
A Review on Photothermal Therapy (PTT) to Treat Cancer

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ABSTRACT

Photothermal therapy has attracted attention from few couple decades because it is non-invasive, easy to perform and its effective outcome to treat tumor. Photothermal therapy destroys the cancer cells with minimum damage to normal cells. In this article the introduction of cancer and Photothermal therapy is given and explained. Because of its unique composition and properties, nanomaterials are utilized to treat cancer cells. In this literature various examples of Photothermal agents (PTAs) like inorganic and organic Photothermal agents are included like various organic dyes, polymers, and carbon based nano system, gold structures, metallic-oxides, metal sulfides, metal chalcogenides are included. In addition, mechanism of action and how Photothermal agents are worked is given in this review article. It will cover the benefits and drawbacks of Photothermal therapy. Furthermore, the challenges and opinion in near future is also addressed. These are the topics included in the review article.

Keywords: *Cancer Treatment, Drug Delivery, Mechanism of Action, Photothermal Agents.*

INTRODUCTION

Nowadays, as the research progresses world has achieved great success in treating disease. The invention of vaccines, novel delivery methods, latest surgery methods and some major medical developments are utilized to cure diseases. Unfortunately, the treatment of cancer, one of the major worldwide causes of death, is still a challenge today. Cancer one of the major leading reason of deaths all over the world [1]. Nowadays, conventional cancer therapies involving surgery, therapies such as radiation therapy and chemotherapy, and others combination methods have own intrinsic drawbacks. Surgery does not remove all cancer cells lead in serious morbidity. In addition, surgery is utilized to remove lot numbers of tumors which are close to cancer tissue structures. Furthermore, radiation therapy and chemotherapy have their own several side effects, which are making the patients, lot of suffering [2].

Newer strategies, like selective accretion of nanodrugs by compromising their physical and chemical properties or the by compromising their physiochemical properties or the use of these nanodrugs formed in toxicity and was not sufficiently successful considering induce side effects by use of nanoparticles. Newly, great attempts are made to develop a novel immunotherapeutic plan that effectively directs immune cells to manage against invasive cancer cells. The immune system, it contains immune checkpoints, the dendritic cells and the tumor micro environment or macrophages can be suitable operated to get the appropriate anticancer effect. Moreover, nanoparticles are at once utilized in contrast with other techniques; great anticancer efficacy can be gotten. Particularly, the utilization of nanoparticles in combination with tumor vaccines and natural killer cells, or Photothermal therapy for the kill the tumors are considered a very effective strategy [1].

Hyperthermia has got great attention because it leads to death by protein denaturation or

break of the cellular membrane and afterwards result in tumor shrinkage because of removal of cancer cells by macrophages, which get more benefits over conventional cancer therapies including minimal invasion, easy to perform, and possibilities to treat situated tumors in essential regions where surgery is not available. Yet, to treat basic tumors, the activation energy source need not only adequately penetrate healthy tissues, but also efficiently kill tumors without invasion to healthy tissues. Therefore, particular energy absorbing nanoagents are serious, which are situated in particular tumors to absorb energy and ease of thermal therapy. Nowadays, some heating sources such as microwaves, laser light and centered ultrasound are engaged in thermal cancer treatment [2].

Photothermal therapy (PTT) is another treatment which increases interest in scientific community rather than conventional therapy. Because it has therapeutic efficacy, low toxicity, high targeting, good acceptability it becomes more popular. It is also an invasive technique [3]. Photothermal therapy has drawn appreciable observation because of its excellent tumor tissue clear out ability and almost no harm to simple tissues [4]. In Photothermal therapy many photothermal agents are used that absorbs the radiation near in the spectral region and convert the absorbed energy light into heat through a non radiative procedure without oxygen consumption. Photothermal method is mostly utilized nanomaterials because shows more absorption in the NIR region of the electromagnetic spectrum. Nanomaterials increase permeability and retention effect. Photothermal agents inside tumors result from energy transfer from light to heat, which rises temperature to destroy tumors cells. Tissue harm is obvious within few minutes when the temperature of tissues rises up to 55–95°C. Many organic light absorbers in tissue including water, oxyhemoglobin, hemoglobin, and melanin can convert light to heat, which shows in increase in the temperature cause harm in both tumors and healthy tissues. Still, the near-infrared light persuade least Photothermal temperature increase in both tumors and tissues, as the absorption of biological tissues consisting of blood and water is minimal in a NIR region 700nm-900nm [2]. Therefore, particular Photothermal nanoparticles that can absorb NIR light to affect the particular tumor with negligible damage to the nearby healthy tissues by conversing NIR light to heat have been developed and systematically investigated, which possess high Photothermal conversion efficiency, and strong absorbance and good photostability in the NIR region. For Photothermal therapy, a favored means of cancer treatment, it is very important in this, we review article some nanoagents and its applications in cancer treatment [4]. To find an appropriate Photothermal agent to achieve a great effect in cancer tissue destroying [2].

In Photothermal therapy, both inorganic and organic Photothermal agents are used. In organic Photothermal agents include dyes like cyanine, croconaine, and porphyrin are used. Polymers like polyaniline, polypyrrole, chitosan link polymers are used. Carbon based nanoparticles like carbon nanotubes, carbon sphere, carbon dots, grapheme are widely used organic Photothermal agents. In inorganic Photothermal agents gold- based nanoparticles like gold nanocages, gold nanoshells, gold nanostars, and gold nanorods are used and platinum and silver nanoparticles are used. Metallic oxides, metal chalcogenide and metal sulfides are also widely used as Photothermal agents. These are the basic introduction about cancer, Photothermal therapy and Photothermalagents.

Photothermal Agents (PTAs)

Photothermal agents can convert energy from light into heat to increase the temperature of the surrounding environment. Ideally, Photothermal agents are expected to only increase the

temperature locally to reduce the damage to healthy tissues, where the PTA is absent or outside the scope of laser irradiation. Inorganic PTAs own higher PCE and better Photothermal stability than their organic agents. But organic PTAs may win out regarding biodegradability and biocompatibility [5].

ORGANIC PHOTOTHERMAL AGENTS- DYES

Cyanine

Cyanine dye derivatives synthesized as NIR (Near infrared) dyes mainly utilized in fluorescent imaging during recent years. The cyanine derivatives used as an adequate photothermal agent as well as a fluorescent imaging. Though, limitations like restricted aqueous stability, quick body clearance, and poor cell uptake severely limit the direct use of free NIR dyes in photothermal cancer therapy. [2] This technique is non-invasive method it gives increase temperature or singlet oxygen respectively, produced from irradiated light to destroy cancer cells with negligible damage to the surrounding tissue [6]. Cyanine dyes such as indocyanine green, IR820, IR780, IR825 and cypate having ingestion in NIR region have developed as brilliant imaging joined phototherapeutic agent in cancer. IR820 and IR780, a fundamentally comparative dye to Indocyanine green but with higher fluorescence force and better dependability are few examples of other clinically accepted cyanine dyes [3]. Presently, cyanine derivatives containing nanocarriers are broadly used in vitro and in vivo practical. Moreover, the intrinsic tumor targeting capacity and effective photo conversion capacity of cyanine are of high significance in image guided phototherapy of different tumor models [6].

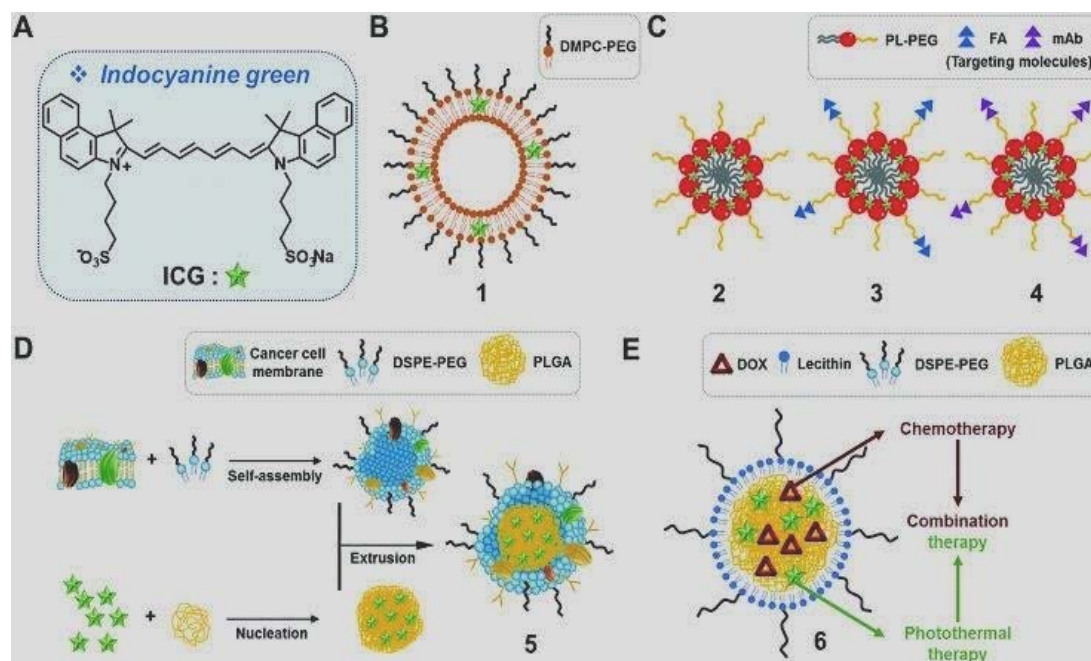


Fig 1. A) Indicate indocyanine green dye structure. B) ICG / DMPC based liposome C) ICG/ PEG targeting molecules. D) DSPE-PEG attaches with PLGA and cell membrane E) ICG encapsulated lipid layer and it is used in Photothermal and combinational therapy [7].

