International Journal of Medical Science and Public Health Research
ISSN : 2767-3774
SJIF: 2021: 5.456, 2022: 5.681, 2023: 6.591
IJMSPHR

TYPE Original Research
PAGE NO. 27-34
DOI 10.37547/ijmsphr/Volume06Issue01-04

Importance of photodynamic therapy in proliferative processes

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OPEN ACCESS

SUBMITTED 22 October 2024
ACCEPTED 24 December 2024
PUBLISHED 25 January 2025
VOLUME Vol.06 Issue01 2025

CITATION

Nigora F. Abdukhalikova. (2025). Importance of photodynamic therapy in proliferative processes. International Journal of Medical Science and Public Health Research, 6(01), 27–34.
https://doi.org/10.37547/ijmsphr/Volume06Issue01-04

Abstract: Currently, photodynamic therapy is being introduced into biological research and practical medicine in many countries worldwide. This technology holds great potential for preventive purposes. In our research, we utilized a water-soluble substance known as psoralen, which was isolated from the fig plant (Ficus caricae). This plant is prevalent in the Republic of Uzbekistan. Psoralen was selected as our photosensitizer of choice. To induce proliferative inflammation, we employed a "cotton plate" model. The evaluation of our findings involved analyzing the levels of TGF β1 in the blood and examining any alterations in the structure of mitochondrial membranes of hepatocytes.

Keywords: Photodynamic therapy, psoralen, transformation growth factor β1, mitochondrial permeability transition pore, mitoK+ATP - channel.

Introduction: The photodynamic therapy (PDT) is based on the targeted introduction into the body of light-sensitive drugs - photosensitizers (PS), which have high tropism for target cells (tumor cells, inflamed tissues, microbes and viruses) [2; 13]. Under the influence of light of a certain wavelength, PS begins to produce atomic (singlet) and other types of oxygen in cells, which damage various molecules (proteins, unsaturated fatty acids, nucleic acids) and cellular structures (membranes, enzyme systems, mitochondria, genetic apparatus, etc.) which leads to disruption of their activity and inactivation of pathogens [20].

Under the influence of photodynamic therapy, cells die primarily in three ways:

1. Direct cell death. Cell membranes, mitochondria and lysosomes are the main targets of the damaging effect of a photosensitizer on the cell. Oxidation of membrane lipids by peroxides can lead to disruption of its integrity, increased permeability and the appearance of structural defects of the membrane.

As a result of the effect of PDT on integral proteins of the cell membrane, the activity of receptors and ion channels is disrupted, and the transmembrane permeability of molecules and ions is disrupted [5; 11; 14]. Another important target of PS is mitochondria, which are the energy stations of cells. Under normal conditions, they synthesize ATP, which is necessary for all energy-consuming processes in the cell (DNA, protein synthesis, transport of substances, cell division, etc.). Violation of ATP synthesis leads to disruption of all cell functions and its death [11; 14; 28].

Along with oxidation-phosphorylation reactions, reduction reactions occur in the body, in which oxygen is not completely reduced (one-, two- and three-electron), resulting in the formation of its active (radical) forms. Under both pathological and physiological conditions, the formation of reactive oxygen species (ROS) occurs in several biological systems, one of which is the mitochondrial respiratory chain. Under the influence of PS, the formation of ROS in the mitochondrial respiratory chain increases [20]. It should be noted that under the influence of ionizing radiation, ozone, ultraviolet rays and other physical factors, the formation of ROS increases [12]. In general, many processes associated with the oxidation of biological molecules are accompanied by the formation of ROS [8].

The resultant ROS participates in two simultaneous biochemical processes, namely catabolism and the synthesis of new molecules, which occur continuously. ROS assists in the oxidation of lipids and proteins that need to be eliminated from the cell. This process further supports the subsequent activity of degradation enzymes as they exhibit a specific affinity towards the oxidized substrate [12]. Therefore, ROS plays a pivotal role in the ongoing catabolic processes within the cell.

