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Chapter 10

Paulownia tomentosa (Princess Tree) Extract Reduces DNA Damage and Induces DNA Repair Processes in Skin Cells

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Skin DNA damage and repair

Skin is the largest and one of the most complex organs in human body, accounting for almost 15% of total body weight. It serves as an important environmental interface and thus acts as a first line of defense against various environmental insults [1]. Skin is organized into three main layers, epidermis, dermis and subcutaneous layer. The epidermis, an outermost avascular layer, is formed by keratinocytes at the epidermal basal layer that differentiate into corneocytes at the outer layer of the epidermis. The dermis lies below the epidermis separated by a basement membrane and is composed mainly of fibroblasts. The primary function of skin is to constitute an efficient barrier to protect the organism both from water evaporation [2] and from damage, as such skin is exposed to many external and internal aggressors which can induce DNA damage, including ultraviolet radiations (UVR). The ultraviolet radiation component of sunlight is the most important environmental inducer of damage in the skin. Ultraviolet radiations can induce damage on DNA bases by direct absorption of photons resulting in the direct effect of cyclobutane pyrimidine dimers (CPD) or the 6-4 photoproducts formation both created by dimerization of contiguous pyrimidines on the DNA [2,3]. Ultraviolet radiation can also induces significant damage to skin cells through the generation of Reactive Oxygen Species (ROS) which produce secondary damage to DNA nucleobases and the sugar phosphate backbone [2]. Different forms of DNA damage can result from the type of ROS generated (singlet oxygen and hydroxyl radicals through the formation of superoxide radicals), different modifications are generated to DNA such as bulky (8-oxo- guanosine, as

guanine is the most easily oxidized base, Thymidine and Cytosine glycol) and non-bulky (cyclo purine and etheno adducts) base modifications, spontaneous hydrolysis of a normal or damaged nucleobase leading to an abasic site, (see review [4). Finally ROS may also generate other forms of DNA damage such as single strand breaks (SSB) or double strand breaks (DSB) when the free radical attack is located on the poly- deoxy- ribose chain [2]. In addition to ultraviolet radiation, pollution and cigarette smoke can also act as external aggressors and favor DNA damage onset by depleting intracellular anti-oxidant molecules such as glutathione and thus shifting the oxidative balance to favor oxidation by ROS. In addition to external aggression, cells are also subjected to internal aggression from ROS generated by oxidative metabolism or respiration as well as to the attack of genotoxic or photo-sensitizers coming from the diet [2].

The integrity of DNA is one of the key factors affecting the viability of healthy organisms, living cells have developed strategies not only to prevent DNA damage but also to minimize the impact of DNA damage by efficiently repairing any damaged DNA. In human cells, DNA is repaired by different mechanisms: Base Excision Repair (BER), Nucleotide Excision Repair (NER), Single and Double stranded Breaks Repair (SSBR and DSBR), Homologous Recombination (HR) and Mismatched repair. Basically, DNA alterations without strand breaks are repaired mainly by excision repair mechanisms where the damaged bases are removed from the DNA molecule by excision and then replaced the right bases [2]. In the case of the Nucleotide Excision Repair (NER) an oligonucleotide fragment of approximately 25-30 nucleotides is removed around the damaged DNA and the gap generated in the DNA duplex is filled by DNA synthesis using the opposite, normal DNA strand as a template. To complete the process of NER, the last nucleotide incorporated is covalently joined to the extent DNA by ligation [5]. BER consists of four to five steps in which specific enzymes play a role: excision of the damaged base by a glycosylase, incision of the resulting abasic site, processing of the generated termini at the strand break, DNA synthesis and ligation [6,7]. A third mechanism called mismatched repair occurs when only one nucleotide mismatch appears in the DNA double chain. This mechanism is particularly effective for the repair of DNA error arising during replication due to the limited fidelity of the replicative machinery. Finally, DNA double strand breaks can be repaired by a specific process called homologous recombination and non homologous end joining [2,8].

The importance of the DNA repair process and its relevance in the skin physiology is apparent in genetic disorders affecting genes responsible for DNA repair. Xeroderma Pigmentosum (XP), Cockayne syndrome (CS) and Ataxia telangiectasia (AT) are genetic diseases resulting from rare autosomal recessive pathologies involving DNA repair enzymes that are deficient due to inactivating mutation in their genes [9,10,11]. These diseases are characterized at the level of the skin by extreme sensitivity to sunlight, resulting in sunburn, pigmentation changes, an early onset of the appearance of skin aging signs and a greatly elevated incidence of skin cancers in particular for XP disorder [12]. These changes can be explained by long lasting DNA damages that induces prolonged cellular inflammation through the activation of the NF-κB pathway [2,13,14,15,16] and an acquired immune deficiency [17] as well as rapid accumulation of mutation leading to cell apoptosis, senescence and cell tumorigenesis [18,19,20,21].