Croconaine

The team of B. D. Smith pioneered utilize of croconaine dyes for Photothermal treatment. These chromophores are adorable for croconaine dye molecules secured within a macrocycle are set up to be tested as photothermic agent. This pH sensitive croconaine dye permitted a

particular NIR- light absorption only when the molecule was situated in an acidic environment like the one found in intracellular vesicles; for the moment it remained inactivated under physiological conditions [7].

Results indicated that photothermic heating created upon 808nm laser irradiation on mouse cancer cells treated with this croconaine based dye brought in cell death which may be ascribed to a dye uptake into acidic intracellular vesicles. Cell harm was only delivered on irradiated cells, with no harm showed in surrounding cells. In significant reactive oxygen species discharged was distinguished.

Thus, the impact was ascribed to a pure photothermic method. Croconaine dye initiated a sub cytotoxic concentration of 100 μ m on macrophages and tumor cells. From the outcomes acquired it can be concluded than these types of near-infrared dyes have demonstrated extraordinary guarantee as Photothermal agents, giving a great chance to achieve a spatiotemporal control on photothermal cancer therapy or their high photostability and low fluorescence quantum yields, as well as their very short-lived excited state lifetimes.

Croconaine dyes and derivatives contain they have provided important insights that may use future developments. However, it is significant to note that in comparison with other types of PTT agents, croconaine dyes require significantly higher laser power to attain successful photoirradiation [8].

Porphyrin

In photothermal cancer therapy, Porphyrin and its subsidiaries are another kind of organic dyes which are been utilized. Example, Zheng et al. created liposome-like nanoagents called "porphysomes" through self-group of porphyrin lipids [2].

These porphysomes could retain and change light into heat with great productivity because of the high porphyrin filling density. It has properties like magnetic resonance imaging-sensitive and non-photo leachable irradiation. Further improvements have been also done porphysomes were effectively developed as proficient photothermal nano-agents through incorporating manganese particles into porphysome nanoparticles.

Additionally, different types of porphysomes have been applied in photodynamic therapy, positron emission tomography and ultrasound imaging. A Porphyrin based micelle bind with polymer PEG and porphyrin utilized as combination of Photothermal impact and synergistic chemotherapy gave incredible chemo sensitivity to malignant cancer cells and accomplished tumor relapse, which avoid symptoms of chemotherapy.

Porphrin are exceptionally biodegradable and biocompatible, and also utilized as productive nanocarriers and light absorbers with fascinating multi-functions [7]. The moderately short retention frequency (600-700 nm) seriously restricts the change efficiency *in vivo* [2]. Therefore, improved porphyrin based photothermal agents with solid NIR absorbance is expected in the near future. Moreover, the preclinical and clinical studies on porphyrin based photothermal nano-agents are major used in PTT and different clinical applications.

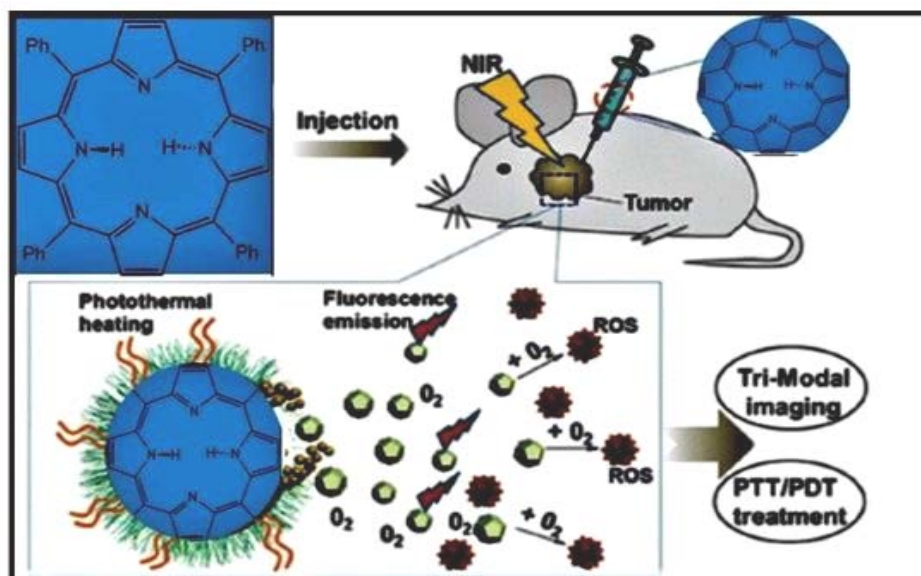


Fig 2. Illustrate Porphyrin produce Singlet Oxygen used in PTT. [9]

Squaraine

Several squaraine dyes have been created for biological imaging. Squaraine dye have two parts SQ1 and SQ2. Disregarding that, squaraine dyes have emission in the second window NIR-II, 1000-1700nm have hardly any reports to a great extent because of the short of a simple and universal design strategy in this commitment, molecular strategy is investigated to create squaraine dyes have NIR-II emission. First NIR-I squaraine dye SQ2 is developed by ethyl-grafted 1, 8-naphtholactam as donor units and square acid as acceptor unit in a donor-acceptor-donor (D-A-D) structure. The Doppler Effect fluorescence emission into NIR-II window, malononitrile, as a very good electron withdrawing group is introduced to strengthen square acid acceptor-engineered squaraine dye SQ1 exhibits a significant red-shift into NIR-II window. To transfer NIR-II fluorophores SQ1 into helpful theranostic agents, fibronectin targeting and further more SQ1 nanoprobe was built and indicated great NIR-II is imaging performance in angiography and tumor imaging including lung metastatic foci in deep tissue. Moreover, SQ1 nanoprobe will be utilized for photoacoustic imaging and photothermal removal of tumors. This research strategy is doable and viable to create NIR-II squaraine dyes [10].

Polymers

Polymer based photothermal materials have category of photothermal agent in biological applications because they show tailorable molecular structures, high photothermal efficiencies and incredible biocompatibility. Combination polymers are popular for their fantastic photoelectric properties owing to the presence of large π conjugated backbones. For a long time in the past few years, conjugated polymers were widely studied in the areas like organic photothermal particles and solar cells, but not biomedicine [11].

Polyaniline

Polyaniline (PANI) can easily transport from emeraldine base state to emeraldine salt state in the presence of strong acids with a stamped red shift of its absorption maximum wavelength toward the NIR spectral. PANI nanoparticles were firstly described to acting as a photothermal agent for in vitro treatment of epithelial cancer [11]. Chemotherapeutic medications were covered within PANI nanoparticles to do the combination of chemotherapy

and photothermal therapy. Polyaniline is the popular, possible and eldest the most helpful conductive polymer because of its outstanding physicochemical properties [12]. Moreover, it is a possible attractive material for applications in biomedical engineering and biochemical combination of methotrexate and PANI both together utilized for cancer treatment. They show NIR light irradiation because of heat generation by PANI. Increase cell apoptosis in vitro as well as improve tumor suppression combination of methotrexate and PANI utilized as tumor focusing cancer treatment [11].

