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Chapter- 5

Use of hyaluronic acid in targeted therapy of cancer

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Keywords: chemotherapy; combination cancer therapy; hyaluronic acid (HA); anomedicine; nanoparticles (NPs); targeted therapy

Abstract:

Currently, cancer is one of the leading causes of death worldwide. That's why scientists all over the world are researching how to deliver drugs against cancer cells better. The use of Hyaluronic acid in drug delivery against cancer cells has shown a glimmer of hope. Being a natural polymer, it is non-toxic, bio-degradable, non-immunogenic and non-inflammatory. At the same time, HA can recognize and bind to several receptors present in cancer cells, such as CD44, Receptor for HA Mediated Motility (RHAMM), Lymphatic Vessel Endothelial Receptor-1(LYVE-1). Not only this HA increases the solubility, bioavailability, stability, targeting efficiency of various anticancer drugs and reduces toxicity. Because of the above advantages HA can be used very successfully in the preparation of various anti-cancer formulations. Conjugation of HA with drugs, formation of HA based nanoparticles and HA coated inorganic nanoparticles are few of them. In this review paper I have tried to detail the application of the above anti-cancer formulations which makes HA suitable for future biomedical applications in cancer treatment.

Introduction:

According to World Health Organization the second most leading cause of death is cancer. About one out of six death is due to cancer (WHO Report on Cancer: Setting Priorities, Investing Wisely and Providing Care for All, 2020). Cancer took 9.6 million lives only in 2018. Not only that, 70% of deaths due to cancer are from developing and underdeveloped countries. The new cancer cases worldwide are predicted to increase from approximately 18.1 million in 2018 to 29.4 million in 2040 (WHO Report on Cancer: Setting Priorities, Investing Wisely and Providing Care for All, 2020). Therefore, a substantial amount of research is going on worldwide to treat cancer. For the last few decades different approaches have been taken to develop anti-cancer drugs. Nanomedicine is one of the most effective approaches to treat cancer. The novel properties of nanoparticles make them more effective as anticancer drugs. Recent research has focused on how these nanomedicines can specifically target cancer cells. This will not only improve bioavailability of the drug but also reduce the side effects on non-target cells. There are several strategies by which we can target a cancer cell, they are broadly divided into two categories-

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active targeting and passive targeting (Sutradhar and Amin 2014; Dadwal et al. 2018). In passive targeting strategies the therapeutic agents can bind different cells of the body including the cancer cells. Therapeutic agents, in this method, can have a detrimental effect on other cells. Active targeting is more effective, because in this method therapeutic agents are targeted towards several cancer specific biomarkers. Therefore, therapeutic agents only bind to cancer cells, thereby reducing the side effects on other healthy cells. Hyaluronic acid (HA) can bind with some cancer cell specific receptors, such as CD44, Receptor for HA Mediated Motility (RHAMM), Lymphatic Vessel Endothelial Receptor-1(LYVE-1) (Jian et al. 2017). CD44, RHAMM, LYVE-1 molecules are over expressed in several types of cancer (e.g., breast cancer, prostate cancer, colon cancer, acute myeloid leukemia, etc.) (Jian et al. 2017). Hyaluronic acid binds specifically with these markers. Therefore, HA is a good agent in active targeting of nanoparticles against cancer. In this paper we have tried to summarize different approaches that uses HA in targeting cancer cells. Additionally, we have included some successful research works and findings in this field to show the potential of HA in active drug delivery against different types of cancer.

Properties of HA that makes it a good agent for drug delivery system:

Hyaluronic acid (HA), also known as hyaluronan is a natural glycosaminoglycan found mainly in connective tissue, neural tissue and extra cellular matrix. Its structure is composed of alternately repeating units of D-glucuronic acid and N-acetyl-D-glucosamine linked by alternating β-(1→4) and β-(1→3) glycosidic bonds. Its chemical formula is $(C_{14}H_{21}NO_{11})n$ and molecular weight ranges from five thousand to twenty million kilo Dalton (Wickens et al. 2017). HA can bind with some cancer cell specific receptors, such as CD44, Receptor for HA Mediated Motility (RHAMM), Lymphatic Vessel Endothelial Receptor-1(LYVE-1) (Jian et al. 2017). Another property of HA that make it suitable for anticancer drug delivery is that it is nontoxic, biodegradable, non-immunogenic, non-inflammatory (Oh et al. 2010). The carboxyl groups of the glucuronic acid unit and hydroxyl groups of the N-acetyl-D-glucosamine unit can be chemically modified to obtain HA derivative. Therefore, HA itself can be surface modified to carry additional drugs, so that they can be specifically delivered to specific cancer cells, not only this it is very easy to attach HA on a suitable nanoparticle for improving bioavailability.

Use of HA in targeted drug delivery against cancer:

HA can be used in several ways for targeting cancer cells. They can be classified into following three broad categories-

1) Drug conjugated HA.
2) HA based nanoparticles
3) Inorganic nanoparticles coated with HA.

Drug Conjugated HA:

Chemotherapy is one of the most common methods for cancer treatment. Doxorubicin, Paclitaxel, Cisplatin, Gemcitabine etc. drugs are commonly used for cancer chemotherapy (Jian et al. 2017; Lee et al. 2020). These drugs are very effective in destroying cancer cells, but they

can impose detrimental side effects on other non-target cells of the body (Schirrmacher 2019). To protect normal body cells from side effect of above said drugs we need to deliver these drugs in a targeted method so that they can specifically bind to only the cancer cells. HA have several properties, discussed earlier, make it very suitable to be conjugated with anticancer drugs (Arpicco et al. 2014; Wu et al. 2019). There are two ways by which drugs can be conjugated with HA. The functional groups of some drugs can be attached directly with the carboxylic, hydroxyl, and acetamido groups of HA. Few drugs need conjugate linkers (such as ester linkers and amide linkers) to attach with HA (Arpicco et al. 2014).

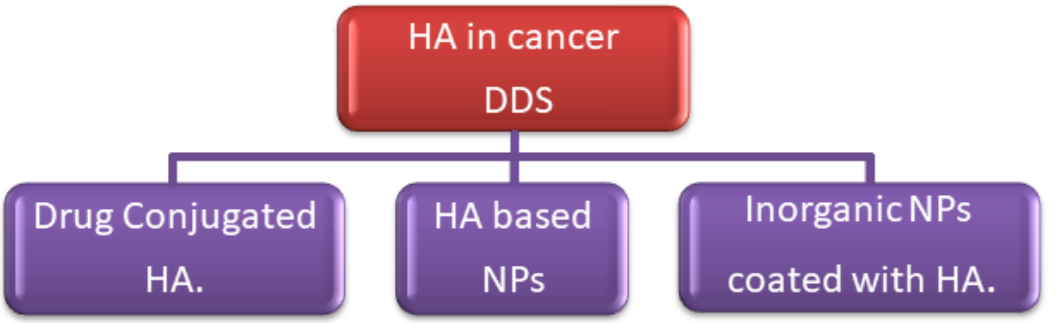


Figure 1. Different approaches of using HA in targeted drug delivery against cancer