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Humans share repair pathways with plants, particularly nucleotide excision repair (NER). NER is essential in removing major damage to DNA which interferes with the genetic code. Due to similarities in DNA damage and repair mechanisms in plants and humans, metabolites such as polyphenols produced by plants may provide beneficial effects in humans [22].

2. Photo protective mechanisms in plants

Sun light is a source of energy to sustain all types of life on earth including plants and animals. Sun light exposure specifically excessive sun light exposure can be harmful to plants and animals. Plants do not have the ability of movement therefore plants developed various mechanisms to protect them from harmful effects of sun light. Most harmful effects come from UVB part of sun light. It is known that excess UVB exposure adversely affects plant growth and development in many ways including nutrient uptake and photosynthesis rates [23]. At a cellular and molecular level DNA is the most important target for UV radiation specifically concerning are exposures from UV-B and UV-C regions of the spectrum [24]. The table below documents adverse effects of UV radiation on some additional cellular and molecular targets of plants. The adverse effects on a molecular level also alter the genetic makeup of cells by introducing mutations in DNA.

Target sites of UV radiation in plants	Effects on the targets	Select References
Proteins	Inactivation of proteins & enzymes	[25, 26]
Amino acids	Photooxidation resulting to decomposition and/or generation of reactive species	[27, 28]
Lipids	Lipid peroxidation mostly at a point of unsaturation	[29, 30]
Growth factors	Degradation, Inactivation, Stimulant	[31] [32]
Pigments	Chlorophylls, Carotenoids	[33]
Membranes	Transport Phenomena	[34]
Photosynthesis	70-80% plants are sensitive to UV radiation	[35] [36]

Table 1. Plants are adversely affected by excessive exposure of UV radiation

To adapt to the continuous insult from excessive sun light exposure, plants developed physical, enzymatic and non-enzymatic mechanisms to not only protect but also to repair the damage done from indiscriminate exposure of UV radiation. Some of the secondary metabolites for example polyphenols such as green tea polyphenols have been studied [37]. Green tea polyphenols plays protective role by mediating DNA repair and reduction in skin inflammation. Polyphenols of various classes used topically [38 or consumed via diet as fruit and vegetables [39] helps to scavenge free radicals produced during exposure of light and also to

mediate additional signaling pathways leading to ultimate damage of DNA at a molecular level.

3. Botanical extracts — Princess Tree as an antioxidant

Paulownia tomentosa is commonly known as Princess Tree, Empress Tree, Royal Empress Tree, Royal Paulownia, Fox glove tree, Kiri (in Japan), PaoTong (China), and Odong-Namoo (Korea). Paulownia plants are well respected in Japan, China and most of East Asia for its tradition, uses and quality of wood. According to traditional literature flowers and leaves are cooked and consumed occasionally for the treatment of fever and pain, and skin ailments [40]. Recently the wood of Princess Tree has also been reported to possess anti-oxidant activity. The major polyphenol found in Princess Tree wood is Paulownin which belongs to a class of chemistry called lignan.

4. Phytochemical profile

Paulownia plants are a rich source of phytochemistry documented by many studies and are reviewed comprehensively [41]. Expressed phytochemistry as a function of a part of the Paulownia tomentosa plant is shown in Table-1 below. Fruit, flower, and leave express specific chemistries of prenylated flavonoids, essential oil, and terpenoids resp. There are other examples of non-specific expression of flavonoids and phenolics by aerial parts and woody parts of the plant.

Class of Chemistry	Part of the plant	Select Examples
Flavonoids	Leaves, bark, fruit, Stem, Flowers	Apigenin, kaempferol, Luteolin, Quercetin, Catechin, Naringenin, Taxifolin.
Prenylated Flavonoids	Fruit	Prenylated taxifolin
Geranylated Flavonoids	Flower, Fruit	Mimulone, Diplacone, Diplacol, Schizolaenone C, Prokinawan, Tomentodiplacone, Tomentin
Phenolic glycosides	Bark, Stem, wood	Syringin, coniferin, Acteoside, Campenoside, Ilicifolioside, Isoverbascoside, Cistanoside
Lignan / Phenolics	Wood, Leaves, bark, Flowers	Paulownin, Sesamin, Piperitol, Vanillic acid, gallic acid, cinnamic acid, coumaric acid
Quinones	Stem, Bark	Furanoquionones, plumbagin
Terpenoids	Leaves	Iridoids: Paulownioside, catalpol, aucubin, tomentoside
Glycerides	Leaves exudates	Acyl glycerols
Essential Oil	Flower	Cosanes, benzyl alcohol

Table 2. Phytochemicals reported from parts of Paulownia tomentosa plant (derived from 2014 review cited above)

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Essential oil from Paulownia flower is reported with identification of major components [42, e.g. benzyl alcohol (13.72%), phenol, 3,4-dimethoxy-methyl ester (3.64%), phenol, 2-methoxy-3-(2-popenyl)-methyl ester (6.24%), 1,2,4-Trimethoxybenzene (8.32%), tricosane (3.28%), and pentacosane (3.26%). A number of additional studies are also reported with similar chemical composition of Paulownia flower oil [43 and their anti-microbial activities. The heartwood of Paulownia is known to express Paulownin, Sesamin, lapachones, sterols, and naphoquinones.

