

Review

Application of marine-based gold nanomaterials in cancer therapy: A mini-review

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Abstract: Cancer is one of the health concerns in modern societies. The application of nanotechnology in medical sciences has created new possibilities for the diagnosis, imaging and the treatment of tumors in humans. The present article reviews the application of marine-based gold nanoparticles in diagnosing and treating cancer. The main data were collected from research article on the application of different marine-based gold nanoparticles in detecting and imaging cancer cells as well as in drug delivery system in treatment of cancer. Chitosan is the most used marine natural compound used to fabricate gold nanocomposites and the most reported application of this type of nanocomposites is related to drug delivery system. Despite the excellent anticancer potential of different marine natural products, less studies have been conducted on the use of their compositions with gold nanoparticles in cancer therapy than other materials. Moreover, most reports available in this filed are related to their application as a drug delivery system not anticancer drug. In general, there are still challenges and limitations to the use of nanoparticles in medicine, it is hoped that in the near future nanoparticles will create a dramatic revolution not only in oncology but also in medicine.

Keywords: cancer; gold nanoparticles; marine; drug delivery; imaging; detection

1. Introduction

Despite progress in detection and treatment of cancers, cancer is still one of the most common causes of death today. According to WHO, cancer caused approximately 10 million deaths in 2020 in worldwide [1] and was the second leading cause of death following heart disease [2,3]. Some carcinogens are physical factors such as ultraviolet radiation, chemical factors such as cancer-inducing chemical compounds, cigarette smoke, unbalanced diet, occupational factors, hereditary factors, hormonal factors, metabolic factors and biological factors, especially some bacteria and viruses [4-9]. The most common types of tumors leading to death worldwide are lung, colon and rectum, liver, stomach, and breast tumors, respectively [10]. Today, the most important treatment for cancer is chemotherapy and radiotherapy [11-13], which in addition to numerous side effects [14,15], also create drug resistance in the patient [16,17]. Other disadvantage of common cancer treatment methods is that in these methods, both healthy and cancer cells are affected by the drug and undergo changes, which cause that not enough drug reaches the cancer cells and the excretion of those drugs also increases [18]. Thus, it is essential to enhance the rate of drug injection, which is not economical and is not be possible depending on the general condition and tolerance of the patient. Another important obstacle in treating cancer is its late diagnosis [19,20], which unfortunately causes to have no enough time to treat cancer and

it mostly ends up with death of the infected person shortly after the diagnosis. Therefore, studies are ongoing on finding effective and non-destructive strategies for early diagnosis of cancer and it is yet needed to discover a suitable drug or carrier of medicine to be used as an effective chemotherapeutic agent.

Nowadays, nanomedicine, the application of nanotechnology in healthcare, has come to the aid of treatment and diagnosis of several diseases [21]. In this context, new strategies for diagnosing and treating cancer have been proposed due to better understanding of tumor biology and advances in cancer nanotechnology [22]. Nanometer-scale particles act in amazing ways as the properties of materials at the nanometer scale change and they exhibit special optical, electronic and structural properties [23-25]. Due to these unique properties, nanoparticles can be used in imaging, diagnosing and treating cancers [26,27]. In modern medical science, using these features, nanoparticles are engineered to be able to deliver high doses of cytotoxic drugs to the cancer site while protecting healthy cells from the side effects of cytotoxic drugs [28]. Moreover, to diagnose cancer at an early stage, scientists must be able to detect molecular changes (even if they occur in a small percentage of cells). Meanwhile, the ability of nanostructures to enter cells and analyze them is promising [29]. Among different nano particles, gold nanoparticles (AuNPs) have extensively attracted attentions as a leading nanomaterial for hybrid cancer therapy [30].

In recent years, owing to the side effects of chemotherapy drugs [31,32], people prefer to use natural products to treat cancer [33]. One of these natural resources with high healing properties are plants and living organisms in different depths of the sea. Deep sea has resulted in natural compounds with high therapeutic properties due to conditions such as darkness, lack of oxygen, high pressure and low temperature [34]. The results of scientific studies on medicinal properties of these products are promising for the treating many diseases, including cancer, and are able to reduce the toxicity of other drugs due to their antioxidant properties [35].