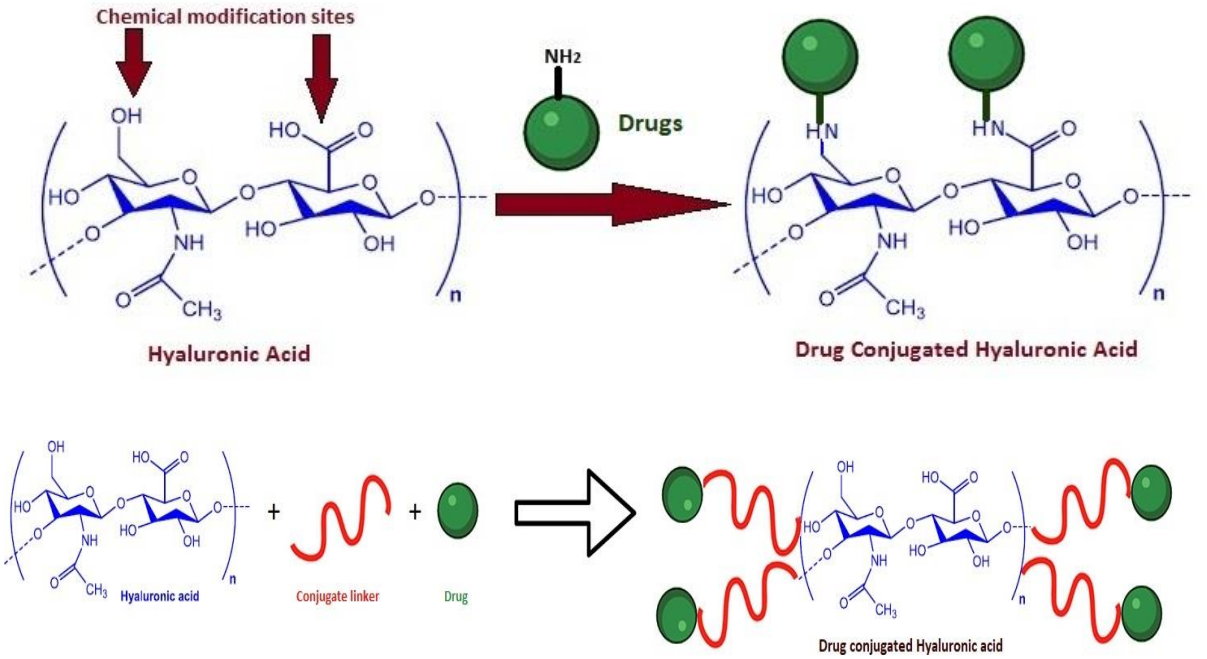


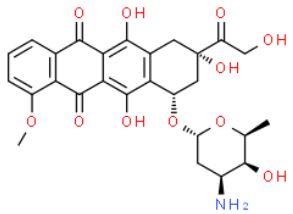
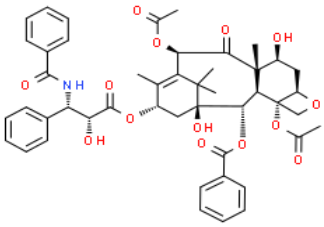
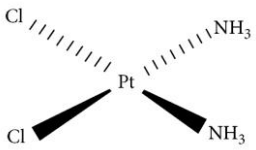
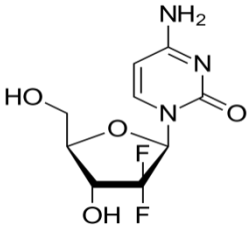
Figure 2. Conjugation of drugs with HA, either by direct linking or by using conjugate linkers.

Drug-conjugated HA improves targeting of drugs, stability of drugs, and better uptake of drugs by the cancer cells (Choi et al. 2012). These drugs conjugated HA selectively target cancer cells and improve the efficacy of the drug due to enhanced permeability and retention.