However, it should be noted that ROS also plays a crucial role in the continuous synthesis of new molecules. Specifically, the oxidation of unsaturated fatty acids within phospholipids, which are essential components of biological membranes, by free radicals leads to the production of physiologically active substances such as leukotrienes, thromboxane, and prostaglandins [12]. As a result, ROS is actively involved in both catabolic and anabolic processes, allowing cells to adapt to changing environmental conditions by modifying the composition of membrane phospholipids and updating the protein composition. Furthermore, oxygen metabolites act as regulators and effectors in cellular and humoral immune reactions. Notably, neutrophil granulocytes and mononuclear phagocytes produce oxygen radicals, which play a significant role in the bactericidal, cytotoxic, and immunoregulatory functions of these cells. The superoxide anion radical, in particular, directly participates in the formation of chemotaxis factors. Recent studies have provided evidence indicating the involvement of the superoxide anion radical in the generation of chemotaxis factors, which effectively trigger the movement of leukocytes towards the inflamed area [12]. Additionally, it has been established that the mechanism underlying most phagocytosis reactions is closely linked to the processes involved in cerebrospinal fluid formation [12].

Cell death due to vascular damage. Damage to blood vessels during PDT leads to a deterioration in the supply of nutrients and oxygen to cells. As a result, the cells indirectly die. Endothelial cells are highly sensitive to PDT [3], macrophages [16], neutrophils [6] and is manifested by platelets. Under the influence of light, PS initiates a cascade of physiological events: vascular endothelial cells are damaged, the integrity of blood vessels is disrupted, they narrow, platelet aggregation and adhesion (agglutination) of leukocytes and neutrophils occur. As a result, the blood supply to the pathological focus is disrupted [3].

2. Immunological reaction to PDT. Photodynamic therapy activates the body's local immune response against pathological cells. Damage to pathological cells and vascular endothelium serves as an initial factor in the development of immune reactions. Photooxidation processes lead to the release of mediators that trigger a local inflammatory reaction. The occlusion of microvessels and the enhanced cytotoxic activity of killer cells against pathological cells are the outcomes of these processes. Recent research has unveiled that exposure to PDT can result in systemic neutrophilia, stimulation of acute phase proteins, elevated levels of circulating components of the complement system, and the release of proinflammatory cytokines. All these alterations point towards an escalation of systemic inflammation and the activation of various parts of the immune system [23]. Local and systemic PDT also activate B-lymphocytes, cytotoxic T lymphocytes, and natural killer cells (NK cells), which are considered pivotal in the immune response. NK cells have natural cytolytic activity and produce cytokines and chemokines. They contain azurophilic granules containing perforin, granzymes, granulicins and other components with the help of which contact cytolysis is carried out [23; 1].

Transforming Growth Factor Beta 1 (TGF β1) is an intricate polypeptide with profound ramifications on crucial cellular processes, including cell cycle regulation, growth and development, differentiation, synthesis of the extracellular matrix, hematopoiesis, chemotaxis, and immune response [31; 32]. Transforming growth

factor β1 (TGF β1) is a pleiotropic cytokine with local and systemic effects. TGF β1 is also actively involved in the management of inflammatory processes [21]. Based on these and other observations [30], TGF β1 is generally considered an overactive suppressor of inflammation. When its activity ceases, systemic inflammatory processes develop [4]. The biological effects of TGF β1 can be classified into three primary types. First, it effectively restrains the proliferation of various cell types. Second, it demonstrates an immunosuppressive impact. Lastly, it plays a crucial role in promoting the formation of the intercellular matrix. Additionally, TGF β1 acts as a regulatory element in the immune response, particularly in controlling the inflammatory response, by decreasing the proliferation of T and V cells [22]. TGF β1 is involved in wound healing processes by modulating inflammatory processes.

Mitochondria house a diverse array of molecules capable of triggering inflammatory responses. The activation of immune system cells through mitochondrial molecules is believed to stem from various factors [24], including:

1. Mitochondrial proteins, which bear resemblance to bacterial proteins.
2. Mitochondrial cardiolipin.
3. Adenosine triphosphate (ATP).
4. Mitochondrial DNA (mtDNA).
5. Reactive oxygen species (ROS).

