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Treatment for various diseases by new therapies: A review

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Abstract

Drug therapy is a process for cure the patient diseases. And in this study several studies can involve such as Photodynamic therapy (PDT), Music therapy, and Chewing gum as drug delivery system. Photodynamic therapy is a relatively new procedure used for the treatment of acne. Music has frequently been used as a therapeutic agent from the ancient times. The concept of Music Therapy is dependent on correct intonation and right use of the basic elements of music. Chewing gum is an obvious drug delivery system for local treatment of diseases in the oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure.

Key-Words: Photodynamic therapy (PDT), Music therapy, Chewing gum therapy, Cancer, Photosensitizing agent

Introduction

Photodynamic therapy (PDT) is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light. When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells[1, 2, 3]

The application of ALA produces large amounts of porphyrins in these areas. An LED or laser light source is used to activate these porphyrins causing the production of oxygen free radicals which then specifically destroy those surrounding cells. Recovery time is approximately 7-14 days from this treatment and usually 1-3 sessions are required[4.]

Photodynamic therapy, matured as a feasible medical technology in the 1980s at several institutions throughout the world, is a third-level treatment for cancer involving three key components: a photosensitizer, light, and tissue oxygen. It is an approved treatment for wet macular degeneration, and is also being investigated for treatment of psoriasis. Treatment of internal organs may be achieved through the use of endoscopes and fiber optic catheters to deliver light, and intravenously-administered photosensitizers.[5, 6, 7.]

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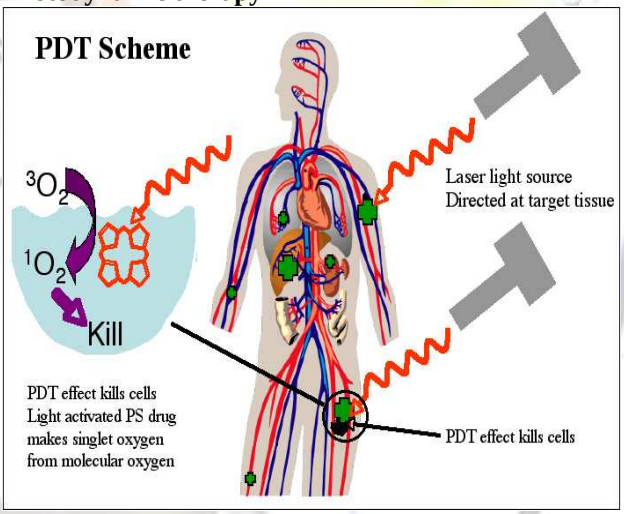
Photodynamic therapy



Epidemiology of cancer

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). Tumors can grow and interfere with the digestive, nervous, and circulatory systems and they can release hormones that alter body function. Tumors that stay in one spot and demonstrate limited growth are generally considered to be benign.

Causes of cancer

Cancer is ultimately the result of cells that uncontrollably grow and do not die. Normal cells in the body follow an orderly path of growth, division, and death. Programmed cell death is called apoptosis, and when this process breaks down, cancer begins to form. Unlike regular cells, cancer cells do not experience programmatic death and instead continue to grow and divide. This leads to a mass of abnormal cells that grows out of control.

Classification

There are five broad groups that are used to classify cancer**.**

1) Carcinomas are characterized by cells that cover internal and external parts of the body such as lung, breast, and colon cancer**.**

2) Sarcomas are characterized by cells that are located in bone, cartilage, fat, connective tissue, muscle, and other supportive tissues.

3) Lymphomas are cancers that begin in the lymph nodes and immune system tissues.

4) Leukemias are cancers that begin in the bone marrow and often accumulate in the bloodstream.

5) Adenomas are cancers that arise in the thyroid, the pituitary gland, the adrenal gland, and other glandular tissues.

Photosensetizer: As a material

Wide array of photosensitizers for PDT exist. They can be divided into porphyrins, chlorophylls and dyes.[7] Some examples include amino levulinic acid (ALA), Silicon Phthalocyanine Pc 4, m-tetrahydroxy phenylchlorin (mTHPC), and mono-L-aspartyl chlorin e6 (NPe6).Several photosensitizers are commercially available for clinical use, such as Photofrin, Visudyne, Levulan, Foscan, Metvix, Hex vix, and Laserphyrin,with other in development e.g. Antrin, Photochlor, Photosens, Photrex, BF-200 ALA [10] Amphinex.[11]

Although these photosensitizers can be used for wildly different treatments, they all aim to achieve certain characteristics.[12]

1. High absorption at long wavelengths
2. High singlet oxygen quantum yield
3. Low photo bleaching
4. Natural fluorescence
5. High chemical stability
6. Low dark toxicity
7. Preferential uptake in target tissue

The major difference between different types of photosensitizers is in the parts of the cell that they target. Unlike in radiation therapy, where damage is done by targeting cell DNA, most photosensitizers target other cell structures. For example, mTHPC has been shown to localize in the nuclear envelope and do its damage there.[14] In contrast, ALA has been found to localize in the mitochondria[15] and Methylene Blue in the lysosomes[16].