Doxorubicin conjugated HA has shown great potential as liver-targeted, pH-responsive and dose-dependent drug delivery system in the prevention and treatment of liver cancer (Tian et al. 2019). Doxorubicin conjugated HA have also shown more effectiveness against murine breast cancer cell line 4T1 & Female BALB/c mice when compared to free drugs. It has also shown stronger inhibitory effects and lower systemic toxicity than the free drug (Yu et al. 2020). Similar effects were found in MDA-MB-231 and 4T1 breast cancer cell lines (Vogus et al. 2017). Hyaluronic acid-doxorubicin conjugate coated with gold have been used successfully against melanoma cells for bioimaging, chemotherapy and thermotherapy (Kim et al. 2012) Paclitaxel conjugated with HA have shown improved biodistribution and increased cytotoxicity against colon cancer, ovarian cancer, breast cancer cell lines (Leonelli et al. 2008). Paclitaxel conjugated HA have shown improved targeting and apoptosis in Multi-Drug Resistance and Triple-Negative Breast Cancer Cell lines (MCF-7, MDA-MB-231, and MCF-12A) (Gote et al. 2021). Paclitaxel-hyaluronic acid bioconjugate (HYTAD1-p20) showed efficient inhibitory effect against RT-4 and RT-112/84 bladder cancer cells (in vitro) and also on BALB/c, SCID mice & Fischer female rats (in vivo) with less damage to mucosal membrane (Rosato et al. 2006). Ultra small hyaluronic acid-Paclitaxel nanoconjugates have been successfully used to control brain metastases of breast cancer cells (MCF-7 & MCF-7/AdrR cell line) (Mittapalli et al. 2013). HA conjugated cisplatin targets CD44 positive lung cancer cells and increase the efficacy of the drug with no side effects (Fan et al. 2015). Hyaluronic acid- Cisplatin conjugate breast cancer cells (MCF7 and MDA-MB-231) metastasis to regional lymph nodes with no adverse effects (Cai et al. 2008). Cisplatin–hyaluronan conjugates have reduced toxicity of cisplatin and improved drug delivery to lung cancer of Sprague–Dawley rats (Xie et al. 2010). Similar effects were found when HA conjugated cisplatin was applied against head and neck squamous cell carcinoma of Nu/Nu mice (Cohen et al. 2013). HA conjugated gemcitabine have shown improved cellular uptake, cancer targeting and therapeutic efficacy inhibiting proliferation of CD44-overexpressing HuCCT1 biliary cancer cells when compared to free drugs (Noh et al. 2015). Gemcitabine-conjugated HA has been successfully applied in targeting, imaging, and killing of $CD44^+$ pancreatic cancer, colon cancer, melanoma cell lines (Dubey et al. 2017). HA-conjugated nimesulide showed remarkable anti-cancer effect by inducing apoptosis in the colorectal cancer (cell line HT-29) xenograft mice model without noticeable changes in the liver or kidney functions (Jian et al. 2017). In all of the above-mentioned studies, the anticancer effects of the anti-cancer drugs have been improved a substantial amount when conjugated to hyaluronic acid (HA). This is because HA targets CD44, which is over-expressed in different types of cancer. Effective targeting of drugs to the cancer site has improved their overall efficacy.

Table 1: Recent research on chemotherapy using Drug-conjugated HA.

Drug Used	Type of Cancer	Model used	In vitro/ in vivo	Reference
Doxorubicin	Liver cancer	Human hepatic cell line (HepG2) & BALB/c mice	Both	(Tian et al. 2019)

	Breast Cancer	Murine 4T1 cell line & Female BALB/c mice	Both	(Yu et al. 2020)
	Breast cancer	MDA-MB-231 cell line	In vitro	(Vogus et al. 2017)
	Melanoma	B16-F1 cell line	In vitro	(Kim et al. 2012)
Paclitaxel 	Colon tumors	HCT-116 cell line	In vitro	(Kim et al. 2012)
	Ovarian cancer	SK-OV-3 cell line	In vitro	(Kim et al. 2012)
	Breast cancer	HBL-100	In vitro	(Leonelli et.al.2008)
	Breast Cancer	MCF-7, MDA-MB-231, and MCF-12A cell lines	In vitro	(Gote et al. 2021)
	Bladder cancer	BALB/c, SCID mice & Fischer female rats	In vivo	(Rosato et al. 2006).
	Bladder cancer	RT-4 cell line	In vitro	(Rosato et al. 2006).
	Brain metastases	MCF-7 & MCF-7/AdrR cell line	In vitro	(Mittapalli et al. 2013).
Cisplatin 	Lung cancer	LCC cell line	In vitro	(Fan et al. 2015)
	Lymphatic metastases	Rat	In vivo	(Cai et al. 2008)
	Lung cancer	Sprague–Dawley rat	In vivo	(Xie et al. 2010)
	Head and neck squamous cell carcinoma (HNSCC)	Nu/Nu mice	In vivo	(Cohen et al. 2013)
Gemcitabine 	Breast cancer	MDA-MB-231 cell line	In vitro	(Vogus et al. 2017)
	Biliary cancer	HuCCT1 cell line	In vitro	(Noh et al. 2015)
	Pancreatic cancer	PANC-1, PANC-0403 cell lines	In vitro	(Dubey et al. 2017)
	Colon cancer	CT-26 cell lines	In vitro	(Dubey et al. 2017)
	Melanoma	B16-F10, MDA-MB 435 Cell lines	In vitro	(Dubey et al. 2017)
Nimesulide	Colorectal cancer	HT-29 cell line	Both	(Jian et al. 2017)