This review tries to summarize studies conducted on the application of marine based gold nano composites in cancer cell therapy and suggest some ideas for future studies in this field. For this purpose, advances of gold nanomaterials and marine natural compounds in cancer therapy are briefly described and then, marine based nano gold materials used in cancer therapy are summarized and discussed. Finally, some suggestions are provided for future studies in this field.

2. Advances of gold nanomaterials in cancer treatment

Gold nanomaterials have unique properties compared to other metal nanoparticles that have made them suitable for using in cancer nanotechnology (Figure 1). Gold nanomaterials are strongly suitable drug carrier owing to simplicity in their modification with special ligand, drug or protein to bind selectively to cancer cells, and their large capacity to load drug because of the large ratio of surface area to volume. For example, the application of gold nanomaterials in delivery of cisplatin, carboplatin, nedaplatin and oxaliplatin have been reported [36-38]. Owing to their versatile surface chemistry [39], unique optical and surface plasmon resonance (SPR), photoresponsive properties, long body circulation times, selective accumulation at target sites via the enhanced permeability and retention (EPR) effect or modifying surface, great absorption in the near-infrared region, and easy functionalization, they have been greatly used for imaging cancer cells using different techniques such as computerized tomography (CT), photothermal/photoacoustic imaging, and Raman spectroscopy. Gold nanomaterials have applied in radiosensitization to increase efficacy of radiation therapy, which causes effective cancer cells killing. In general, the radiosensitization mechanism is yet unclear, but it can be attributed to enhanced adsorption of photon of high-Z elements and transferring a larger amount of primary ionizing photon energy to cancer cells. The use of gold nanomaterials in inducing hyperthermia (40–45° C) of tumor has been also reported [40]. Gold nanomaterials are promising gene delivery vehicles, due to their easy surface modification and large specific surface area. Besides abovementioned applications, gold nanomaterials have been used to stabilize other drug carriers and to promote releasing drugs. On the other hand, AuNPs are of

interest to scientists for in vivo studies because they are non-reactive in biological systems, bio compatible and low toxic. Despite the importance and advances of GNPs in treating cancer, according to <https://clinicaltrials.gov/>, there have been limited clinical trials on the use of this nanomaterial in cancer therapy.

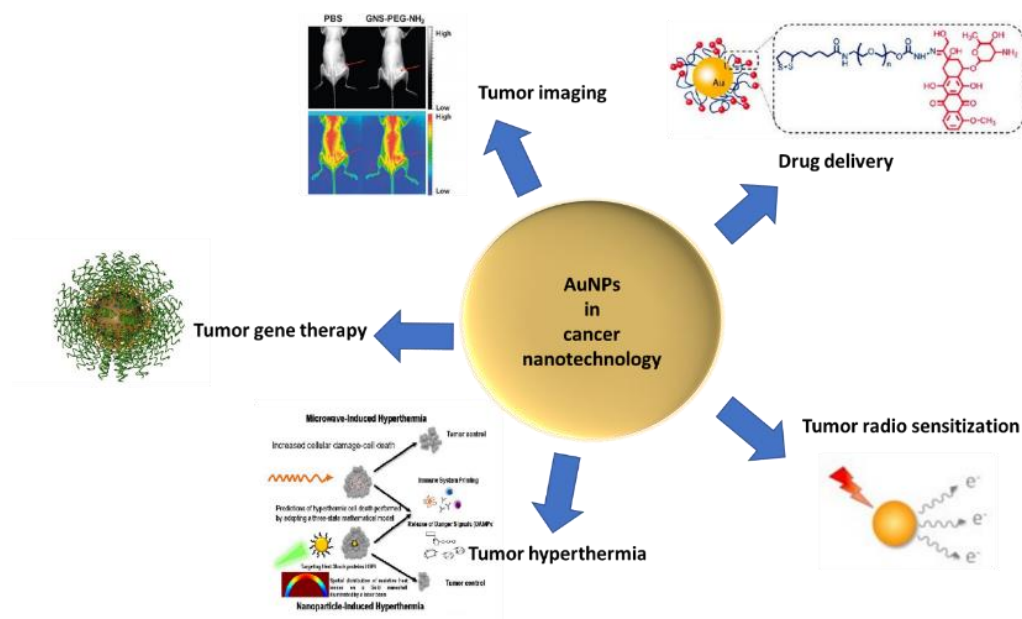


Figure 1. Applications of AuNPs in cancer diagnosis and treatment.