5. Princess Tree reduces UV-induced reactive oxygen species and cellular inflammation

5.1. Free radicals & ROS

Antioxidants primarily mitigate the negative effect of free radicals through their radical-scavenging ability. These antioxidants stabilize radicals by donating electrons and thus preventing oxidation of DNA or other cellular components. While the body is equipped with its own defense system against reactive oxygen species (ROS) and other free radicals produced in the body, it also relies on external (exogenous) antioxidants including those contained in food. As environmental conditions lead to premature aging, a search for a suitable antioxidant product is vital [22].

Free radicals cause damage in the body because of their instability and high reactivity. ROS are of particular interest. During aerobic respiration, mitochondrial electron transport results in the formation of a ROS (superoxide) as a by-product. Solar UV radiation also leads to formation of ROS. Oxygen is particularly vulnerable to radical formation due to its electronic configuration with two valence shell unpaired electrons. Thus, there are several types of ROS including superoxide, hydrogen peroxide, nitric oxide, and hydroxyl radical. Free radicals of other atomic species specifically nitrogen are also formed within the body [22].

ROS can potentially react with other cellular entities including DNA which can lead to DNA modification and ultimately bodily harm. The guanine base in DNA is particularly susceptible to attach by ROS formed by solar UV radiation. Oxidation reactions which modify the guanine base may also lead to single-strand breaks in DNA [44]

While the effects of oxidative stress on the body vary according to type and duration, cells often halt division (enter G0 phase) and may even undergo apoptosis under severe stress. The general response to oxidative stress is cell cycle arrest through the expression of various inhibitor proteins (such as p21). Nevertheless, ROS also serve useful roles within the body including intracellular and intercellular communication [44].

5.2. Antioxidants combat oxidative stress

While broad-spectrum sunscreen which absorbs and reflects harmful solar radiation remains the most effective protection against immediate solar UV damage (which result in CPD

formation), antioxidants are crucial in combating oxidative stress caused by ROS. Skin's antioxidant system consists of vitamins (vitamins C and E), enzymes (catalase and superoxide dismutase), glutathione, and coenzyme Q10 (CoQ10). As these antioxidants perform their protective actions and are degraded by ROS, they are reactivated by other antioxidants. Because several types of ROS may be formed through environmental insult, several types of antioxidants are produced in the skin. Thus antioxidants come in various forms (vitamins, enzymes, etc.) and may be either lipophilic or hydrophilic to function in a variety of areas [22].

During tissue damage and the subsequent inflammation, a number of mediators are released which have been shown to modulate DNA repair. The activation of the Melanocortin Receptor 1 (MCR1) by either its natural ligand, the α-Melanocyte stimulating Hormone αMSH or synthetic analogs [20,21] can enhance the DNA repair activity in cells. Also two interleukins (IL), IL12 and IL23 known to display anti-tumor activity [45,46,47,48] have been shown to accelerate the repair of UVB induced CPDs [2]. Activation of detoxifying mechanisms such as the NRf2 pathway may enhance also DNA repair [49]. Finally mono- and poly- ubiquitilation as well as sumoylation play an important role in the regulation of DNA repair (see review [50]). Thus inflammatory mediators can directly affect the DNA repair process and therefore could be regulatory factors either enhancing or repressing DNA repair. Recent studies have identified that the NF-κB pathway, which is a key regulator in the expression of inflammatory proteins, may be an important mediator in DNA damage and the subsequent repair [2].

Paulownin and Paulownin rich extracts from wood of Paulownia tomentosa were studied for their anti-oxidant and for skin protective effects. Preincubation with Princess Tree wood extract at concentrations from 0.1% to 5% significantly attenuated hydrogen peroxide production in a dose-dependent manner (Figure 1A, *P<0.05 compared with UV exposed vehicle treated epidermal equivalents). UV-induced hydrogen peroxide formation was determined using a modification of the method of Martin et al.,. Through free radicals scavenging activity Princess Tree wood extract may protect skin from oxidative stress that could result in DNA damage.