HA-based nanoparticles:

Nanoparticles have been used successfully used against different types of cancer. The use HA to form nanoparticles is due to its ability to form different nano-sized structures, such as liposomes, micelle, dendrimers, hydrogel, polymerosome etc. (Kim et al. 2018; Lee et al. 2020). HA has several functional groups that allow a plethora of drugs to be conjugated in the nanoparticle. These nanoparticles do not elicit inflammation; they are non-immunogenic; and they are easily degraded in a biological system. These HA-conjugated nanoparticles easily bind to the cancer-cell specific CD44, RHAMM, LYVE-1 receptors. Nanoparticles made using HA have some excellent features as an anticancer formulation:they improve targeting, permeability, stability, as well as biocompatibility. Table 2 provides a list of nanoparticles synthesized using HA that were successfully used against cancer cell *in vitro/in vivo*.

Table 2: Recent research on HA based Nanoparticles used against cancer.

Type of nanoparticle	Size (nm)	Zeta potential	Polydispersity index	Core	Drug used (if any)	Used on	Reference
Liposome	130.6	-22.6 mV	-	Hyaluronic acid & lipid	siRNA Bcl-2	Hela cells cervical cancer cell line	(Tong et. al. 2020)
	125.43 ± 4.57	−14.29 ± 0.43 mV	0.21 ± 0.02	HA, Magnevist & DOX	Doxorubicin	MDAMB-231 Breast cancer cell line	(Park et.al. 2014)
	126.6 ± 5.62	−23.64 ± 1.49 mV	0.157	HA, Lipid	Dox	A172 (ATCC: CRL1620) human glioblastoma cell line	(Hayward et. al. 2016)
	110 to 160 nm	+50 to +60 mV	-	HA, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE)	Anti-Telomerase siRNA	lung cancer cell lines A549 and Calu-3	(Taetz et. al. 2009)
	147.8 ± 3.3	-20.80 ± 1.70 mV	-	HA, Soy phosphatidylcholine & cholesterol	Paclitaxel	HepG2 and A549 cell lines	(Jiang et. al. 2012)
Micelles	187 nm	-	-	Pyridyl disulfide methacrylate, HA	Doxorubicin	Squamous cell carcinoma (SCC7) cells	(Han et. al. 2015)

	154.8-215.7 nm	-7.29 to -10.7 mV	0.120 - 0.233	HA and poly(l-histidine)	Doxorubicin	MCF 7 breast cancer cell line	(Qiu et. al. 2014)
	144.95 ± 3.88 nm	−27.19 33 ± 1.91 mV	-	Thiolated hyaluronic acid & hydrophobic 6-mercaptopurine	Doxorubicin	colon cancer stem cells	(Debele et. al. 2018)
Hydrogel	-	-	-	Sodium selenite, hyaluronic acid-dopamine	Hydrogel itself used as anticancer agent	Breast cancer	(Yang et. al. 2020)
	-	-	-	Thiol functionalized Hyaluronic acid	Zinc phthalocyanine,Doxorubicine, Indocyanine green	Subcutaneous transplantation tumor-bearing BALB/c mice	(Xu et. al. 2021)
Polymerosome	82 nm	-	0.06	Hyaluronic acid	Mertansine (DM1) toxin	MDA-MB-231 tumor-bearing nude mice	(Zhang et.al. 2018)
	146.2 ± 10 nm	-42.1 ± 0.3 mV	0.12 ± 0.03	HA, polycaprolactone	Doxorubicin	Murine 4T1 and human MCF-7 cancer cell lines	(Shahriari et. al. 2019)
Dendrimer	2.1 ±0.3	+6.1 ± 0.7 mV	0.293 - 0.334	Au	-	Hepatocellular carcinoma (HCC)	(Wang et. al. 2016)
	9.3 ±1.5	−7.02 ± 9.53 mV	-	-	3, 4-difluorobenzylidene curcumin (CDF)	pancreatic cancer cells	(Kesharwani et. al. 2015)

