, et al., 2006  Koga, et al., 2009 |
| *DNAJC15* | Involved in metabolic activation of chemotherapeutic drugs | Muthusamy, et al., 2006 |
| *E-cadherin (ECAD, CDH1)* | Involved in cell-cell adhesion of epithelial tissues, invasion & metastasis | Liu, et al., 2008  Tellez, et al., 2009 |
| *ER-a* | Transcriptional activator | Mori, et al., 2006  Tellez, et al., 2009 |
| *GATA4* | Transcription factor | Tanemura, et al., 2009 |
| *HOXB13* | Regulator of embryonic differentiation | Liu, et al., 2008 Muthusamy, et al., 2006 |
| *HOXD13*  *HOXA9*  *HOXD12* | Regulator of embryonic differentiation | Furuta, et al., 2006 |
| *HSPB6* | Functions as molecular chaperone | Koga, et al., 2009 |
| *IRF6* | Associated with cells sensitivity to IFN, tumour suppression & cell differentiation | Nobeyama & Nakagawa, 2017a |
| *IRF8* | Regulator of the expression of interferon genes | Liu, et al., 2008 |
| *LOX* | Involved in cell migration, signal transduction & gene regulation | Liu, et al., 2008 |
| *LXN* | Inhibitor of mammalian carboxypeptidases | Muthusamy, et al., 2006 |
| *MGMT* | Involved in DNA repair | Hoon, et al., 2004  Liu, et al., 2008  Kohonen-Corish, et al., 2006  Tellez, et al., 2009 |
| *MINT17*  *MINT31* | Create a distinct CIMP pattern  inactivation of tumor suppressor & tumor-related genes (TRG) | Tanemura, et al., 2009 |
| *MT1A* | Associated with the metabolism of trace elements | Nobeyama & Nakagawa, 2017b |
| *MT1G* | Involved in several cellular processes | Koga, et al., 2009 |
| *NPM2* | Involved in several cellular processes | Koga, et al., 2009 |
| *PRDX2* | Regulator of PDGF mitogenic signalling pathway | Furuta, et al., 2006 |
| *PTEN* | Regulator of apoptosis | Mirmohammadsadegh, et al., 2006 |
| *QPCT* | Involved in glutaminyl peptides metabolism | Muthusamy, et al., 2006 |
| *Rab33A* | Involved in silencing of X-linked genes | Cheng, et al., 2006 |
| *RAR-beta 2* | Member of the nuclear  retinoid receptor of genes | Hoon, et al., 2004  Liu, et al., 2008  Tellez, et al., 2009 |
| *RASSF1A* | Regulator of apoptotic & cell cycle checkpoint pathways | Hoon, et al., 2004  Liu, et al., 2008  Spugnardi, et al., 2003 Tanemura, et al., 2009 Tellez, et al., 2009 |
| *RIL* | Involved in cell growth & apoptosis | Tellez, et al., 2009 |
| *SOCS1* | Suppressor of cytokine signalling | Tanemura, et al., 2009 |
| *SOCS1 / 2* | Suppressor of cytokine signalling | Liu, et al., 2008 |
| *SYK* | Involved in coupling activated immune receptors to downstream signalling effectors | Liu, et al., 2008 Muthusamy, et al., 2006 |
| *TFAP2A* | Involved in growth & differentiation of embryonic tissues | Hallberg, et al., 2014 |
| *TFPI2* | Involved in growth, invasion, angiogenesis & metastasis | Liu, et al., 2008  Tanemura, et al., 2009 |
| *TIMP3* | MMP inhibitor | Liu, et al., 2008 |
| *TNFSF10 C/D/A* | Inducer of apoptosis | Liu, et al., 2008 |
| *TPM1* | Involved in assembly &  stabilization of actin filaments & control of cell motility | Liu, et al., 2008 |
| *WIF1* | Antagonist of WNT pathway | Tanemura, et al., 2009 |