Methodology

In the first step of PDT for cancer treatment, a photosensitizing agent is injected into the bloodstream. The agent is absorbed by cells all over the body but stays in cancer cells longer than it does in normal cells. Approximately 24 to 72 hours after injection[1], when most of the agent has left normal cells but remains in cancer cells, the tumor is exposed to light. The photosensitizer in the tumor absorbs the light and produces an active form of oxygen that destroys nearby cancer cells[17, 18, 19]. In addition to directly killing cancer cells, PDT appears to shrink or destroy tumors in two other ways[17, 18, 19, 20]. The photosensitizer can damage blood vessels in the tumor, thereby preventing the cancer from receiving necessary nutrients. In addition, PDT may activate the systems attack the tumor cells. The light used for PDT can come from a laser or other sources of light [18, 21]. Laser light can be directed through fiber optic cables (thin fibers that transmit light) to deliver light to areas inside the body [18]. For example, a fiber optic cable can be inserted through an endoscope (a thin, lighted tube used to look at tissues inside the body) into the lungs or esophagus to treat cancer in these organs. Other light sources include light-emitting diodes (LEDs), which may be used for surface tumors, such as skin cancer [21]. PDT is usually performed as an outpatient procedure (22). PDT may also be repeated and may be used with other therapies, such as surgery, radiation, or chemotherapy [18].

Treatement of skin cancer

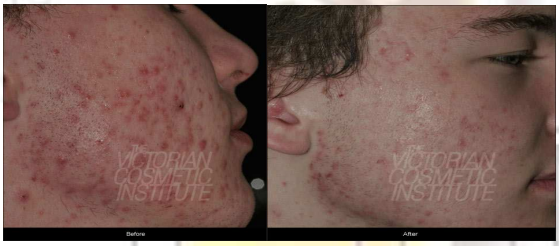
As an example, consider PDT as a treatment for basal cell carcinoma (BCC). BCC is the most common form of skin cancer in humans. Conventional treatment of BCC involves surgical excision, cryogenic treatment with liquid nitrogen, or localized chemotherapy with 5-fluorouracil or other agents.

APDT treatment would involve the following steps.

1. A waiting period of a few hours is allowed to elapse, during which time ALA will be taken up by cells, and
2. A photosensitizer precursor (aminolevulinic acid (ALA) or methyl aminolevulinate (MAL)) is applied. ALA will be converted by the cells to protoporphyrin IX, a photosensitizer (see Porphyrin).

3. Energy is transferred from triplet protoporphyrin IX to triplet oxygen, resulting in singlet (ground state) protoporphyrin IX and excited singlet oxygen;
4. After the treatment the patient will need to avoid excessive exposure to sunlight for a period of time [23].These involve;

- Pretreating the skin with microdermabrasion for at about 30 minutes to help remove the top layer of skin cells and allow the process to work more effectively.
- The skin is then degreased with acetone.
- 20% ALA is then placed on the face from 30 minutes to 3 hours.
- The skin is then exposed to a LED or laser light. Either a blue/red LED light, pulsed dye laser, or Gemini laser is used to activate the ALA.Sun avoidance for 48 hours.



Advantages

Unlike chemotherapy for cancer the effect of PDT can be localised. Specificity of treatment is achieved in three ways.

- First, light is delivered only to tissues that a physician wishes to treat. In the absence of light, there is no activation of the photosensitizer and no cell killing.
- Second, photosensitizers may be administered in ways that restrict their mobility.
- Finally, photosensitizers may be chosen which are selectively absorbed at a greater rate by targeted cells. ALA is taken up much more rapidly by metabolically active cells. Since malignant cells tend to be growing and dividing much more quickly than healthy cells, the ALA targets the unhealthy cells.

PDT can be much cheaper than the alternative radiotherapy or surgical operation and after care. Post operative recovery is typically hours or days rather than weeks[24.]