Paulownin and Paulownin rich extracts from wood of Paulownia tomentosa were studied for their anti-inflammatory activity and for skin protective effects. Preincubation with Princess Tree wood extract at concentrations from 0.1% to 5% significantly inhibited pro-inflammatory cytokine release. In the study shown in Figure 1B and 1C, Epidermal equivalents were topically treated (2mg/cm^2) with Princess tree extracts in 70% ethanol/30% propylene glycol vehicle 2 hours before exposure to solar ultraviolet light (1000W-Oriel solar simulator equipped with a 1-mm Schott WG 320 filter; UV dose applied: 70 kJ/m2 as measured at 360nm). Supernatants were analyzed after 24 hours for IL-1A and IL-8 cytokine release using commercially available kits. These results clearly demonstrate that Princess Tree wood extract can reduce the skin inflammation and damage resulting from UV exposure.

5.3. NF-κB Signal transduction

Nuclear factor-κB (NF-κB) consists of a family of transcription factors that play critical roles in inflammation, immunity, cell proliferation, differentiation, and survival [52. The NF-κB family of transcription factors shares a high-conserved sequence of amino acids within their

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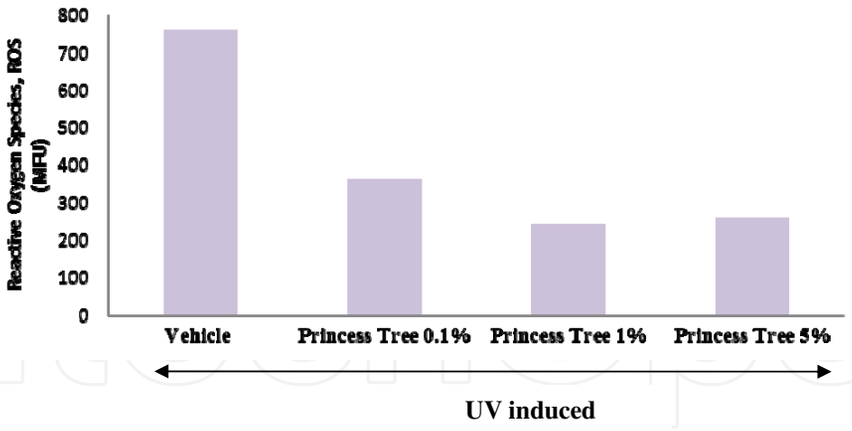

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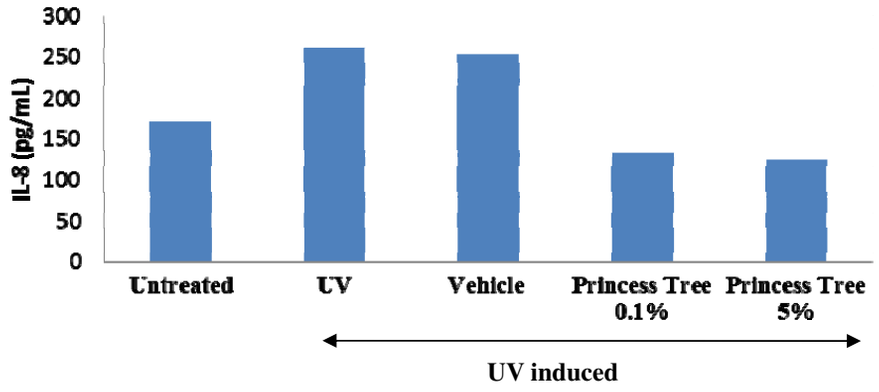

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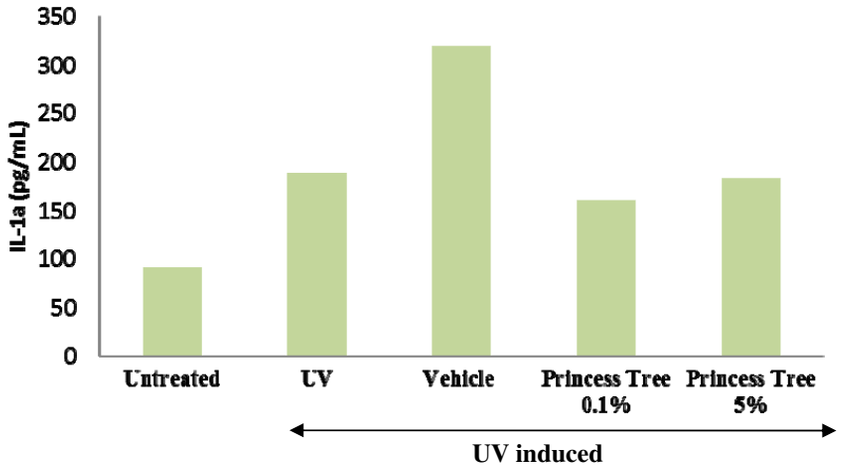

(c)

Figure 1. (a). Princess tree mitigates UV-induced ROS (b). Princess tree inhibits UV-induced pro-inflammatory mediator IL-8 (c). Princess tree inhibits UV-induced pro-inflammatory mediator IL-1α

amino terminus, which contains a nuclear localization sequence that is involved in the dimerization with sequence-specific DNA binding and with the inhibitory IκB proteins [2].