3. Advances of marine natural products in cancer treatment

The seas cover 70% of the earth's surface [41]. The biodiversity of the seas is considerably greater than the land surface and accounts for almost 70% of all living organisms [42]. The marine environment is considered as a rich source of natural products with wide therapeutic applications [43]. Many bioactive compounds with anti-cancer potential have been extracted from diverse marine organisms such as microalgas [44], sponges [45], mollusks [46], tunicates and other marine organisms. According to various studies, their anti-cancer potential is mainly due to their antioxidant [47] and anti-proliferative [48]. These compounds discovered from marine organisms stimulate cell death by various mechanisms such as apoptosis [49], effect on anti-microtubule [50], angiogenic inhibition [51], antiproliferative [52] and cytotoxic [53]. For example, shark cartilage has been shown to have inhibitory effects on angiogenesis, metastasis, cell adhesion and proteolysis. Oral consumption of shark cartilage dry powder has been widely used as a treatment for cancer [54]. The provision of anti-cancer drugs from marine sources has opened a new horizon for treating various cancers with drug-resistant properties. The future of medicine is from that sea, and the sea will play a major role in the discovery of drugs, especially anti-cancer drugs. Some of these compounds reported during recent year have been listed in Table 1. There are about 300 completed clinical trials registered on <https://clinicaltrials.gov/> that 38 of which are related to fish oil.

Table 1. Some of anti-cancer marine natural products reported over 2021.

Compound	Cancer type	Mechanism	Ref.
14-3-3 protein Hsp70 Rab3 Arylsulfatase B Serine protease 4H-chromen-4-one	Ovarian cancer	Anti-proliferative activity	[55]
	Pancreatic cancer Colon cancer	-	[56]
Benzo[g][1]benzopyrano[4,3-b]indol-6(13H)-ones	Cervical cancer Lung cancer Breast cancer	Inhibitory effect	[57]
Dieckol	Pancreatic cancer	Apoptosis and inhibition	[58]
Epiremispore E Epiremispore B Fucoxanthin	Lung cancer	Bcl-2, Bax, and caspase 3 signaling cascade	[59]
	Pancreatic cancer	Up-regulating the expression of integrin β 1, FAK, Paxillin, FYN, AKT, and PPAR γ	[60]
MBS 3.2	Colorectal cancer	-	[61]
Pyrrospirone F Chrysophanol Physsonin Purpuride G Streptoglutarimide H	Lung cancer	Anti-proliferative activity	[62]
	Lung cancer	Anti-glioma activity	[63]
The ethanol extract of <i>Aiptos suberitoides</i>	Breast cancer	Suppressing Cell Viability, Cell Proliferation and Cell Migration	[64]
Tilapia piscidin 4	Synovial sarcoma	Disrupting oxidative status Promoting mitochondrial hyperpolarization Causing calcium overload	[65]

4. Advances of marine based gold nanocomposites in cancer treatment

Different types of marine based gold nanocomposites have been fabricated for various purposes. One of main reasons to fabricate GNPs using marine source is related to the interest of scientists to produce economic and eco-friendly materials through green procedures [66,67]. In general, chemicals and solvents used in chemical synthesis procedures, have hazardous impacts on the environment and human health [68]. Besides, it is well known that marine natural compounds are rich sources of bioactive materials [69]. Therefore, it is expected that we could design affective drugs for different diseases with the aid of bioactive properties of marine natural compounds and unique properties of GNPs. In this regard, some recent reports on the use of these materials in different areas have been summarized in Table 2.

Table 2. Different application of marine based nano gold materials.