In the focus of inflammation, the main functional role is played by migrating cells of the inflammatory infiltrate - various types of leukocytes and mobile active macrophages. During the acute period of inflammation, a process known as the “oxygen-metabolic explosion of leukocytes” occurs, which results in the formation of a large amount of cerebrospinal fluid [7]. Reactive oxygen species (ROS) are intermediates of healthy cellular metabolism and are produced in various cellular organelles such as the endoplasmic reticulum, mitochondria and peroxisomes. These metabolites have strong oxidative properties, oxidizing proteins, lipids, cellular components and causing severe DNA damage. At physiological concentrations, ROS acts as a second messenger and acts as signaling molecules during cell growth, cell adhesion and cell differentiation [27].

Psoralens are furocoumarins of plant or synthetic origin that increase the sensitivity of biological objects to near-UV radiation (UVA radiation, 320–400 nm) [17]. The medical field harnesses the photosensitizing properties of psoralens in PUVA therapy for various skin conditions such as psoriasis, vitiligo, atopic dermatitis, eczema, T-cell lymphoma of the skin, scleroderma (systemic sclerosis), and graft versus host disease. The term "PUVA" signifies the combination of psoralen and ultraviolet A (UVA) radiation, specifically referring to the A spectrum of ultraviolet radiation. This treatment technique involves the administration of psoralens to sensitize the skin followed by exposure to UVA radiation. Moreover, psoralens find extensive application in combating adverse reactions arising from anti-vaccination practices [25; 15; 18; 19; 26; 29]. According to contemporary notions, PUVA therapy demonstrates antiproliferative and proapoptotic impact on keratinocytes and immunocompetent cells, along with its immunosuppressive attributes. Essentially, this treatment approach is characterized by its photochemical and photoimmunotherapeutic nature [25; 15; 18; 19; 26; 29]. When exposed to light of a certain wavelength, psoralen is able to destroy biological molecules in two ways. Molecules that have been excited by light release fluorescence quanta or engage in either type I or type II photochemical reactions [10].

During type I reactions, PS molecules directly interact with biological substrates present in pathologically altered tissues, generating reactive intermediate products. These intermediates subsequently react with oxygen, resulting in the creation of numerous highly active substances, primarily oxygen-active forms. Later, these forms oxidize and participate in reduction reactions. Consequently, peroxide radicals, superoxide anion, and hydroxyl radicals are generated, leading to the activation of lipid peroxidation, damage to cell membranes, and disruption of their functions [9].

In type II reactions, PS molecules initiate a reaction with oxygen, resulting in its transformation into a highly active singlet form. This singlet form subsequently engages with proteins, nucleic acids, and lipids present in the cell membrane, leading to their demise via necrosis or apoptosis [10].

To date, photodynamic therapy with the new water-soluble substance psoralen, a local plant photosensitizer in the proliferative stage of inflammation, is not practiced either abroad or in our country. The effect of PDT on the amount of growth factor β1 in the blood has not been sufficiently studied. Also, at the proliferative stage, the effect of PDT on the structural units of the mitochondrial membrane - high-permeability megapores and the mitoK + ATP channel - has not been studied, which makes the topic relevant and necessary.

METHODS

To create proliferative inflammation, a “cotton plate” model was used. This experimental study was carried out as follows. For the study, 5 groups of clinically

healthy rats with clean skin areas were formed.

Group 1: intact animals.

Group 2: control group of animals - chronic proliferative inflammation was created.

Group 3: animals in which a model of chronic proliferative inflammation was established, to which psoralen was administered intragastrically at a dose of 10 mg/kg.

Group 4: animals with a model of chronic proliferative inflammation and irradiated with ultraviolet light.

Group 5: animals with a model of chronic proliferative inflammation were administered psoralen at a dose of 10 mg/kg intragastrically and irradiated with ultraviolet (UV) light.