In unstimulated cells, NF-κB family proteins exists as heterodimers or homodimers that are sequestered in the cytoplasm in an inactive form by virtue of their association with a member of the IκB family of inhibitory proteins, most notably IκBα, IκBβ and IκBγ [2,53,54]. About 200 extracellular signals can lead to activation through the dissociation of NF-κB from the IκB proteins. These activating signals include viral and bacterial products, oxidative stress, pro-inflammatory cytokines including IL-1 and TNF-α, and phorbol esters [2,55,56,57,58,59]. Ultraviolet (UV) radiation from sunlight induces IL-1 and TNF-α and creates reactive oxygen species that then leads to NF-κB-mediated inflammation [2,60,61]. The kinase activity of IκK phosphorylates two serine residues (Ser32 and Ser36) on IκB proteins, which results in the ubiquitination and degradation of IκB by the proteasome. The degradation of IκB reveals the nuclear localization sequence of NF-κB [53,54]. Free NF-κB can then translocate to the nucleus and bind to a NF-κB *consensus* sequence present within the promoter region of target genes, thereby upregulating the expression of hundreds of genes, including cytokines (IL-1, -2, -6, etc.) [2], immunoreceptors (immunoglobin kappa light chain, MHC class I, etc.), cellular adhesion molecules (ICAM-1, VCAM-1, ELAM-1), and many others [59].

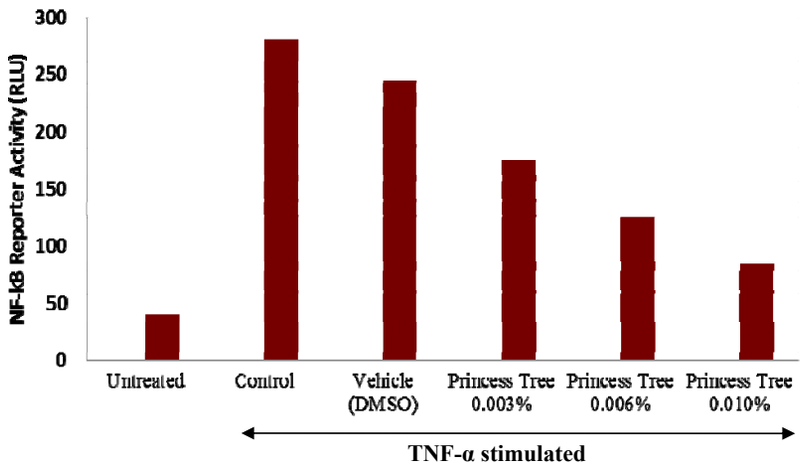

Figure 2. Princess tree inhibited NF-κB promoter activity

Paulownin and Paulownin rich extracts from wood of Paulownia tomentosa were studied for their NF-κB activity. Preincubation with Princess Tree wood extract at concentrations from 0.001% to 0.01% significantly inhibited NF-κB activation. In the study shown in Figure 2, a cell line expressing a NF-κB promoter gene and internal control Renilla luciferase reporter gene were treated with the indicated doses of Princess tree and stimulated with Tumor Necrosis Factor-α (TNFα). Cell lysates were analyzed using Dual-Luciferase Reporter System. These results establish that Princess Tree wood extract can reduce the activation of NF-κB and thus may reduce the cellular damage resulting from UV exposure.

5.4. NF-κB and DNA damage

The NF-κB pathway has been shown to be regulated by ionizing radiation at both the mRNA and protein levels by Brach et al., who demonstrated that NF-κB transcripts were transiently

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increased after irradiation, which was preceded by enhanced DNA binding activity of this transcription factor [62]. Nuclear DNA double strand breaks (DSBs) are one of the most potent DNA damage signals to activate NF-κB [2]. This process can occur within 1–2 h after break induction through activation of the canonical inhibitor of κB (IκB) kinase (IKK) complex and IκBa degradation [15]. NF-κB can be activated by Topoisomerase inhibitors (such as camptothecin) potentially via the generation of double strand breaks as well [16]. Furthermore activation of IKK following treatment with topoisomerase inhibitors was described to be dependent on the zinc finger domain in NF-κB essential modulator (NEMO) [50]. DSBs can trigger two independent signaling cascades that eventually lead to the induction of NF-κB via NEMO [61]. In one case, DSBs can activate ATM, which in turn can bind to and phosphorylate NEMO. In a parallel cascade, the p53-induced protein with a death domain (PIDD) translocates to the nucleus leading to the SUMOylation of NEMO. Consequently, the resulting activation of NF-κB favors cell survival by turning on the transcription of several anti-apoptotic gene [2]s. In response to DSB, PIDD as well as ATM are capable of initiating cascades leading to pro- or antiapoptotic signals, NF-κB presumably being a part of the pro-survival cascade [61]. Miyamoto et al., have summarized this model of NF-κB activation by DNA damage as a 'two signal' model as it requires coincident NEMO SUMOylation and ATM activation by double strand breaks to permit robust NF-κB activation [15]. Taken together these findings suggest that NF-κB may be both have both causal and effector roles in the development of DNA damage [2].