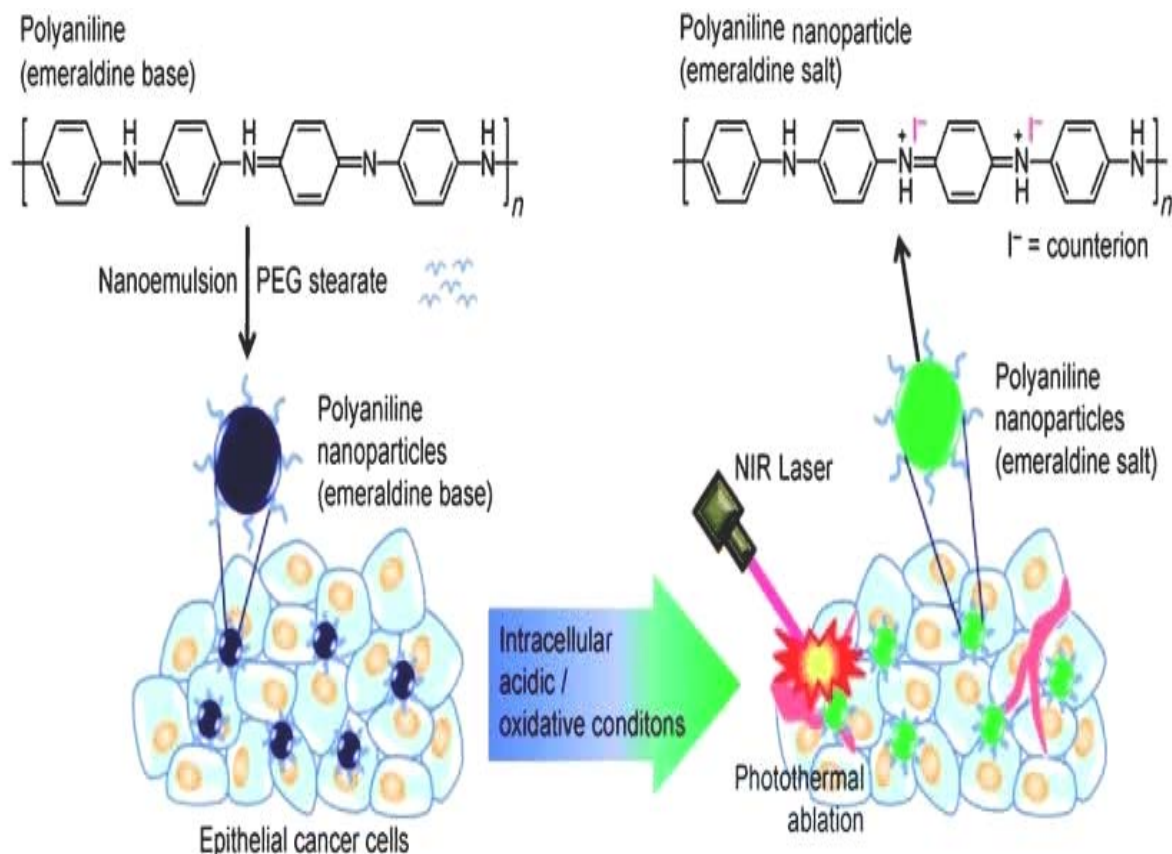


Fig 3. Polyaniline its salt cause cancer cell death by NIR radiation. [13]

Polypyrrole

Polypyrrole (PPy) nanomaterials have been widely expanded and explored in biomedical applications because of elevated conductivity, great stability and very good biocompatibility, Superior stability and excellent biocompatibility. Besides, the strong absorbance of Polypyrrole in the NIR area makes Polypyrrole nanomaterials are promising candidate for effective cancer ablation as photothermal nanoagents. Example 2012, Liu et al. created Polypyrrole nanoparticles as a novel photothermal nanoagent with incredible stability in different biological media has less toxicity [2]. These photothermal nanoparticles create heating under NIR laser irradiation give in effective cancerous cells ablation in vitro and in vivo without seeing adverse effects after treatment. Essentially, the as arranged polypyrrole nanoparticles additionally showed good colloidal stability and high photothermal forming efficiency because of strong NIR absorption and good photostability. In vitro assays demonstrate high cell removal efficiency. Recently, different types of complicated Polypyrrole based nanomaterials have been prepared as photothermal nanoagents [12].

For example, Lee *et al.* had created an electro responsive drug release system based on

Polypyrrole nanowires through electrochemical deposition of a formation of pyrrole monomers and biotin as dopants in a conciliatory template. The outcome demonstrated strong photothermal effects synergistically increase the chemotherapeutic efficacy [2].

Polythiophene

Polythiophene derivatives typically show great light harvesting ability photostability, photostability and simple synthesis positively charged polythiophene that displayed photostabilizes and PH stabilizes, fantastic biocompatibility, powerful oxygen generation capability and large to photon absorption cross areas. Fluorescence of polythiophene is not influenced by interference of biomolecules and metal ions.

Polythiophene utilized as cell imaging and photothermal therapy. Polythene water solution is exposed to 808 nm laser irradiation for 10 min; the temperature is increased from 25°C up to 47°C and confirming the strong Photothermal effect. Multifunctional encapsulated NPs showed a low cytotoxicity and a productive PT effect. The polythiophene polymer used as special photothermal agent to treat cancer [11].

Chitosan Functionalized Nanomaterials

Chitosan is a characteristic cationic polymer described by properties that are significant for biomaterials: nontoxicity, biodegradability, and biocompatibility. Chitosan functionalization of nanoparticles for PTT has several advantages [14].

In reality, chitosan coatings ensure nanoparticles, maintaining irreversible distance and improving their optical stability, thus delivering photothermal ablation more effective. The chitosan-based coating essentially changes the surface properties of nano objects [11].

Chitosan is a very good agent for nanoagents biocompatibilization and stabilization and it can also be utilized as a scaffold structure for securing the antibodies and proteins required for cell targeting due to the presence of amino groups, chitosan can be applied to drug or DNA delivery systems because it can be ionically cross-linked to multivalent elements [15].

Due to its properties, chitosan has already been more utilized for coating metal nanomaterials like gold and silver nanoparticles. Boca *et al.* done on the investigation of chitosan-coated silver nanotriangles for treat human lung cancer cells [11].

Carbon based Nanomaterials

The noble metal nanomaterials referenced before may introduce some problems that have significantly restricted their application in clinical trials, like their non-biodegradability and possible long-term cytotoxicity. To accomplish excellent Photothermal nano-agents with improved biocompatibility and decreased cytotoxicity, carbon based nanoparticles are broadly studied in few years in order to decrease lateral impacts, essentially due to the intrinsic biocompatibility of carbon [15].

Among the broad scope of carbon nanomaterials, we will focus on graphite-related structures like single and multiwall carbon structures, and graphene derivatives, including graphene oxide (GO) and reduced graphene oxide (RGO).

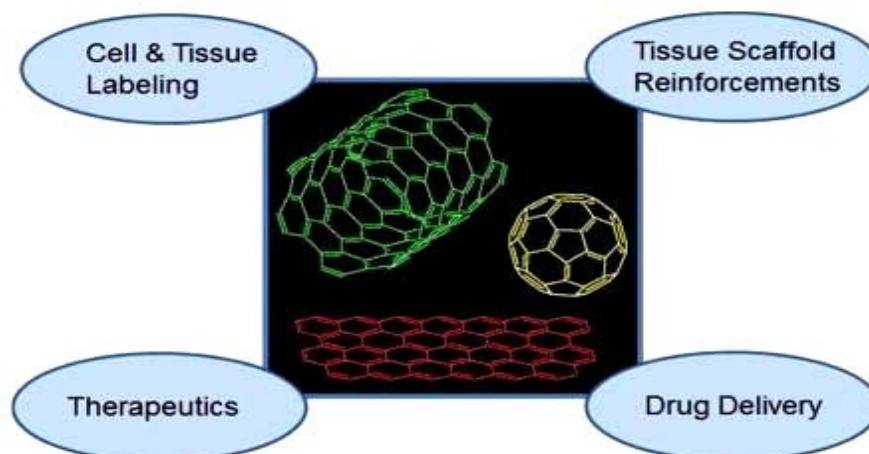


Fig 4. Carbon Structures and its Main Applications. [16]

Graphene

Graphene structure is a single-atomic-layer, two-dimensional system made up of just carbon atoms ordered in a hexagonal honeycomb lattice [17]. It has large precise surface and shows excellent electrical, mechanical, optical and thermal property, which is believed as the most promising carbon material in twenty-first Century. Contrast with other materials, graphene oxide has large absorption coefficient [18]. In the near infrared region, and carries more oxygen- containing functional groups, which compose it well-dispersed in aqueous solution. It also has a large surface area, with low toxicity and low production cost, so that it can be utilized as a new high biocompatible nanomaterial and be applied in the biomedical field [15]. Graphene is widely utilized in Photothermal therapy in cancer cells because of their special electrical properties, optical properties and Photothermal conversion ability Graphene itself has great Photothermal effect, many scientists endue the nano particles having the capacity of drug loading by attaching multifunctional macromolecules on graphene, so as to achieve accomplish the combination of chemical treatment and thermal treatment [19]. Graphene indicates significant concentration- dependent cytotoxic and genotoxic effects, so when it is utilized in vivo, a safe concentration of graphene (lower than 10) is needed in cancer treatments. Therefore, graphene based new structures of nanoagents with productive photothermal therapies under low-power laser with low concentrations is essential [20].

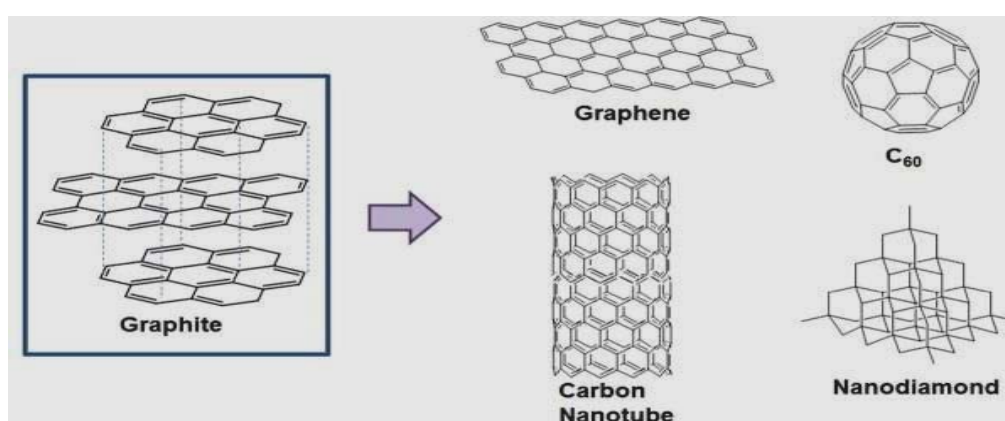


Fig 5. Carbon based Various Structures [16]

Carbon Nanotubes

Carbon nanotubes, because of their ordinary physicochemical properties, they have become famous nanoagent in cancer [21]. CNTs is a hollow tubular structure made up of carbon,

which can be viewed as a monolayer or multilayer graphite hexagonal network plane set up by chiral vector winding along the microtubule hollow, and it is a sort of special material of one-dimensional quantum structure. Nowadays, carbon nanotubes, as a great photothermal material, have received extensive attention and research [22]. CNTs have a strong absorption in the near infrared region due to its brilliant optical absorption properties. It can effectively change light energy into heat and achieve local thermal and thermal destruction of malignant tumor cells [23].