One day before the experiment, the fur on the backs of the rats was carefully shaved. The next day, under sodium-urethane anesthesia, a 1 cm long incision was made in the skin and subcutaneous tissue under aseptic conditions. Then, entering through this incision, a cavity was created in the subcutaneous tissue, where a pre-sterilized cotton ball weighing 10 mg was placed. After this, the wound was closed with 1 stitch.

Table 2.

Scheme of experiments using the "cotton plate" method on rats.

Groups of rats	Using scheme	transmission time and exposure distance 2 hours after drug administration of ultraviolet irradiation			Method of application of psoralen
		Operation day	4-day	7-day	
Group 1: intact animals	Healthy rats	-	-	-	-
Group 2: control group	-	-	-	-	-
Group 3	psoralen 10 mg/kg	-	-	-	The drug was administered into the stomach once every 3 days for 7 days.
Group 4	ultraviolet irradiation	2 minutes from a distance of 50 cm.	2 minutes 30 seconds from a distance of 50 cm.	3 minutes from a distance of 50 cm.	-
Group 5	psoralen 10 mg/kg + ultraviolet irradiation	2 minutes from a distance of 50 cm.	2 minutes 30 seconds from a distance of 50 cm.	3 minutes from a distance of 50 cm.	The drug was administered into the stomach once every 3 days for 7 days.

All animal studies were conducted in accordance with the recommendations of the WHO Declaration of Helsinki regarding the use of experimental animals and precautions.

It was observed that the amount of TGF β1 in rats of the control group increased by 64.5% in this group compared to the intact group ($P < 0.01$) (Table 2).

In comparison to the intact group and the control group (Table 2), the presence of psoralen in rats led to a 125% ($P1<0.001$) increase in the amount of TGF β1 in their blood. Additionally, rats exposed to ultraviolet irradiation (UVI) displayed a 134% ($P1<0.001$) higher level of TGF β1 compared to the intact group, and a 45% increase compared to the control group ($P2<0.01$). These findings highlight the significant impact of UVI on TGF β1 concentration. Moreover, in rats receiving

psoralen UBN, the TGF β1 index was three times (P1<0.001) higher than in the intact group, and twice as high as in the control group (P2<0.001) (Table 2).

Table 2.

TGF β1 values in experimental rats.

Biochemical indicator	intact group	control group	Psoralen group	UVI group	Psoralen + UVI group
TGF β1 pg/ml	34,9±4,5	56,09±6,14	78,43±6,29 P_1<0,001 P_2<0,001	81,61±7,49 P_1<0,001 P_2<0,01	102,47±9,7 P_1<0,001 P_2<0,001

Note: P_1 - significant compared with the indicators of the intact group; P_2 – significant compared to the control group.

According to our enzyme immuneassays, the group that received a combined treatment of psoralen and UVI showed the highest levels of TGF β1. Various cell types such as granulocytes, all types of lymphocytes, as well as macrophages and dendritic cells, are responsible for producing TGF β1. The secretion of active TGF β1 is significantly increased by any inflammatory stimulus that activates macrophages. Considering that macrophages are derived from blood monocytes and play a crucial role in the production of TGF β1, it can be concluded that photodynamic therapy combined with psoralen and UVI demonstrated the highest effectiveness. Additionally, literature supports the notion that reactive oxygen species contribute to an increase in TGF β1 concentration.

In the model of proliferative inflammation, hepatocyte mitochondria were equal to 0.84 ΔE540/10 minutes, an increase of 140% compared to the intact group. This indicates significant damage to the mitochondrial membrane in rats of the control group (Fig. 1).

Based on the results obtained, it was established that the activity of the mitochondrial K+ATP channel of hepatocytes in rats with a model of proliferative inflammation, but without any treatment, was depressed by 45.7% compared to that in intact rats (P<0.01). Thus, the activity of the K+ATP channel in hepatocyte mitochondria can reduce the turnover of potassium ions under the influence of inflammation and, as a consequence, the processes of adaptation to hypoxia in the cell (Fig. 2).