LIMITATIONS

A major limitation of PDT is that the light needed to activate most photosensitizers cannot penetrate through more than one third of an inch (1 cm) of tissue using standard laser technology and low powered LED technology. Laser application of PDT is generally limited to the treatment of tumors on or under the skin, or on the lining of some internal organs. Moreover it is less effective in treatment of large tumors and metastasis for the same reason. However, new high-powered LED technology has been lab-tested to provide a depth of 2 inches from surface in a simulated breast tissue. Also, hollow needles have been used by some units to get the light into deeper tissues. [24.] The main side effect is photosensitivity. That means you will have a Strong reaction to bright light or sunlight for 4 to 6 weeks after this treatment.

Other side effects may occur such as:

- Fever or chills
- Nausea or vomiting
- Diarrhea or constipation
- Light deadness or dizziness
- Tiredness or weakness

Take care of yourself after PDT

Use these precautions while you are sensitive to light (photosensitive):

- Avoid being in direct sunlight for 4 to 6 weeks. This includes Sunlight through windows or skylights. Close window blinds or curtains on windows.
- Avoid strong indoor lighting like halogen lamps or examination Lamps.
- Wear protective clothing and sunglasses outdoors even on a cloudy day. Cover your skin and protect your eyes. Wear long sleeved shirts, long pants or skirts, gloves, wide brimmed hats, socks, shoes and sunglasses.
- Wearing sunscreen does NOT protect your skin from this reaction.

Call your doctor if

- You have problems with any side effects listed

Call right away if

- Your skin becomes red, swollen or blistered at any point after treatment
- Your prescribed pain medicine is not effective
- You are unable to swallow fluids[25.]

Future prospects

Researchers continue to study ways to improve the effectiveness of PDT and expand it to other cancers. Clinical trials (research studies) are under way to evaluate the use of PDT for cancers of the brain,

skin, prostate, cervix, and peritoneal cavity (the space in the abdomen that contains the intestines, stomach, and liver). Other research is focused on the development of photosensitizers that are more powerful[17], more specifically target cancer cells [17, 19, 21.] and are activated by light that can penetrate tissue and treat deep or large tumors [2]. Researchers are also investigating ways to improve equipment [17]and the delivery of the activating light [21.]

Music therapy- It's REVOLUTIONARY NOW

Research has shown that music has a profound effect on your body and psyche. In fact, there's a growing field of health care known as Music, which uses music to heal. This is not surprising, as music affects the body and mind in many powerful ways. The following are some of effects of music, which help to explain the effectiveness of music therapy[26.] Classical music can be used as "music therapy". The music helps physical, emotional, and social needs of individuals of all ages. It promotes healing and enhances the quality of life. It also decreases the intensity of pain. It also lowers your heart rate, blood pressure, and breathing rate in addition to relieving stress. Classical music can do many things to us whether it is to listen to music or to help other people with stress or with their problems [27.]. Music therapy works because it is nonverbal communication and it encourages people to improve in nonmusical skills as well. Music therapy is for a variety of people including those with depression, children with autism, and the elderly [27].

- **Brain Waves:** Research has shown that music with a strong beat can stimulate brainwaves to resonate in sync with the beat, with faster beats bringing sharper concentration and more alert thinking, and a slower tempo promoting a calm, meditative state. Also, research has found that the change in brainwave activity levels that music can bring can also enable the brain to shift speeds more easily on its own as needed, which means that music can bring lasting benefits to your state of mind, even after you've stopped listening[29.]
- **Breathing and Heart Rate:** With alterations in brainwaves comes changes in other bodily functions. Those governed by the autonomic nervous system, such as breathing and heart rate can also be altered by the changes music can bring. This can mean slower breathing, slower heart rate, and an activation of the relaxation response, among other things. This is why music and music therapy can help counteract or prevent the damaging effects of chronic stress, greatly promoting not only relaxation, but health [30.]
- **State of Mind:** Music can also be used to bring a more positive state of mind, helping to keep depression and anxiety at bay. This can help prevent the stress response from wreaking havoc on the body, and can help keep creativity and optimism levels higher, bringing many other benefits[31.]
- **Other Benefits:** Music has also been found to bring many other benefits, such as lowering blood pressure (which can also reduce the risk of stroke and other health problems over time), boost immunity, ease muscle tension, and more. With so many benefits and such profound physical effects, it's no surprise that so many are seeing music as an important tool to help the body in staying (or becoming) healthy[32.]

Forms of music therapy

There are a few different philosophies of thought regarding the foundations of music therapy. One is based on education and two are based on music therapy itself, both of which will only be briefly covered here. In addition, there are philosophies based on psychology, and one based on neuroscience. Different approaches from education are Orff-Schulwerk (Orff), Dalcroze Eurhythmics, and Kodaly. The two philosophies that developed directly out of music therapy are Nordoff-Robbins and the Bonny Method of Guided Imagery and Music. [27, 28.]