Material	Application	Ref.
(PABA-SAL)@AuNPs	Biomedical applications	[70]
APTMS-CS-AuNPs	Antimicrobial	[71]
AuNPs/CS-GR-IL-Fc cry/SPCE	Measuring prostate-specific antigen	[72]
AuNPs/Lac/Alg	Detection of Fe(III)	[73]
CS-AuNPs	Biomedical devices	[74]
CS-AuNPs	Raman spectroscopy	[75]
CS-AuNPs	Biosensor	[76]
CS-AuNPs	Antimicrobial	[77]
CS-AuNPs	siRNA delivery and silencing	[78]
CS-AuNPs	Detection of uric acid	[79]
CS-AuNPs	Nanocatalyst	[80]
CS-AuNPs	Biomemristor	[81]
CS-AuNPs	Antibacterial	[82]
CS-TiNPGF	Determination of acetaminophen	[83]
Fe ₃ O ₄ @Alg-Au NPs	Nanocatalyst	[84]
GNPs-chitosan-horseradish peroxidase	Biosensor	[85]
Ibuprofen lysinate-CS-AuNPs	Anti-inflammatory	[86]
Nano gold-marine algae sodium-Alg	Electric transport	[87]
PAA/CS/Au nanocomposite hydrogel	Antimicrobial activity	[88]
SA-AuNPs	Detection of ascorbic acid	[89]
Sea urchin-PVP-AuNPs	Transient immune activation	[90]
SUGNPs	SERS platform	[91]
ZnSA-AuAMP hydrogel	Controllable regulation of nanozyme activity	[92]

Abbreviations: (PABA-SAL)@AuNPs: Gold nanoparticles/polyaniline boronic acid/sodium alginate aqueous nanocomposite, APTMS: 3-aminopropyltrimethoxysilane, AuAMP: 5'-monophosphate capped Au nanoclusters, AuNPs/Lac/Alg: gold nanoparticles on novel nanocomposite lactose/alginate, CS-GR-IL-Fc: Chitosan, graphene, ionic liquid and ferrocene, NPGF: Nano-porous gold film, PAA/CS/Au: Polyacrylic acid/chitosan/gold, PVP: Polyvinylpyrrolidone, SA-AuNPs: Reduced/stabilized gold nanoparticles, SERS: Surface Enhanced Raman scattering, SPCE: Screen-printed carbon electrode, SUGNPs: Sea urchin-like gold nanoparticles.

Despite marine based gold nanocomposites have been widely investigated for diverse medicinal properties [93], to the best of our knowledge, limited investigations have been reported on the use of marine based gold nanocomposites in cancer therapy. Table 3 shows a list of marine based nano gold materials used for different purposes in cancer nanotechnology. This list was provided through searching key words "gold" and "cancer" and "marine, alga, micro alga or sponge" and "nano, nanoparticle, nanocomposite or nanomaterial" at Google Scholar database. According to Table 3, despite the wide variety of marine natural compounds and their great potential as anticancer drug, their composites with gold mostly limited to chitosan-gold NPs in which chitosan plays role as stabilizer not anticancer drug. The role of gold in these compounds is mostly as a drug carrier.

Table 3. Application of marine based gold nanomaterials in cancer nanotechnology.

Type of cancer	Nano-composite	Species	In vivo/In vitro	Application	Ref.
Brain cancer	Apt-Dox-CS-Au-5FU NPs	Human	<i>In vitro</i>	Anticancer	[94]
Breast cancer	Actinomycetes-AuNPs	Human	<i>In vitro</i>	Anticancer	[95]
Colon cancers					
Breast cancer	CMC-AuNPs	Human	<i>In vitro</i>	Drug delivery	[96]
Cervical cancer					
Lung cancer					
Breast cancer	CS-GNPs	Human	<i>In vitro</i>	Drug delivery	[97]
Breast cancer	CS-GNPs-DOX	Human	<i>In vitro</i>	Drug delivery	[98]
Breast cancer	CS-g-PNVCL nanofibers-G-GSNPs	Human	<i>In vitro</i>	Drug delivery	[99]
Breast cancer	DOX-Apts-CS-AuNPs	Mouse	<i>In vivo</i>	Drug delivery	[100]
Lung cancer					
Breast cancer	FA-CS-GNP-5-FU	Human	<i>In vitro</i>	Drug delivery	[101]
Breast cancer	FCG5-FU-NPs	Human	<i>In vitro</i>	Drug delivery	[102]
Hepatic cancer					
Kidney cancer					
Breast cancer	G1	Human	<i>In vitro</i>	Drug delivery	[103]
Breast cancer	GC-AuNPs	Human	<i>In vitro</i>	PAI	[104]
Breast cancer	J-Au-CS	Mouse	<i>In vivo</i>	Imaging	[105]
Breast cancer	PTX-COS-AuNPs	Human	<i>In vitro</i>	Drug delivery	[106]
				PAI	
Breast cancer	SPION@Au-CS-DOX-FA NPs	Human	<i>In vitro</i>	Anticancer	[107]
Cervical cancer	Folate HTCC-AuNPs	Human	<i>In vitro</i>	Drug delivery	[108]
Colon cancer					
Liver cancer					
Cervical cancer	Au@CS-PMPC NPs	Human	<i>In vitro</i>	Drug release	[109]
				Fluorescence im- aging	
Cervical cancer	CS-GNPs	Human	<i>In vitro</i>	Drug delivery	[110]
Cervical cancer	DOX-AuNPs-CMC	Human	<i>In vitro</i>	Drug delivery	[111]
Colon cancer	Alginate hydrogel- GNPs-cisplatin	Mouse	<i>in vivo</i>	Drug delivery	[112]
Colon cancer	alginate-AuNPs	Mouse	<i>in vivo</i>	Drug delivery	[113]
Colon cancer	As-AuNPs	Human	<i>In vitro</i>	Anticancer	[114]
Colon cancer	EPI-CAO-AuNPs	Human	<i>In vitro</i>	Drug delivery	[115]
Colon cancer	Vibrio alginolyticus-AuNPs	Human	<i>In vitro</i>	Anticancer	[66]
Gastric cancer	marine bacterium GNPs	Human	<i>In vitro</i>	Drug delivery	[116]
Lung cancer					
Liver cancer	Chitosan-bee venom-GNPs	Rat	<i>in vivo</i>	Drug delivery	[117]
Liver cancer	Chitosan-GNPs	Human	<i>In vitro</i>	Gene therapy	[118]
Liver cancer	Macroalgae GNPs	Human	<i>In vitro</i>	Drug delivery	[119]