In the group that received psoralen, there was a 0.65 ΔE540/10 minute inhibition of mitochondria isolated from hepatocytes when exposed to Ca2+ ions. This inhibition was 85% higher compared to the intact group and 29.6% lower compared to the control group (P<0.05) (Fig. 1). This finding indicates that psoralen inhibits the mPTP permeability of hepatocyte mitochondria, leading to a partial restoration of the cell's energy state during inflammatory processes. Furthermore, it was discovered that the psoralen-treated group exhibited a 13.1% upregulation in K+ATP channel activity compared to the control group (Fig. 2).

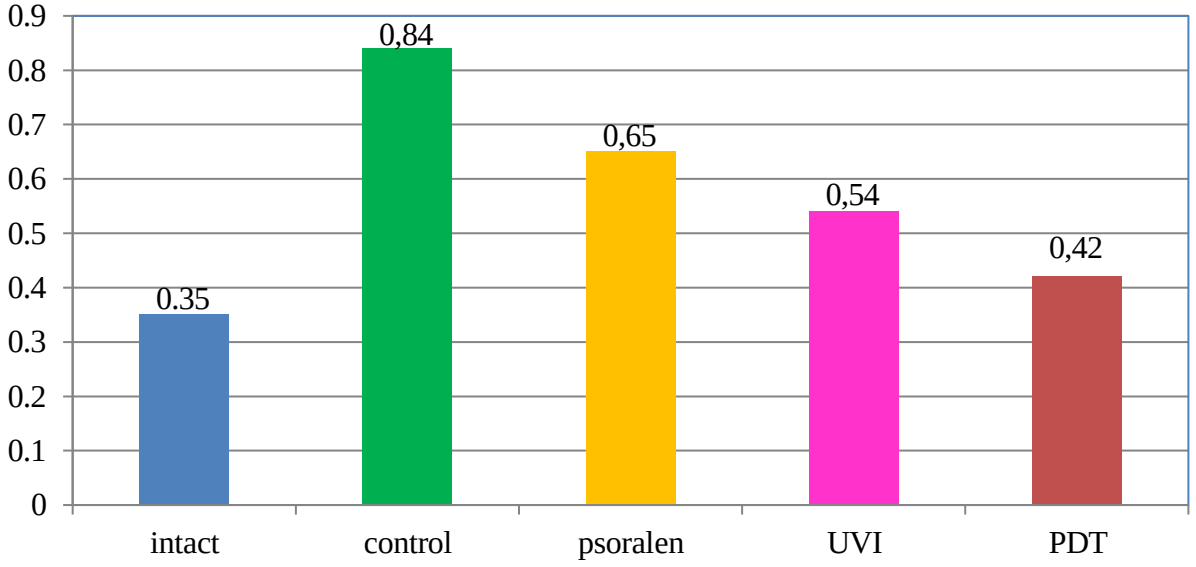

Figure 1. Results of assessing the effect of psoralen, UBN and their complex on the

high permeability pores of mitochondria in rat hepatocytes.

Research has demonstrated that the conductivity of mPTP in hepatocyte mitochondria was observed to be reduced by 35.7% when compared to the control group, registering a value of 0.54 ΔE540/10 min in rats administered with UVI (P<0.01) (Fig. 1). In a similar vein, it was observed that the conductance of the mitoK+ATP channel was activated to 21.1% of the control group values (P<0.05) (Fig. 2). Furthermore, the administration of psoralen to rats with chronic proliferative inflammation followed by exposure to UVI demonstrated a significant reduction in Ca2+-induced mitochondrial swelling in hepatocytes. Specifically, the mitochondrial permeability of hepatocytes in this group was measured at 0.42 ΔE540/10 minutes, displaying a 50% inhibition compared to the control group (P<0.01) (Fig. 1). Lastly, the activity of mitoK+ATP channels in hepatocytes was found to be activated by 30.2±2.4% when compared to the control group (Fig. 2).