Moreover, as a photothermal material, that could simultaneously load drugs on their surfaces and synergistically combined chemotherapy with photothermal therapy to improve cancer treatment. Carbon nanotubes can be divided into single walled, multi walled carbon nanotubes, metal type and non-metallic type single wall carbon nanotubes. Among them, Single-walled carbon nanotubes (SWCNTs) are the most generally used in cancer therapy.

From morphology, Single-walled carbon nanotubes are comparative to biological macromolecules, and can enter cells by endocytosis agents, and accordingly they can smoothly get into the cancer cells during the blood circulation, that they can maximize their impact of PTT [24]. At the same time, owing to the increased permeability and retention effect of SWCNTs (EPR), Single-walled carbon nanotubes can be targeted to accumulate in tumor cells [2]. Furthermore, there is an expected development prospect of SWCNTs in the therapy of PTT and bio-imaging. It is widely utilized in photothermal therapy.

Mesoporous Nanocarbon

Recently, mesoporous carbon nanoparticles are received great attention in the group of carbon-nanomaterials. This increasing interest flows from their properties, like high surface areas, large pore volumes, and great surface properties, provide significant advantages as drug carrier on the basis of more loading capacity and biologic inertness without cytotoxicity [25]. Furthermore, Mesoporous nanocarbon could also be utilized as NIR-absorbing nanomaterials with high photothermal conversion efficacy. For example Qu et al. created hyaluronic acid surface modified Mesoporous nanocarbon as nanocarriers for helpful dual activate synergistic cancer therapy [26].

In further study, hollow porous carbon nanoparticles with C-dots inserted in carbon shell was created addition of DOX had fundamentally increased release rate under NIR laser irradiation due to excellent Photothermal activity [27]. It shows synergistic impact in chemotherapy and Photothermal therapy.

Carbon Dots

Carbon dots are quasi-spherical carbon nanoparticles with diameters of 2–10 nm, and comprise of oxygen, nitrogen elements and other doped heteroatoms. Because of their high quantum yield, predominant chemical and photostability, low cytotoxicity and low cost, C-dots are commonly considered as a promising candidate in cancer therapeutic. Carbon dots are very good nano carriers due to their promising optical and biocompatible capabilities, most effective and more secure for patients [28].

Nanodiamonds

Nanodiamonds (NDs) is a bulky diamond-like structure look like promising carbon nanomaterials in biomedical applications mainly because to their high surface area, optical properties, high biocompatibility, nontoxicity, colloidal stability, great mechanical strength,

and high surface functionality. The size of nanodiamonds is between 1 to 100nm. [29] Generally, NDs have been utilized as luminescent biomarkers able of intracellular high-resolution tracking, and recently have been act as excellent nano thermometers that can be used for thermal imaging of single cells [30].

INORGANIC PHOTOTHERMAL AGENTS – METALLIC NANOSTRUCTURES GOLD NANOPARTICLES

Gold Nanorods

Gold nanorods structures are gold based nanoparticles mainly used in cancer and Photothermal treatment. Gold nanorods structures can absorb appropriate and scatter forcefully in NIR region. The wavelength is around 650-900 nm. Nowadays, gold nanorods used as novel agent in both cancer therapy and molecular imaging [31].

Antibody conjugated nanorods attach to surface of cancer cells together with a high affinity on the plasma membrane of cancerous cells. Accordingly, the red light scattered from the nanorods in the dark field, saw with the use of simple microscope. The cancer cells are clearly diagnosed and imagined from the microscope rather than nonmalignant cells. It is discovered that, after submission to nonstop red laser with 800 nm malignant cells need half of the laser energy to be photothermally destroy than nonmalignant cells [32].

Thus, both selective Photothermal therapy and effective cancer cell diagnostic are shown at time. They are also utilized as tumor diagnosis, theramostic agents, and tumor treatment.

Gold Nano-Shells

Gold nanoshells are made to absorb radiation at different capacities. Once the nanoshells are joined to the cancer cells, only laser light is utilized to treat cancer. Gold nanoshells are gold based nanostructures used for mainly PTT and CT scan. Gold nanoshells are more biocompatible rather than other gold structures. They are surface Plasmon resonant (SPR) nanomaterials made up of silica core coated with an ultra-thin gold shell [33]. Changing the part of the core diameter of shell and the shell thickness leads the scattering properties and absorption of nanoshells in NIR region and visible region of electromagnetic spectrum. This group of nanoparticles has great variety of uses, including uses in sensing, optical filters and cancer treatment. Such as, our famous nanoshells products has a great strong Plasmon resonance at 800 nm and it has very high absorption in the near infrared is the premise of therapies that utilize the localized heating of nanoparticles to eradicate cancerous cells and lead to destroy cancer cell it doesn't affect normal cells [34]. These are created to absorb radiation of different capacities and certain types of radiation. Once the nanoshells are conjugated to the cancerous cells, only laser light utilized to treat cancer [35]. Utilized for targeting, imaging, drug transfer, radiotherapy, and PTT.

Branched Gold Nanostructures

Among gold-based nanostructures, anisotropic multi branched nanoparticles like gold nanostars and nanoflowers are more popular in nowadays. These nanostructures have few sharp branches which can act as hot spots and result in the electromagnetic field and result in a high light-to-heat conversion efficiency [36]. Furthermore, ease of synthesis for large-scale production and LSPR (localized surface Plasmon resonance) in the NIR region makes them major candidates for photothermal therapy [33].

Gold Nanostars

Gold nanostars are most popular because it has multi branched structure and unique properties. They have physicochemical and optical properties [37].

The size of nanostars from 60 to 100 nm in diameter. Gold nanostars have great Plasmon characteristics that transfer photon radiation into heat for Photothermal cancer therapy. Nanostars, with many long branches and small capsule size, show high absorption cross sections that are adjustable in NIR with very low scattering effect and make them efficient Photothermal agents. Gold nanostars are utilized for photo ablation and tracking both in vivo and *in vitro* [38]. With the help of SKBR3 (breast cell) cells breast cancer cells set with revealed nanostars, they displayed Photothermal ablation within 5 minutes of irradiation of wavelength 980 nm.

On mouse PEGylated nanostars are systematically injected for 2 days, irruption of nanostars was spotted and restricted Photothermal ablation was showed o n dorsal window chamber with in 10 mins of irradiation (785 nm). This preliminary lead to increase hypothermia is encouraging and has outlined the ability of gold nanostars structure as very good Photothermal agents in cancer therapy [37].

Gold Nanoflowers

Gold nanoflowers are novel gold nanoparticles. Gold nanoparticles are grown in fruit juice and used for Photothermal cancer treatment. When the nanoflowers are injected into tumor and it leads to increase in the temperature and destroy the cancer cells [39]. They are used for photosensitizers, proteolysis, and DNA binding and drug and gene carriers.

Gold Nanocages

Gold nanocages look like hollow, porous gold nanoparticle the size between 10 to 150 nm. Gold nanocages have minimal size of 20-50 nm, direct and precise used for localized surface Plasmon resonance, and great absorption cross section per volume that is especially utilized for Photothermal conversion. Generally, such distinct nanocages will be created with sizes in the range of 35-60 nm while the LSPR is tuned to 800 nm. The pores can be controllably opened and closed by coating the nanocages with a smart polymer, thermo sensitivity that enlarge and covers the pores at low temperatures and uncover the core at rise in temperatures. These ideal characteristics of gold nanocages are getting through the utilization of a simple galvanic replacement procedure between a silver template and gold Salt. Gold nanocages can affect tumors in vitro by attach with antibodies by the gold-thiolate linkage. Once gold nanocages reveled to laser radiation, formed heat can essentially damage tumors in both in vivo and in vitro experiments [40]. They have very good drug loading capacities.

Gold Nanospheres

Small gold nanospheres basically absorb light and give peaks near 520 nm, while larger spheres shows increased scattering and give peaks that broaden significantly and shift towards longer wavelengths (known as red-shifting). Big spheres diffuse more light because they have more optical cross sections, and also because of their ratio of diffusing to total elimination increases with size [41]. Gold nanoparticles are often utilized as bioimaging tags in dark field microscopy techniques, where the scattering from individual nanoparticles with diameters larger than 40-50 nm can be observed. Gold nanospheres absorb photons and convert them to heat to kill cancer cells [42]. They are mainly utilized in diagnostics, therapeutics, pathogen detection, control drug target, nanocoatings and biomedical

nanodevices.