In India

Indian classical 'Ragas' have been acclaimed By Vedic science to have healing effects. Music has frequently been used as a therapeutic agent from the ancient times. Music plays an effective role in subduing the so-called emotional imbalance. India's First Music Therapist Dr. Bhaskar Khandekar is a well known practitioner of Indian Music Therapy (Since 1993).Dr.Bhaskar has obtained his Masters degree in Music and had Ph.D. in very rare subject called "Music Therapy". He is a Classical Violinist. The Music Therapy Day is celebrated on 13 May of each year in India.

In treatement of heart diseases

Some music may reduce heart rate, respiratory rate, and blood pressure in patients with coronary heart disease, according to a 2009 Cochrane review of 23 clinical trials.[29] Benefits included a decrease in blood

pressure, heart rate, and levels of anxiety in heart patients. However, the effect was not consistent across studies, according to Joke Brad, PhD, and Cheryl Dileo, PhD, both of Temple University in Philadelphia. Music did not appear to have much effect on patients' psychological distress.

In treatement of epilepsy

Research suggests that listening to Mozart's piano sonata K448 can reduce the number of seizures in people with epilepsy his has been called the "Mozart effect". However, in recent times, the validity of the "Mozart Effect" and the studies undergone to reach this theory have been doubted, due to reasons such as the limitations in the original study and the difficulty in proving the effect of Mozart's music in subsequent studies.[27.]

Chewing gum as drug delivery system

It is well known fact that the right drug delivery system is critical to the success of a pharmaceutical product. A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and, thus, conserve or increase revenue. Chewing gum as drug delivery system holds tremendous potential not only in smoking cessation and oral health care arenas but also in other indications [33.]

Chewing gum as drug delivery system[35, 36.]

Chewing gum provides new competitive advantages over conventional drug delivery system:

- Fast onset of action and high bioavailability
- Pleasant taste
- Higher compliance (easy and discreet administration without water)
- Ready for use
- High acceptance by children

Systemic effect

Active substances can be absorbed through the buccal mucosa and/or through the GI tract when saliva is swallowed. Once the active substance is present in the blood, systemic affect can be obtained.

Fast onset of action

Fast onset of systemic effect is seen for active substances absorbed through the buccal mucosa, as the active substances pass by the jugular veins directly to the systemic circulation.

Local effect

Chewing gum is an obvious drug delivery system for local treatment of diseases in the oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure[36].

Effect on dry mouth (Xerostomia)

Dry mouth is a side effect of many types of medicament (e.g. antidepressants) and it is also part of the symptomatology of several diseases (e.g. sjogren's syndrome-an autoimmune disorder characterized by lymphocytic infilteration of the salivary and lacrimal glands). Chewing gum stimulates salivary secretion thereby decreasing dryness in the mouth[37].

APPLICATION

Dental caries- Prevention and cure of oral disease are obvious targets for chewing gum formulations. It can control the release rate of active substances providing prolonged Active substances can be absorbed through the buccal mucosa and/or through the GI tract when saliva is swallowed. Once the active substance is present in the blood, systemic affect can be obtained. Fast onset of systemic effect is seen for active substances absorbed through the buccal mucosa, as the active substances pass by the jugular veins directly to the systemic circulation. Chewing gum is an obvious drug delivery system for local treatment of diseases in the oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure[36].

Local effect. It also re-elevates plaque pH which lowers sintensity and frequency of dental caries. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia.Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oraland pharyngeal infections. It can also be used for inhibition of plaque growth. Chlorhexidine chewing gum offers numerous flexibility in its formulation as it gives less staining of the teeth and is distributed evenly in the oral cavity. The bitter taste of chlorhexidine can be masked quite well in a chewing gum formulation.

1) **Systemic *therapy***- chewing gum as a drug delivery system is beneficial to a number of indications, some of which are discussed below:
   i. **Pain**- Treatment of minor pains, headache, muscular aches can be successfully accomplished.
   ii. **Smoking cessation**- Chewing gum formulation containing nicotine, lobeline and silver acetate have been clinically tested as aids to smoking cessation. Nicotine is a natural alkaloid occurring in the leaves of tobacco plant. It is a therapeutic agent intended to help smokers break the psychological habit of smoking by reducing the nicotine withdrawal symptoms normally experienced when smoking is stopped. The formulation nicoretteÒ available as mint and classic with different flavor and

dosage, is developed with ion-exchange resin, released 90% of drug after 30 min chewing (Russel et.al 1980). The release rate was controlled by the rate and vigour of chewing. Thus the patient can control the drug intake to match his needs. Increasing the pH of the medium in which it is dissolved can enhance nicotine absorption.

iii. **Obesity**- Active substances like chromium, guaran and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.

iv. **Other indications**- xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety etc are all indications for which chewing gum as drugdelivery system could be beneficial. [83,84.]