5.5. NF-κB and the DNA repair process

Although the mechanisms by which NF-κB affects DNA damage are not fully established, one possibility is that NF-κB may either directly or indirectly regulate DNA repair processes in cells. Protecting cells from apoptotic cell death following DNA damage is one of the major ways that NF-κB activation regulates the DNA repair process [2]. Wang et al., have demonstrated that NF-κB functions as a positive modulator of cellular senescence, an intrinsic tumor suppression mechanism, by showing that human fibroblasts lacking NF-κB activity prematurely exit from senescence [63]. Others have shown that skin cells devoid of NF-κB activity exhibit deregulated growth correlating with impaired cell-cycle control [64,65]. It has been proposed that the role of NF-κB in cellular senescence could be cell type specific, differentially initiating senescence or acting further downstream in the DNA repair process to maintain the senescent state [2,63]. DNA damage caused by chemical genotoxic agents, such as camptothecin, has been described to activate the Ataxia Telangiectasia-Mutated (ATM) kinase and NEMO (IκB kinase), leading to the inducing of NF-κB p50/p65 heterodimer [66]. In a parallel signaling pathway, ROS can be generated by genotoxic agents in sufficient quantities to activate the NF-κB pathway. ROS can also act as signaling molecules in immune responses, cell death and inflammation, where NF-κB is involved [66]. Depending on the relative degree of DNA damage, multiple mechanisms of NF-κB activation are engaged. Physical genotoxic agents such as UVA or hydrogen peroxide lead to extensive oxidative damage within the cytoplasm which can signal the activation of NF-κB pathway in the absence of DNA damage [2].

Among the various types of DNA damage, repairing double strand breaks can be particularly challenging to cells [67,68], and may contribute to genomic instability associated with most cancers [68,69,70,71]. Wiesmuller et al., have shown that NF-κB is involved in double strand removal and repair via a stimulatory action on homologous repair, involving the targets ATM and the tumor suppressor gene BRCA2 [72]. NF-κB is known to bind to the BRCA2 promoter and activate BRCA2 gene expression [73]. The role of NF-κB in ATM function and DNA repair was demonstrated by Siervi et al., in T-cells where levels of ATM mRNA and protein were significantly reduced by NF-κB blockade [74]. Activation of NF-κB by ATM results in an anti-apoptotic signal in the cells. Wiesmuller et al. have also described that NF-κB utilizes multiple mechanisms to enhance homologous recombination, including stimulation of the activity of CtIP–BRCA1 complexes to trigger DNA end processing, and upregulation of ATM and BRCA2 for strand transfer [72].

The nuclear factor p53 controls several physiological processes including DNA repair and cell cycle arrest. Cross-talk between NF-κB and p53 has been established by multiple groups ([75,76]; see review [77]), including results that suggest NF-κB may have both anti- and pro-apoptotic roles. Only a limited number of studies have investigated the role of NF-κB in DNA damage and repair in skin cells (including: [64,65,78,79,80,81]). Evaluation of the p53-NFκB cross-talk by Puszynski et al. in HaCat keratinocytes cells showed that inactivation of NF-κB improved p53-mediated DNA repair and prevented arsenite-induced malignant transformation of HaCaT cells [80]. Marwaha et al. have shown that in primary skin cells, such as dermal fibroblasts and keratinocytes, treatment with T-oligos led to the up-regulation and activation of p53, coinciding with decreased NF-κB DNA binding activity and inhibition of transcription from NF-κB-driven promoter constructs [79]. Thyss et al. have demonstrated that the sequential activation of NF-κB, Egr-1 and Gadd45 cascade induces UVB-mediated cell death in epidermal cells [81], a process that was crucial in order to eradicate the cells that bear the risk of becoming tumorigenic. In HaCat keratinocytes, hydroxytyrosol (main component of olive oil shown to be an inhibitor of NF-κB), has been shown to significantly reduce the DNA strand breaks caused by UVB, and also attenuate the expression of p53 and NF-κB in a concentration-dependent manner [78].