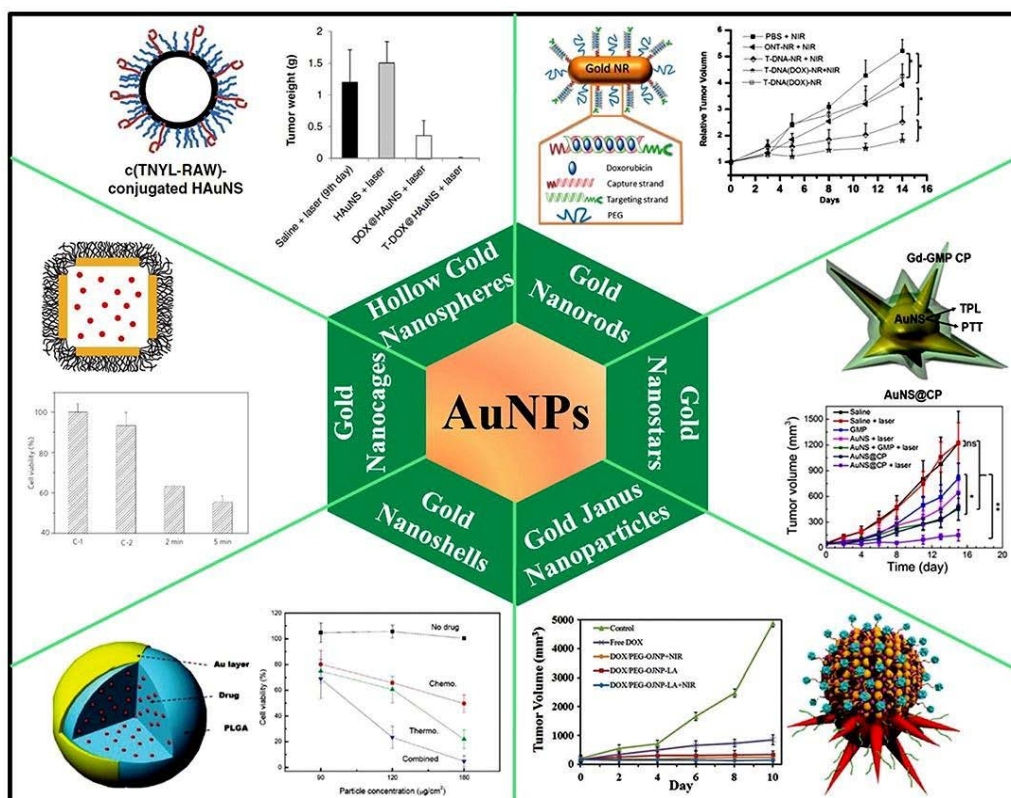


Fig 6. Gold based gold nanorods, gold nanostars, gold nanoparticles, gold hollow spheres, gold nanocages, gold nanoshells and gold Janus particles in Photothermal therapy. [26]

Palladium Nanoparticles

Palladium is very valuable metal. It has electrical catalytic and mechanical properties. Palladium nanoparticles and Pd sheets are utilized in therapy of cancer. Palladium nanoparticles show high biocompatibility and photothermal efficacy. The nanoparticles go into cancer cells with great efficiency; stay in the cell cytoplasm no causing direct cell harm, and cause thermal excision under harmless near infrared laser irradiation. It shows ablation and simultaneous imaging of Pd particles utilizing remain spectroscopy and may prompt to new forms of cancer therapeutics [44].

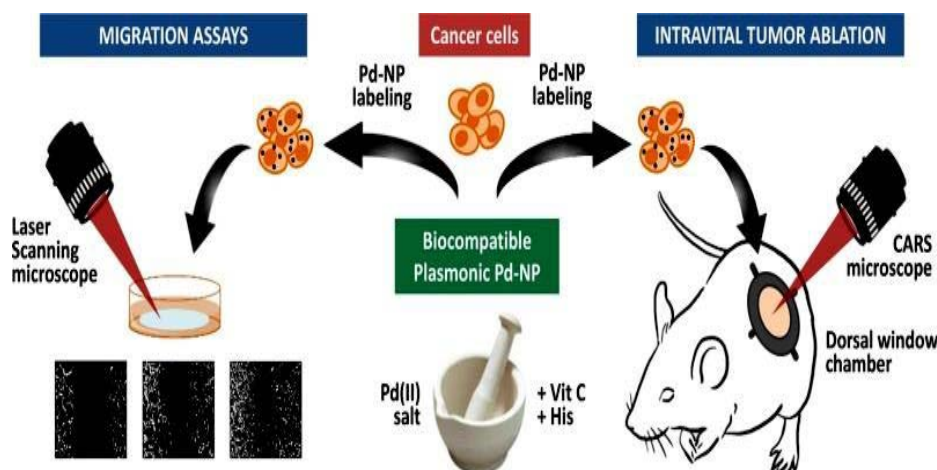


Fig 7. Palladium Nanoparticles injected in the Mice cause Tumor Death [43]

Platinum nanoparticles

Platinum nanoclusters, unique noble metals, have similarities with silver and gold nanoclusters, have low biological toxicity. Platinum nanoparticles have shown very good biocompatibility no matter in vitro and in vivo. Platinum nanoparticles were generally utilized as catalysts for oxygen reduction reaction and enzyme mimetic to cancerous cells. Platinum nanoparticles show less cytotoxicity and low systemic toxicity in vivo. It can easily reach 50 °C at the tumor sites under irradiation compared to the phosphate buffered saline (PBS) solution, showing excellent photothermal potential [21].

Silver nanoparticles

As a significant member of the metal nanoparticles, contrasted to other metal nanoparticles, silver nanoparticles have characteristics physicochemical properties, incredible clinical application. Like, silver nanoparticles have a great inhibitory effect on bacteria and viruses, such as human immunodeficiency virus and *Staphylococcus aureus*. Furthermore, silver nanoparticles have great optical properties and narrow separation peaks, and the particular surface Plasmon resonance (LSPR) quality factor Q from UV to visible and near infrared bands of Ag is significantly higher than that of other metals, such as Al and Au. Apart from the photothermal property silver nanoparticles also give surface improved Raman scattering effect, a sort of abnormal surface optical phenomenon. So the silver nanoparticles can often be utilized as a sensor. Nano silver, as a precious metal particle, has strong absorption ability in the near infrared light. Nano silver applies its photothermal effect through plasma resonance effects on the particle surface. When the light beam on the silver nanoparticles, the light will cause the single electron resonance of the nano silver surface, The electronic will absorb the light energy to form a slightly same exothermic electron gas, after that the exothermic electron gas instantly given the energy to the silver nano particle dot matrix, and then the energy was given to the surrounding environment lead in temperature increase. Silver increased the biocompatibility of rare earth particles and give the nanoparticles photothermal effect. The nanoparticles will reach the best mortality approaches 95% under 980 nm NIR and have power density of 1.5 W cm², while Au nano-shells and Au nanorods need a higher power density, which shows very good photothermal potential [21].

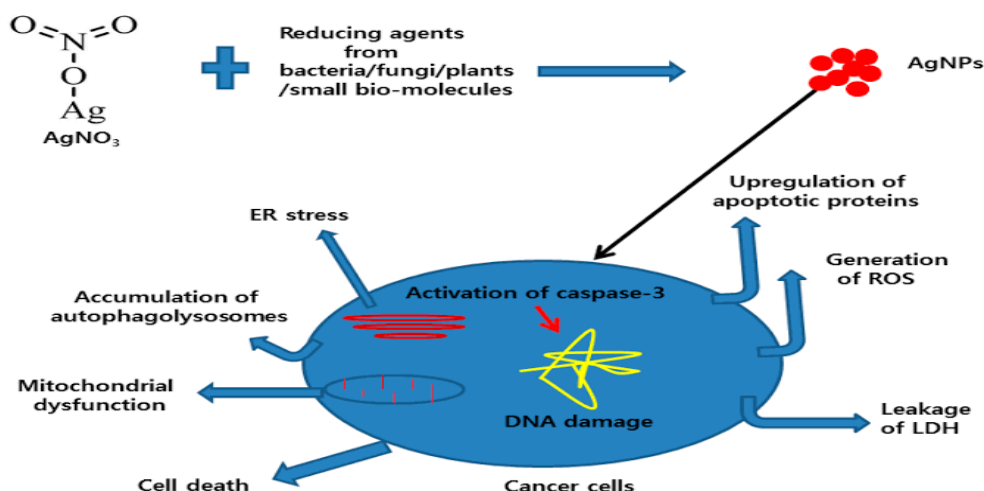


Fig 8. Silver Nanoparticles and its Mechanism to DNA Damage and Cancer Cell Death [46].

Metal Chalcogenide

The industrially vital and scientifically significant metal chalcogenides (S, Se, and Te) have obtained a lot of attention in the past couple of decades because of their anisotropic property. In general, transition elements of groups IV to VII B attach with VI A group elements, such

as S, Se, and Teto form binary stable layered crystalline structures Transition metal dichalcogenide (TMD) have caused great increase of research on biomedical application because of its good thermal effect This kind of material is generally layered structure, such as tungsten disulfide and molybdenum disulfide [40]. Two dimensional chalcogenide materials have a vast absorption band in the near infrared region (NIR), and these materials also have great extinction coefficient in the near infrared and visible light meanwhile they can also create tunable absorption characteristics accompanied by layered structure changes, which make it possible for the use of photothermal therapy Materials such Bi_2Se_3 , Bi_2S_3 , Ag_2S and CuS have been widely utilized in the photothermal therapy of cancer. WS_2 is also mainly use as photothermal agent. As photothermal materials, Bi_2Se_3 is also in the research flow nowadays. Scientists understand the combination treatment of cancer by changing the morphology of materials, surface modification and attaching other nanoparticles. Bi_2Se_3 and FeSe_2 utilized in PTT [21].