**Table 2:** Up-regulated expression of mi-RNAs in skin cancer

|  |  |  |  |
| --- | --- | --- | --- |
| mi-RNA | Cancer type | Function | Reference |
| Let-7 | BCC | Involved in regulating cell  proliferation | Heffelfinger, et al., 2012 |
| miR-17 | BCC | Involved in apoptotic inhibition & increased cell growth | Sand, et al., 2012 |
| miR-18a | BCC | Involved in apoptotic inhibition & increased cell growth | Sand, et al., 2012 |
| miR-18b | BCC | Involved in apoptotic inhibition & increased cell growth | Sand, et al., 2012 |
| miR-19b-1 | BCC | Involved in apoptotic inhibition & enhanced cell growth | Sand, et al., 2012 |
| miR-21 | BCC  SCC  Melanoma | Involved in *PTEN* & *PCDC4* repression | Heffelfinger, et al., 2012 Darido, et al., 2011 Dziunycz, et al., 2010 Grignol, et al., 2011 |
| miR-93 | BCC | Involved in apoptotic regulation through targeting E2F1 | Sand, et al., 2012 |
| miR-106b | BCC | Involved in apoptotic regulation through targeting E2F1 | Sand, et al., 2012 |
| miR-130a | BCC | BCL-2 regulator | Sand, et al., 2012 |
| miR-137 | Melanoma | Regulator of cell growth, maturation, apoptosis & pigmentation | Bemis, et al., 2008 Haflidadottir, et al., 2010 |
| miR-148 | BCC Melanoma | Regulator of cell growth, maturation, apoptosis & pigmentation | Heffelfinger, et al., 2012 Haflidadottir, et al., 2010 |
| miR-155 | Melanoma | Increases cell proliferation & invasion | Grignol, et al., 2011  Peng, et al., 2017 |
| miR-181c | BCC | Regulator of *NOTCH4* and *KRAS* | Sand, et al., 2012 |
| miR-182 | BCC Melanoma | Regulator of *FOXO1*, *MITF* & *FOXO3* | Heffelfinger, et al., 2012 Sand, et al., 2012  Segura, et al., 2009 |
| miR-183 | BCC | Inhibitor of invasion & metastasis | Heffelfinger, et al., 2012 |
| miR-184 | SCC | Inducer of cell transformation & carcinogenesis | Dziunycz, et al., 2010 |
| miR-221 | Melanoma | Mediator of cell cycle deregulation | Kanemaru, et al., 2011 |

**Table 3:** Down-regulated expression of mi-RNAs in skin cancer

|  |  |  |  |
| --- | --- | --- | --- |
| mi-RNA | Cancer type | Function | Reference |
| miR-29c | BCC | Involved in methylation of tumour suppressor genes | Sand, et al., 2012 |
| miR-34a | SCC | Interacts with SIRT6 to regulate TP53 | Lefort, et al., 2013  Lodygin, et al.,2008 |
| miR-124 | SCC | Mediator of abnormal cell proliferation | Yamane, et al., 2013 |
| miR-199a | SCC | Inhibitor of proliferation & migration | Wang, et al.,2014 |
| miR-199a-5p | SCC | Inhibitor of cell invasion & migration | Wang, et al., 2016 Kim, et al., 2015 |
| miR-200a | Melanoma | Regulator of proliferation & metastasis | Bustos, et al., 2017 |
| miR-203 | SCC | p63 antagonist-involved in cell senescence | Dziunycz, et al., 2010 |
| miR-211 | Melanoma | Regulator of MITF & KCNMA1 activity | Mazar, et al., 2010 |
| miR-214 | SCC | Mediator of abnormal cell proliferation | Yamane, et al., 2013 |
| miR-375 | Melanoma | Regulator of cell proliferation, invasion & motility | Mazar, et al., 2011 |

**Figure Legends**

**Figure 1. Hydrolysis of glucosinolates by myrosinase.**

Activation of the myrosinase-glucosinolate system, also known as mustard oil bomb, results in the formation of an unstable aglycone intermediate metabolite called thiohydroximate-O-sulfate. A subsequent non-enzymatic reaction and a simultaneous rearrangement of the core structure of GLs produce diverse chemically and biologically distinct compounds, including thiocyanates, isothiocyanates, nitriles and indoles. Usually, a Losen rearrangement occurs that promotes the isothiocyanate formation.