Lung cancer

Prostate cancer Cs/PVA/AuNPs Human *In vitro* Drug delivery [120]

Abbreviations: As-AuNPs: A. spicifera-mediated gold nanoparticles, CMC-AuNPs: N,O-carboxymethyl chitosan effectively stabilized gold nanoparticles, Cs/PVA/AuNPs: Chitosan/Poly (Vinyl Alcohol) Blend Doped with Gold Nanoparticles, DOX-Apts-CS-AuNPs: Doxorubicin and aptamer against Forkhead box M1 chitosan-Gold nanoparticles, DOX-AuNPs-CMC: Doxorubicin immobilized on gold nanoparticles capped with carboxymethyl chitosan, FA-CS GNP-5-FU: Folic Acid Conjugated Conjugated-Chitosan Functionalized Gold Nanoparticles, FCG5-FU-NPs: Folate linked counterpart 5-fluorouracil encapsulated chitosan functionalized gold nanoparticles, G1: Chitosan-functionalized gold nanoparticles, GC: glycol chitosan, GC-AuNPs glycol-chitosan-coated gold nanoparticles, HTCC: N-(2-hydroxy)propyl-3-trimethylammonium Chitosan Chloride, PAI: Photoacoustic imaging, PMPC: benzaldehyde-terminated poly[(2-methacryloyloxy) ethyl phosphorylcholine], PTX-COS AuNPs: Paclitaxel-loaded chitosan oligosaccharide-stabilized gold nanoparticles, TCA: Taurocholic acid.

5. Conclusion and future outlook

The current review highlighted advances of GNPs, marine natural products and marine based gold nanomaterials in different aspects of cancer therapy. GNPs have unique properties making them good candidate for using in biomedical areas specially in cancer nanotechnology. The use of these nanoparticles has been reported in drug delivery, imaging, radio sensitization, hyperthermia and gene therapy for cancer. Despite the great interest of scientists to use of this nanoparticle for medical purpose, there has been no registered clinical report on the use of it in cancer therapy according to <https://clinicaltrials.gov/>. There are many available reports on the anticancer activity of a variety of marine natural products and numerous clinical reports on the use of it in cancer therapy have been registered in <https://clinicaltrials.gov/>. Considering the advances of both GNPs and marine natural products in cancer therapy, it is expected combining them results in more effective drugs and delivery systems, which are also imaging contrast agents. Reviewing studies performed on marine based gold nanocomposites showed these compounds mostly contain chitosan as a stabilizer of GNPs and are used as drug delivery systems. Accordingly, it is greatly recommended to conduct studies on synthesizing these compounds as anticancer drugs and imaging contrast agents. Moreover, most of the studies have been conducted under in vitro condition, designing in vivo studies using these materials is greatly recommend considering the biocompatibility, low toxicity and bioinertness of these materials.

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