Two-Dimensional Transition Metal Dichalcogenides

Two-dimensional transition metal dichalcogenides (2D TMDCs) are made up of a surface of transition metal atoms fitted between two layers of chalcogen molecules. Their simple formula is MX_2 , where M is a transition metal of groups (Ti, Zr, Mo, Ta, W, Nb, V, etc.) where X is a chalcogen. Single-layered 2D TMDCs shows great characteristics, like strong near infrared absorbance, more photothermal conversion ability also very good photothermal stability, and gives the possibility to be excellent photothermal agents. Great photothermal agents give themselves with well organized cargo loading capacity as drug carriers for chemotherapy. These new 2Dimensional multinary layered metal chalcogenide nanomaterial shows some different characteristics compared to 2Dimensional binary transition metal dichalcogenide parts, so holding very good promise in different potential applications including electronics, optoelectronics, catalysis, sensors, biomedicine, and energy storage and conversion with improved performances [26]. The uses of two dimensional metal sulfides are in biomedical imaging, catalysis, drug delivery, biosensing, hydrogen evaluation and Photothermal therapy.

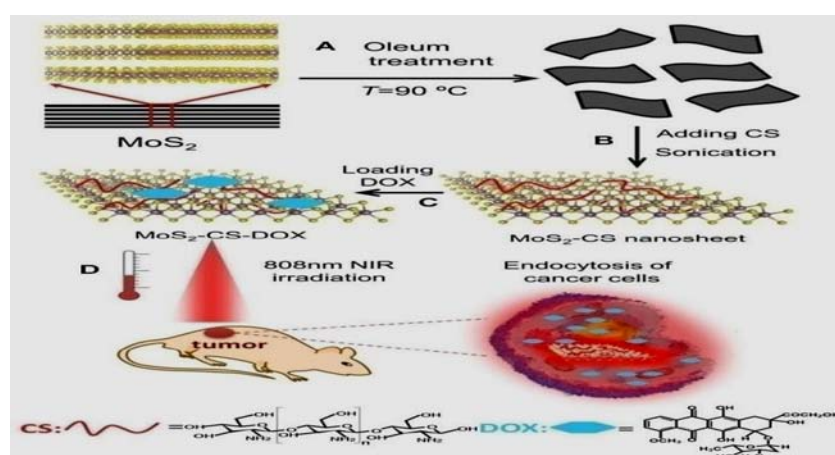


Fig 9. Molybdenum disulfide and CS sheets cause cancer cell death by NIR irradiation [47]

Metal Sulfides

Just now, metal sulfides have increased more consideration due to their low production cost, high photothermal conversion efficiency, and good photothermal stability as photothermal agents. Integrated PTT systems based on metal sulfides have been demonstrated to have potential to increase the efficiency of cancer therapy [26]. Nanomaterials can be classified in two distinct groups: two-dimensional (2D) and three-dimensional (3D) metal sulfide nanostructures. The applications of metal sulfides are doping effects, composite formation, porosity effects, and hetero structure formation.

2D Metal Sulfides

From the different group of 2Dimensional nanomaterials, 2Dimensional transition metal sulfides have enhanced the major point of different research studies and clinical uses. 2Dimensional transition metal sulfides regularly comprise of a layer of transition metals (such as W, Bi, Ti, Mo, Zr, and *etc*) fixed between two layers of sulfur particles. Molybdenum disulfide (MoS₂) is one of the major investigated 2Dimensional metal sulfide nanosheets utilized as drug nanocarriers for PTT because of its specific surface area and effective Photothermal treatment. However, due to its lower ability MoS₂ were dissolved in aqueous environment. These drawbacks of MoS₂ nanoagents can be treated by surface modification with different biopolymers together with serum bovine albumin, PEG, chitosan, glutathione, silk fibroin, and soybean phospholipids and poly acrylic acid. MoS₂ nanosheets were treated with lipoic acid with PEG and a particular cancer cell targeting possibility was increased by attach of folic acid to the surface which tie to the folate receptors on cancer cells drug-loaded MoS₂ nanocarriers shown remarkable in vivo synergistic antitumor effects. In contrast to linear once, it is revealed that more branched polymers are more effective in increase blood circulation at time. Folic acid grafted bovine serum albumin with MOS₂ used to treat breast cancers increase dispersibility and colloidal stability chitosan functionalized MOS₂ nanosheets are efficient and appropriate in PTT. Surface changes using silica are looked in order to monitor problems like poor colloidal dispersity after drug loading and structural limitations to the types of compatible drugs with these nanocarriers. Mesoporous silica nanostructures are mainly utilized in drug delivery due to excellent biocompatibility, more surface and cavity volumes, porosity, efficient stability, and easy modification. MOS₂ nanosheets with DOX (doxorubicin) molecules combination used as photothermal agents and drug moeity, photoacoustic imaging. In vivo practical showed that release of covered DOX (doxorubicin) molecules was triggered by NIR laser irradiation and the synergistic PTT caused significant coagulation necrosis of tumor tissues [26].

Tungsten disulfide (WS₂) nanoagents are another metal sulfide nanoparticles assessed for CT scan and PTT. Cheng et al. revealed the in vivo tumor death potential of WS₂ nanosheets as photothermal agents for the first time. WS₂ nanoagents with more surface area are unique for physical or chemical drug feeling. WS₂ quantum dots with small lateral size layered structure less than 5 nm have more potential for medical uses due to their great size for avoid the reticuloendothelial system absorption and effective excretion via kidney. WS₂ nanosheets can also use as a good imaging contrast agents. Cheng *et al.* observed coating of IONs assembled WS₂ with porous silica and PEG for multimodal imaging and photothermal therapy [33].

3D Metal Sulfides

Recently, cooper sulfides are other type of nanoparticles with variable Photothermal transfer

efficiency developed as major agents in cancer therapy. From these nanomaterials, copper sulfides nanomaterials not just have same near infrared (NIR) absorption as gold but they have some advantages rather than gold such as less toxicity, less production cost, nonstop NIR light absorption and simplicity of synthesis. The most used type of CuS nanostructures studied for PTT is their mesoporous form with silica coating. These nanostructures can deliver local heat to NIR light irradiation for cancer treatment and release load from the mesoporous silica core in a PH and NIR light responsive way for chemotherapy. CuS coated mesoporous carbon sphere was searched by Zhang et al. act as better drug carrier for effective PTT. They are mainly used in multimodal imaging and efficient Photothermal tumor targeting. [33].

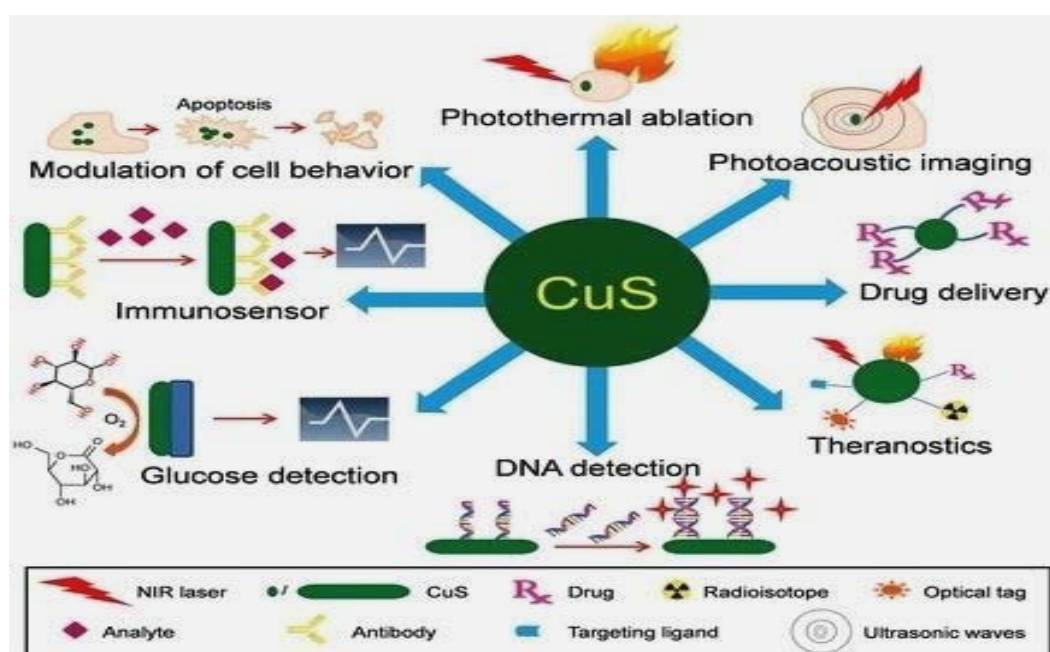


Fig 10. Illustrate the cooper sulfide nanoparticles and its applications. [46]

Bismuth sulfide nanoparticles are other 3D metal sulfides which owing to their high X-ray attenuation coefficient, biological tolerance, long circulation half-lives, and cost-effectiveness long circulation half-lives can be utilized in the biomedical uses.