Concept of formulation developmrnt [38, 39, 40.]

A piece of chewing gum usually consists of gum core, which may or may not be coated. The core is composed of an insoluble gum base resin, elastomers, emulsifiers, fillers, waxes, antioxidants and softeners, sweetens, flavoring agents, and in case of medical chewing gum, active substances. Methods to increase rate and extent of the release include the addition of buffering agents or solubilizing agents and coating/encapsulating the active substances. In contrast, hydrophillic active substances are rapidly released and it may therefore be necessary to slow down the release rate by means of various methods, like encapsulating the active substances or by increasing the amount of gum base. The water content of gum base is very low and the gum binds lipophillic substances very firmly.

Formulation

The main components of medicated chewing gum are:

Active substances- vitamins, oral contraceptives, nicotine, minerals, analgesics, antacids, muscle relaxants, antihistamines, decongestants, anesthetics etc.

Flavors- Essential oils like citrus, peppermint, spearmint, anise and wintergreen oil are employed as flavors. Synthetic flavors are also used.

Sweeteners- Sugar free chewing gums contain sweetening agents like sorbitol, mannitol, saccharin etc

Gum base- Natural or synthetic gum base is used. Example of synthetic gum base includes styrene butadiene rubber, polyethylene and polyvinyl acetate. Smoked rubber is natural source. Today, the gum base could also be made from styrene butadiene, poly (vinyl acetate) or polyethylene. The sugar is for sweetening the product. In addition to above ingredients various additives are also used to improve properties of chewing gum, like plasticizers, elastomers, lipids (soyabil), emulsifiers (lecithin), softners and fillers, texture agents (talc), coating and binding agents, film formers, coloring agents etc. Corn syrup keeps the gum flexible and fresh. Xylitol has been investigated to play a significant role in dental caries. [41]

Manufacturing process

In general, chewing gum is manufactured by sequentially adding the ingredients to a commercially available mixer known in the art. After the ingredients have been thoroughly mixed, the gum mass is discharged from the mixer and shaped into the desired form such as extruding in to chunks or casting into pellets which are then coated or panned.

Oral mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. The epithelium cells increases in size and becomes flatter as they travel from the basal layer to the superficial layers. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. Buccal mucosa on the other hand is more suited for sustained delivery applications as it is less permeable and has immobile mucosa.The buccal mucosa consists of 20-40layers of cells with a total thickness of 450-600mm. The main barrier of the buccal mucosa is situated in the outer one third of the epithelium. The submucosa is highly vascularized and rapidly removes any permeated active substances to the systemic circulation thus avoiding first pass metabolism. [42.]

In-Vitro testing

The absorption of active substances through the buccal mucosa can be examined by both in vitro and in vivo methods. The most common method utilizes Ussing chamber where excised buccal mucosa (either from human or animal) is placed as a barrier between two chambers. A second method employs a human TR146 cell culture model for investigating permeability effects and toxic effects. TR146 cells are derived from human buccal carcinoma and grown in layers with morphologically resemble human buccal mucosa. [43.]

In-Vitro apparatus

An apparatus was specially designed and constructed for release testing of medicated chewing gums. The tested gum formulations comprised nicotine, meclizine,dimenhydrinate and xylitol. The apparatus proved to be suitable in product control of commercial batches but also a useful tool in the research and development of medicated gum formulations[43.]

In Vivo studies

Buccal absorption of active substances can also be tested by various in-vivo methods. Beckett and Triggs introduced a mouth wash procedure in 1967, in which a buffered solution of the active substances is swirled in the oral cavity for a known period of time. The difference between the amount of active substance contained in the original solution and the amount recovered is the amount of active substance absorbed from the oral cavity. [48.]

Limitation of chewing gum

Chewing gum has several disadvantages as the drug released into saliva disappears rapidly from the oral cavity because of involuntary swallowing. Also, The controlled release rate also reduces the risk of side effects, as high plasma peak concentrations are avoided

Future trends

Chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances. [46.]

Conclusion

Researchers continue to study ways to improve the effectiveness of PDT and expand it to other cancers. Clinical trials (research studies) are under way to evaluate the use of PDT for cancers of the brain, skin, prostate, cervix, and peritoneal cavity (the space in the abdomen that contains the intestines, stomach, and liver). Chewing gum offers several advantages compared to chewable tablets, lozenges and other related formulations hence in the coming years it is very likely that chewing gum will become a common drug delivery system.

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