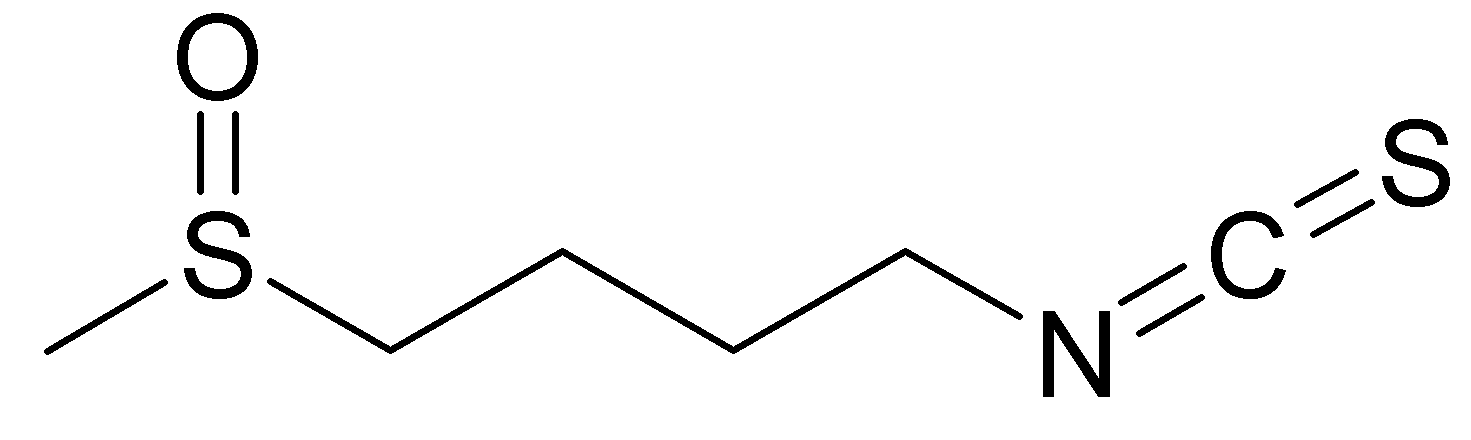
**Figure 2. Representative structures of major isothiocyanate (ITC) compounds.**

**Figure 3. Schematic presentation of the proposed cellular pathways targeted by ITCs**.  
ITCs chemo-preventive action is mainly attributed to a plurality of anti-cancer properties including i) inhibition of cell growth by causing cell cycle arrest and apoptosis, ii) inhibition of phase I and induction of phase II detoxification enzymes, iii) inhibition of metastasis and angiogenesis and iv) regulation of the epigenetic machinery. The effect of ITCs in cell proliferation is mediated through modulation of diverse regulatory pathways, including various signalling transduction pathways (e.g. PI3K/AKT, MAPKKs, etc.), increased generation of reactive oxygen species (ROS) and mitochondrial dysfunction.

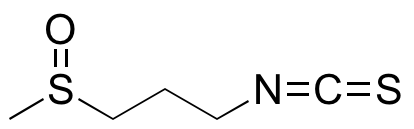
**Figure 1**



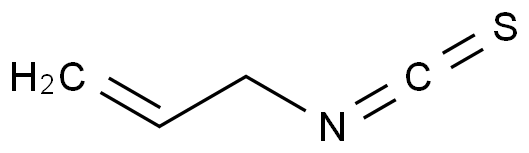
**Figure 2**



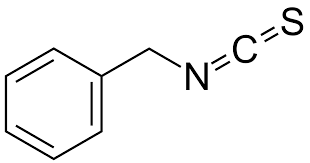
Sulforaphane (SFN)



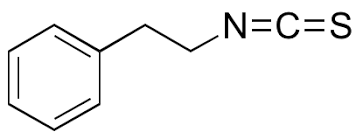
Iberin (IBN)



Allyl-ITC (AITC)



Benzyl-ITC (BITC)



Phenethyl-ITC (PEITC)

**Figure 3**

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