Porous PEGylated Bi₂S₃ is simple but more powerful multimodal imaging and act as PTT nano-agent for precise and efficient cancer treatments. The multifunctional Bi₂S₃ nanoplatform indicates excellent cancer targeted bioimaging and cancer metastasis prevention [43].

Metallic Oxides

Metal oxides are translucent, porous, and hybrid nanostructures consisting of metal nodes and organic linkers. They have indicated great affinity in biomedical uses and also in cancer therapy as theranostic agents for synergistic combination therapy. Metal and metal oxide nanoparticles have risen as inventive device to direct the development of new therapeutic anticancer agents single or in combination with the classical treatments. The potential use of such nanoparticles against cancer is based on the apoptotic activity and autophagy, cell growth and metastasis inhibition, and formation of reactive oxygen species moreover radiosensitizing properties [43].

Zinc Oxide

Zinc oxide having a group of metal oxides has a broad band gap semiconductor which absorbs in the ultraviolet region. Zinc oxide nanoparticles are biocompatible and have antibacterial activity and show toxicity against splitting cancer cells. [48] Generation of reactive oxygen species is main cytotoxic mechanism ZnO nanoparticles leading to cell apoptosis. Nanoscale operation Zinc oxides have more numbers of valence band holes and conduction band electrons are available on the surface due to crystal defects. These electron-hole pairs get trapped by dissolved oxygen in the aqueous solution inside the cell resulting in the production reactive of oxygen species (ROS) [49]. Generally, cancer cells themselves produce more ROS than normal cells owing to their faster metabolic rate. Therefore, exogenous ROS forming agents like ZnO nanoparticles produce more ROS in cancer cells than normal cells resulting in great oxidative stress in the cancer cell and eventually killing the cell. The selective toxicity of ZnO nanoparticles will further be improved by external stimulation like photo activation. ZnO nanoparticles produce more electrons and holes which increases their ability to create ROS which could further enhance the growth inhibition of cancer cells. [50] Thus, ZnO nanoparticles could assume an important role in the PTT. The others use of zinc oxide particles are antidiabetic, bioimaging, gene delivery, immunotherapy, antibacterial, anticancer and drug delivery.

Copper Oxide Nanoparticles

Copper oxide nanoparticles are spherical in shape and the size of copper oxide nanoparticles are between 1-30 nm. Copper oxide nanoparticles mainly used in cancer treatment. Copper oxide nanoparticles dangerous effects on breast cancer cells and human lung cancer cells. In vitro studies show cuprous oxide causes apoptosis of tumor cells in vitro. After sometimes, some authors also studies antitumor effect of CuO particles in vivo, copper oxide nanoparticles used to treat lung tumors. CuO nanoparticles inhibit growth of metastasis of cancer tumors in mice. Copper oxide nanoparticles were fundamentally more toxic on human cell than other metal oxides nanoparticle. The antitumor effect of copper oxide nanoparticles were exhibited preclinically in different cancer types like nasopharynx cancer, cervical carcinoma, lung carcinoma, pancreatic carcinoma and hepatocellular carcinoma. The procedure of antitumor activity of CuO nanoparticles involve increase reactive oxygen singlet production (ROS) and oxidative stress which cause DNA destruction, increase death receptor expression and apoptosis caused cell death. CuO nanoparticles are also used as microbial agent. Used in wound healing, immunosensing. The antitumor activity of CuO nanoparticles has been demonstrated preclinically in various cancer types including hepatocellular carcinoma, lung carcinoma, nasopharynx cancer, breast cancer, cervical carcinoma, and pancreatic cancer. The procedure of the antitumor activity of CuO nanoparticles involves the increase of ROS (reactive oxygen species) production and oxidative stress which causes DNA damage, increased death receptor expression and ultimately apoptosis mediated cell death [49].

Titanium Oxide

Titanium oxides are frequently used nanoparticles in medical and therefore in cancer studies utilized in PDT, PTT, and drug transfer systems. The principle included photodynamic therapy is that a photo sensitizer comprising of a hydrophobic organic molecule is moved with electromagnetic radiation in the extent of visible or UV light to produce cytotoxic ROS that cause apoptosis. The nearest photodynamic therapy deal made use of inorganic and polymeric nanoparticles as passive carriers to increase the dissolution of the hydrophobic molecules and as plans for their delivery to the tumor site. A different approach contains the

use of inorganic nanoparticles, like titanium oxide, as immediate photo-sensitizing agents that can therefore be utilized in place of photosensitive molecules. Photo catalyzed titanium dioxide (TiO₂) nanoparticles were shown to death of cancer cells. However, the needed in situ presentation of UV light limits the utilization of such therapy in humans. One technique to control the disadvantage is the surface functionalization of TiO₂. Cell viability was shown to depend on particle concentrations, surface chemistry and cell types. Specifically, -NH₂ and hydroxyl (-OH) groups showed significantly higher toxicity than carboxyl (-COOH). The outcome proposes that functionalized TiO₂, and evidently other Nano particles, can be surface engineered for targeted cancer therapy. [49] Titanium oxide nanoparticles used in food and drug colorant, cosmetics, sunscreen component, photo catalyst, batteries, drug delivery, PDT and PTT.

Cerium Oxide Nanoparticles

Cerium nanoparticles are type of novel agents and very interesting material for radiation treatment; they have “smart” ability to prompt death of irradiated cancer cells, to protecting the surrounding tissue from radiation cause damage and oxidative stress. Hence, nanoparticles have the interesting element of acting as radio-protecting, also radio-sensitizing agents simultaneously. These nanoparticles specifically increased oxidative stress and apoptosis in cancer cells, while protecting normal tissues. [51] It was hypothesized that the selective toxicity of nanoparticles against cancer cells is due to the inhibition of the catalase like activity of cerium nanoparticles that done in acidic medium. The addition of other chemotherapies with Cerium NPs give a new plan in the therapy of cancer, with high lead for patient, at increasing cancer treatment and decreasing the harming side effects [49]. Cerium oxide nanoagents are also very well utilized metal oxides. Cerium oxide nanoparticles are utilized in anticancer activity, cytotoxicity, antibacterial activity, genotoxicity and antioxidant activity.

Iron Oxide (Fe₃O₄) NPs

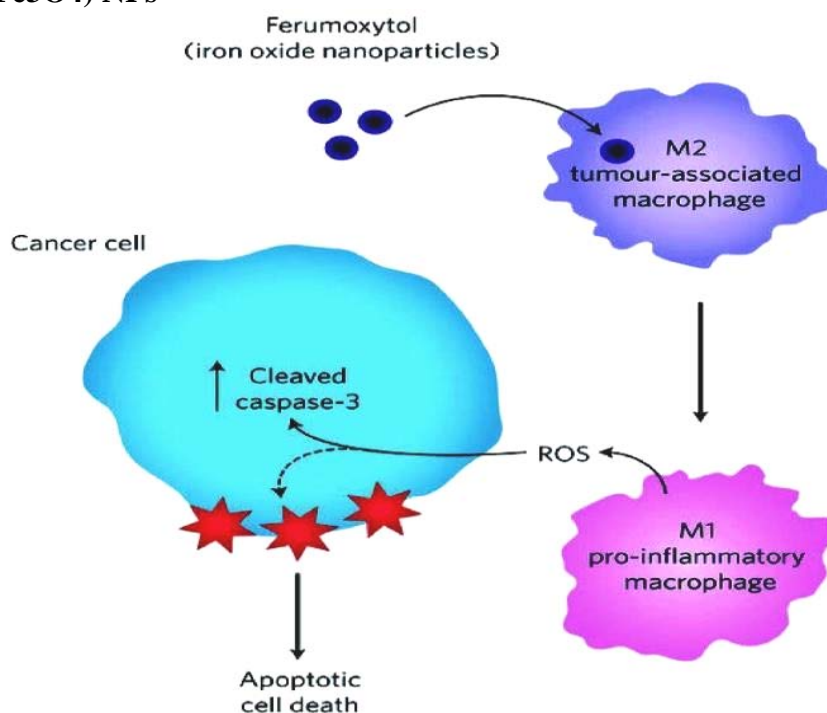


Fig 11. Iron oxide nanoparticles release ROS and lead to apoptosis of cell. [58]

Iron oxides nanoparticles are included in metal oxides. Iron oxides are widely used in Photothermal therapy due to its unicity, biodegradability and biocompatibility. They have wide applications in medicine of science. Iron oxides are utilized in various drug delivery, cell targeting and also in CT scan and MRI. Furthermore, they have unique surface they penetrate deeply in the tissue and target cancer cells and tissues [49]. Iron oxides increase the temperature due to high temperature increase they are used in cancer therapy. Iron oxides are available in different forms. They generate light and covert into heat increase in the temperature cause the cell death of cancer. Ferric ions are good candidate for cancer treatment. Iron oxides are combining with other Photothermal agents and form hybrid structure and used in Photothermal and various biological applications. These are basic details about iron oxides and role in cancer Photothermal therapy [52]. Iron oxides used in bioseparation, biosensor, targeted drug delivery, ROS regulation, immunoassay and tumor theranostics.