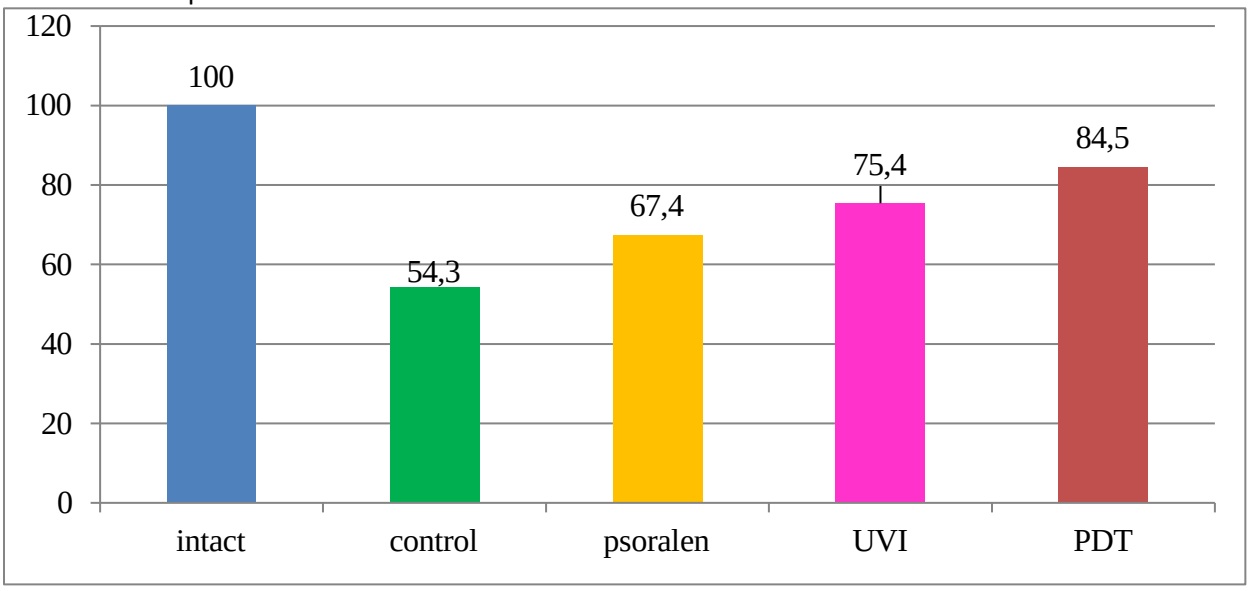

Figure 2. Results of assessing the effect of psoralen, UV irradiation and their complex on the activity of mitoK$^+_{ATP}$ - channels in rat hepatocyte mitochondria.

Mitochondria are the most widespread and first responding structures within cellular structures during inflammatory processes. Under conditions of chronic inflammation, with the separate use of UV irradiation and psoralen, the permeability of the megapore of mitochondria - mPTP - is partially reduced. However, under the same conditions, the complex action of UVI and psoralen reliably inhibits this conductivity, reduces the penetration of water and ions into the matrix, and reduces its swelling. As a result, damage to the outer membrane of mitochondria, the release of cytochrome C and pro-apoptotic proteins from the matrix into the cytosol, and the occurrence of cell apoptosis are prevented. In our experimental chronic inflammatory condition, complex exposure to UBN and psoralen activated the permeability of the mitoK+ATP - channel in the hepatocyte mitochondrial membrane. This is the initial stage of adaptation processes under conditions of cellular hypoxia.

CONCLUSION

All treatments used in the experimental groups were found to increase blood levels of TGF β1. The highest rate was recorded in the group undergoing photodynamic therapy with psoralen. When psoralen and UVI were used separately in the “Cotton Plate” model, the permeability of the megapore of hepatocyte mitochondria - mPTP - was partially reduced. However, when photodynamic therapy with psoralen was carried out under the same conditions, the permeability of megapores was significantly inhibited. In this model, the highest rate of activation of the permeability of mitoK+ATP channels in

hepatocyte mitochondria was observed in the group that used psoralen in photodynamic therapy. Determining the quality of the proliferation phase in inflammatory processes can be done by checking the amount of TGF β1 in the blood.

Establishing the significance of mitochondrial membrane structures in experimental inflammatory processes may indicate the subcellular level of disease development.

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