5.6. Princess Tree reduces DNA damage

The skin is the largest organ protecting the body against external threats such as physical, environmental and biological insults. Among the harmful environmental factors, solar ultraviolet radiation (UVR) is the major one causing cellular and molecular modifications in the skin like photo-aging and eventually leading to genomic instability and cancer ([3, 82]. UV-induced generation of Reactive Oxygen Species (ROS) such as O_2 , H_2O_2, OH° in the skin, develops oxidative stress when their formation exceeds the antioxidant defense ability. UVR penetrates the skin, reaches the cells, and is absorbed by DNA, leading to the formation of photoproducts that inactivate the DNA functions. Oxidation of DNA can product different types of DNA damages: strand breaks, sister chromatid exchange, DNA-protein crosslinks, sugar damage, abasic sites and base modifications [83,84]; [4]. One of the major DNA oxidation products formed as a result of such damage is 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-

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dG). DNA damage by UVB irradiation results also from photochemical reactions consequent to direct absorption of photons by DNA bases [51]. The UV-induced DNA lesions that have been studied in most detail are the cyclobutane pyrimidine dimer (CPD) and the 6-4 pyrimidine–pyrimidone photoproduct (6-4PP) at adjacent pyrimidines [51,85,86].

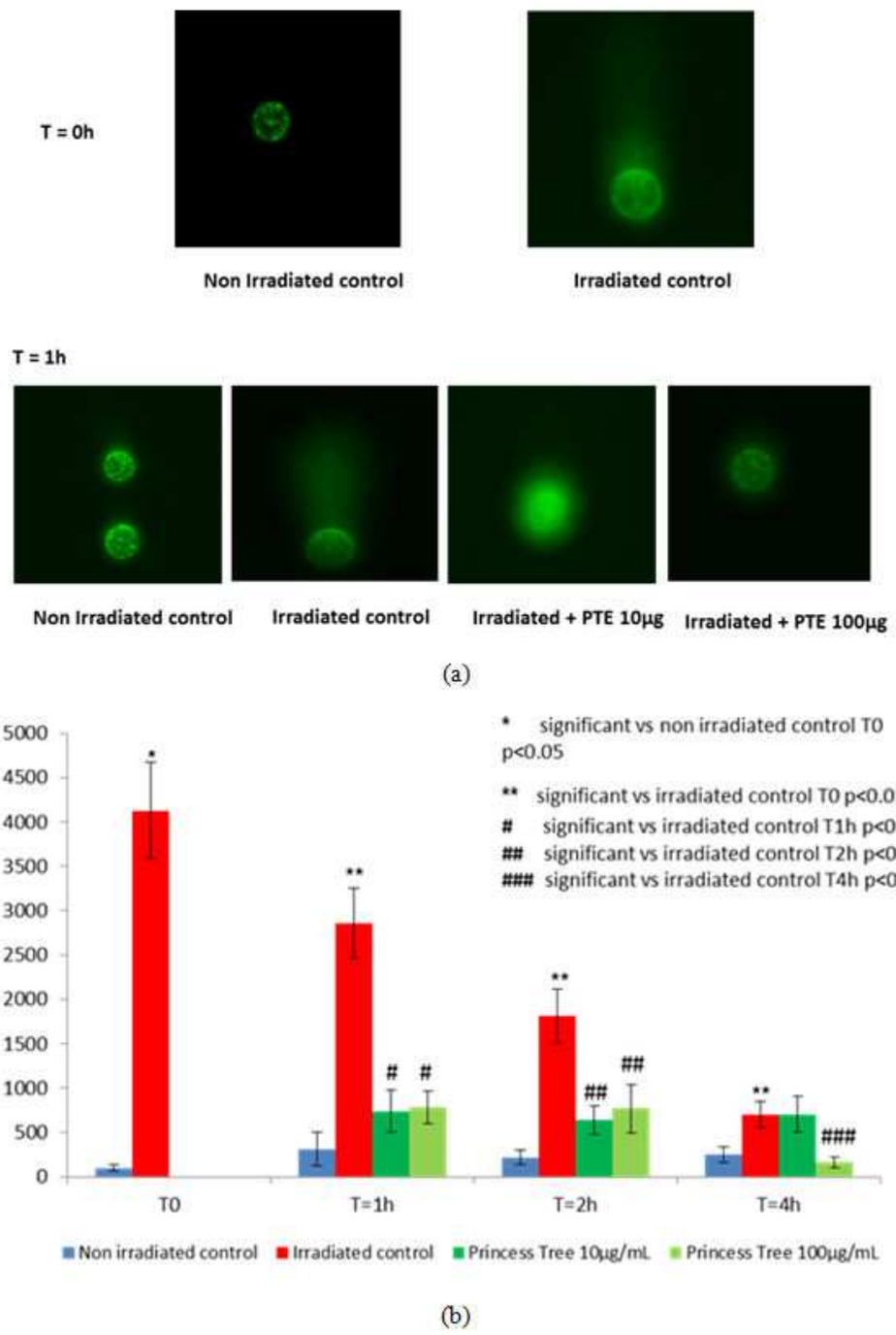

Figure 3. (a). Treatment of primary human keratinocytes with Princess Tree increased repair of UV-induced DNA damage (b). Treatment of primary human keratinocytes with Princess Tree increased repair of UV-induced DNA damage.