MOA of PTT (Photothermal Therapy)

In Photothermal treatment through electromagnetic waves we can cure different medical conditions like cancer therapy. In this technique with the help of particular band light a photosensitizer is displayed. The activation of this sensitizer leads to sensitizer into an excited state and releases heat. The formed heat kills the cancerous cells. In Photothermal treatment there is no need of oxygen to react with cells. [53] According to studies Photothermal therapy use longer wavelength and low energy light. This doesn't cause harm to surrounding cells and tissues. Process of Photothermal therapy is that while the agents absorb photons, some of the energy is released in the form of photons and release heat from it. When the heat is released it dilates tissues and increase blood flow and also accelerates the temperature is also known as photosensitizer. Photosensitizer absorbs heat and converts into by electromagnetic radiation, microwaves, visible light or radiofrequency. It increase temperature and caused hyperthermia and it causes protein denaturation and aggregation, damage to cytosol and celllysis of living cells also cause apoptosis and cell death lead to antitumor activity [54]. Photothermal agents generate heat lead to death of cancer cells and nano agents come out from body through renal. The selection of Photothermal agents is done according to their properties and therapeutic activity and they have high good Photothermal conversion and compatibility to tumor targeting. These are the basic detail about the Photothermal therapy how it works and how Photothermal agents produce heat [55].

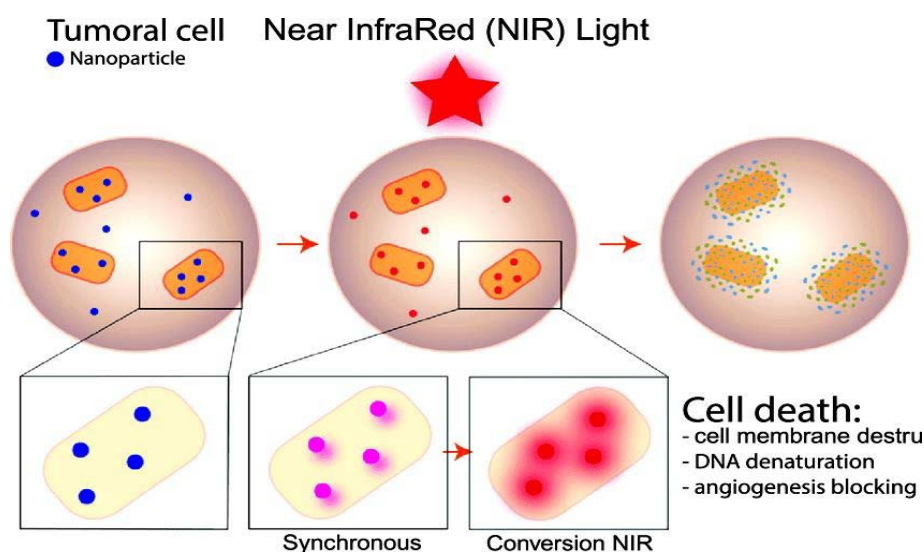


Fig 12. Mechanism of Photothermal Therapy [57].

Advantages

- 1) Main advantages
- 2) It has spatiotemporal selectivity.
- 3) PTT is oxygen independent.
- 4) It is immunogenic.
- 5) Invasive technique.
- 6) High targeting.
- 7) Good acceptability.
- 8) It is most popular because it doesn't cause the death of normal cells.
- 9) It increases efficacy and safety.
- 10) It increases water solubility.
- 11) It reduces systemic toxicity.
- 12) It has ability of antigen targeting.
- 13) They are used to overcoming drug resistance.
- 14) They provide strongly localized heating.
- 15) It is used in superficial malignant tumors.
- 16) It improved temporal and spatial parameters of drug therapy.
- 17) Real time temperature is also measured through this technique.
- 18) They are also used for CT imaging and MRI.
- 19) They use to delivery of high payload radio nuclides to tumor cell.
- 20) They provide specific multivalent attachment of targeted molecules to surface of nanocarriers.
- 21) They provide selective application of heat to cancer cells only.

Disadvantages

- 1) Leakage of the drug to normal organs.
- 2) Chances of incompatibility with the immune system.
- 3) It causes radiotoxicity.
- 4) Long term application of carbon nanotubes may have cancer risk.
- 5) The chances of allergic reactions.
- 6) Limited for use preliminary in superficial malignant tumors.
- 7) The inhomogeneity of NIR density.
- 8) Possibility of thermotolerance and thermoresistance in some sets of patients.
- 9) Heterogeneous distribution of nanoparticles.

FUTURE PROSPECTS OF PHOTOTHERMAL THERAPY

Past two decades, nanomaterials play a major role in development of every field. Advancement in nanotechnology is increases day by day in the globe. Nanomaterials have broad scope in the future. Nanomaterials are widely used in clinical diagnosis, controlled drug delivery, and especially in tumor therapy due to their nano size, biocompatibility, surface chemistry, good stability, and low toxicity in biological systems. Nanomaterials in tumor therapy have great applications they will improve current methods of tumor cell detection, tumor imaging, and tumor therapy and it has low toxicity than conventional tumor treatments. The main problem of nanomaterials is chronic and acute toxicity. The virulence of nanomaterials is not ignored in antitumor therapy [56].

Nanomaterials attach to cyto membranes by adsorption and cause cell damage by protein denaturation, DNA damage, and producing reactive oxygen species. Carbon nanotubes damage lung tissue, damage respiratory and cardiovascular system also induce cell apoptosis.

Carbon nanotubes can improve their water solubility, biocompatibility and safety which are currently insufficient. It is mandatory to ensure its safety before administration into human body. Carbon nanotubes can improve their properties and then it should enter into specific body. It is indicated that before use in antitumor therapy need to understand about nanomaterials deeply. Therefore, the lasting toxicity of nanomaterials in human body is also studied. Evolution of tumor therapy may be a multidisciplinary field, which contain research on tumor biology, tumor immunology, molecular biology, and nanomaterials. Nanomaterials are utilized in treatment of tumor therapy [1]. The future of anticancer therapy will involve the combinations of nanomaterials to obtain great anticancer effect. To get good effect the materials should be combining in well manner by understanding its mechanism its side effects to crash tumor. Combinational therapy to treat cancer will be designed [1].

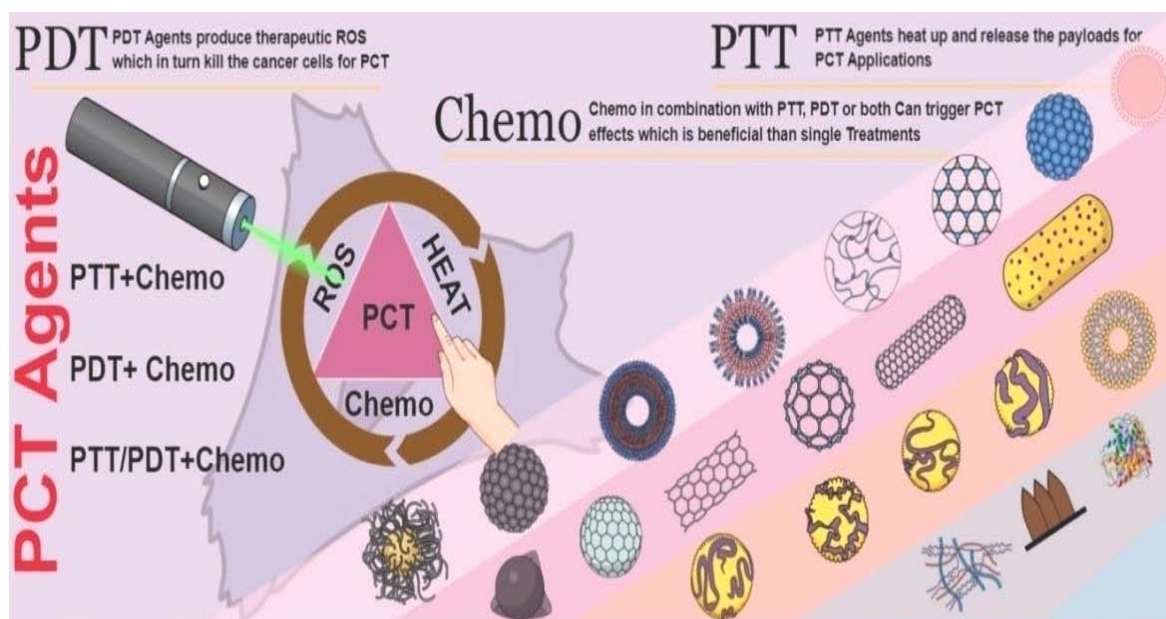


Fig 13. In the future combinations of chemotherapy, PDT and PTT are beneficial for better cancer treatment [59].

CONCLUSION

Overall, from this review article it can be concluded that various Photothermal agents are developed with great therapeutic efficacy to treat cancer. In addition, that various organic and inorganic Photothermal agents have their own properties, and they show their selective non-invasive cancer treatment. PTT continues used for clinical applications. In the future, Photothermal agents and their combinations will satisfy the need of tumor therapy. Photothermal agents their applications are studied. Photothermal therapy will be widely used in future.

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