Mammalian cells have evolved several DNA-repair pathways to remove all the categories of DNA base lesions, relying in particular on DNA excision mechanisms. One of these, nucleotide excision repair, removes bulky adducts and is thus an essential mechanism for correcting UV-induced DNA damage [87,88]. The base excision repair pathway corrects small base modifications such as oxidized and alkylated bases [88,89]. The importance of repair mechanisms is demonstrated by the hazardous consequences of genetic defects in DNA repair [88,90,91].

Princess Tree wood extract was investigated for the capacity to promote DNA repair after UV insults (6DEM) using Comet assay. After 1 hour treatment, both concentrations of Princess Tree (10 and 100 μg/ml) reduced significantly UV-induced DNA damage in Normal Human Epidermal Keratinocytes (NHEK) when compared to UV-irradiated control as shown by the fluorescent images and the quantification of the comet tail (Fig 3A and 3B, $p<0.05$). The Princess Tree wood extract treatment increased the DNA damage repair rate. Indeed, 4 hours were needed for the UV-irradiated control to reach the same level of DNA damage/repair compared to the Princess Tree wood extract treated conditions.

Princess Tree wood extract direct effects on mitigating DNA damage may be by an indirect mechanism, such as the inhibition of NFkB pathway known to be regulated by ionizing radiation at both the mRNA and protein levels [62]

6. Summary and conclusions

6.1. The use of botanical extracts for protection from DNA damage and DNA repair

Skin is under continual assault from a variety of damaging environmental factors such as ultraviolet irradiation and atmospheric pollutants. As organisms age the cumulative damage exceeds the capacity of endogenous antioxidant defenses resulting in oxidative damage. Furthermore, during oxidative stress the elevation of NF-κB transcriptional activity may contribute to the decrease in DNA repair capacity of skin cells and thereby lead to the accumulation of DNA damage. Since NF-κB is activated by DNA damage, there is a potential for a vicious circle to take place as more NF-κB may decrease the capacity of the cell to repair damages and lead to a longer persistence of the DNA damage. Plants have adapted to chronic exposure to ultraviolet irradiation by producing phytochemicals which can mitigate reactive oxygen species and repair damaged DNA. Botanical extracts such as Princess Tree (Paulownia tomentosa) which can modulate the NF-κB pathway, a primary pathway linking inflammation and DNA damage, can prevent the deleterious effects of DNA damage in cells (Figure 4). Through the ability to scavenge free radicals, inhibit NF-κB activation, reduce DNA damage and induce repair of damaged DNA, Princess Tree may protect skin from numerous external aggressions encountered daily and reduce the damage to oxidatively challenged skin.

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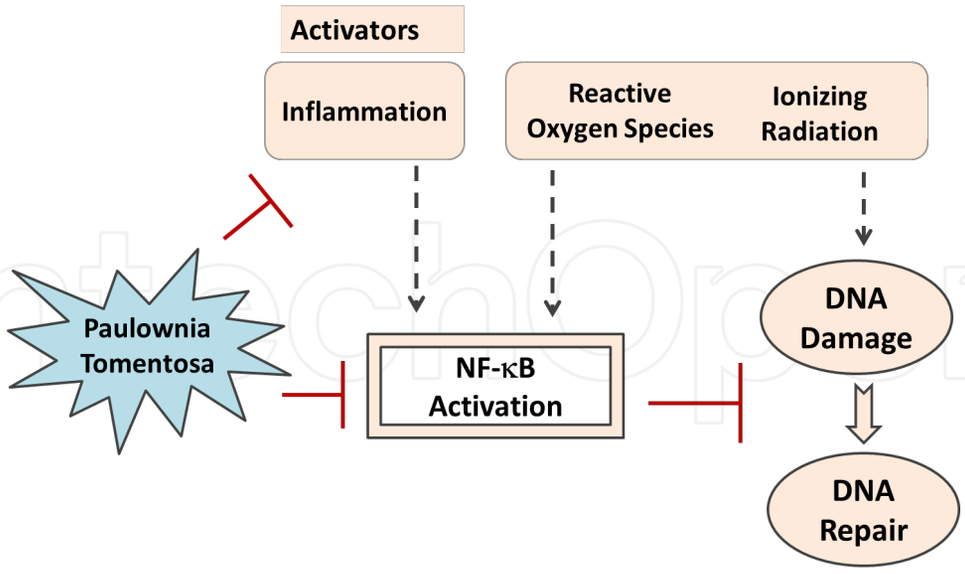

Figure 4. Proposed model showing the effects of Paulownia tomentosa on DNA damage and repair

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