Liposome:

Liposomes are small vesicles made of phospholipid bilayers. Their amphipathic nature makes them very efficient in carrying both hydrophilic drugs (in aqueous solution) & hydrophobic drugs (across the membrane) (Rawat et al. 2008). Liposomes are very good vehicles for drug delivery.

HA can be conjugated covalently to liposomes by two ways. In first method, HA is conjugated with phosphatidylethanolamine of a liposome by an amide linkage between carboxylate of HA

and amino group of liposomes (Peer and Margalit 2004). In second method, HA is first conjugated with separate phosphatidylethanolamine molecules, and then these HA-phosphatidylethanolamines are used with other lipids to synthesize liposomes (Surace et al. 2009).

HA based liposomes improve solubility, drug stability, long circulation and targeting of drugs to cancer affected cells only, thereby reduce side effects on healthy cells (Taetz et al. 2009). Liposomes decorated with specific antibodies or ligands make them very good tissue-specific vehicles for anticancer drug delivery. Due to the high rate of angiogenesis in tumors, blood vessels in tumor tissues contain large gaps (600 to 800 nm) between adjacent cells. This allows the liposomes to extravasate from blood vessels and accumulate in the tumor (Taetz et al. 2009).

HA-based liposomes have been successfully used against cervical cancer, breast cancer, glioblastoma, lung cancer and hepatic cancer (Taetz et al. 2009; Jiang et al. 2012; Park et al. 2014; Hayward et al. 2016; Tong et al. 2020).

Micelles:

HA can self-assemble into amphiphilic micelles, with a hydrophilic outer layer and a hydrophobic core. Hydrophobic drugs can be incorporated in the hydrophobic core by physical, chemical, or electrostatic interaction with hydrophobic groups of HA (Chen 2010; Yang et al. 2016; Din et al. 2017).

HA micelles have several advantages as nano-sized drug carriers: they can carry hydrophobic drugs specifically to the target cancer cells; they decrease the rate of degradation of the drug and reduce blood clearance (Biswas et al. 2013); and they improve drug stability, controlled release, enhanced permeability and retention (EPR) effect (Hrubý et al. 2005; Lo et al. 2009; Yin et al. 2013; Rao and Khan 2013). Given that HA-based micelles are smaller in size than non-conjugated micellular structures, they have more tumor penetration potential, when compared with liposomes (Blanco et al. 2009). Micelles also allow the hydrophobic anticancer drugs to be incorporated within them, thereby facilitating their delivery. The hydrophilic corona of micelles also protects the anti-cancer drugs from recognition by opsonin proteins, thereby preventing phagocytic clearance (Blanco et al. 2009).

HA based micelles have been successfully used against Squamous cell carcinoma (SCC7) cells, MCF 7 breast cancer cell line and colon cancer stem cells (Qiu et al. 2014; Han et al. 2015; Debele et al. 2018).

Hydrogels:

Hydrogels are produced by physical or chemical crosslinking of polymers. They are hydrophilic, can absorb water but do not dissolve in water. HA can form hydrogels very easily by conjugating with hydrophobic groups *e.g.*, methacrylate group, cholesterol, acetyl group etc. nano sized HA-hydrogels are very useful in cancer drug delivery system as they are biodegradable, stable in colloid, can carry large payload of drug, prevents aggregation of drug, rapid drug release (Xu et al. 2012). But due to their rapid degradation, they are not a very good

option for use as a drug delivery agent. HA can be used to fabricate the surface of hydrogels and can be tuned as required. These HA-fabricated hydrogels can be used to study cancer cell behaviors *in vitro* (Goodarzi and Rao 2021).

HA based hydrogels have been successfully used against breast cancer and subcutaneous transplantation tumor-bearing BALB/c mice (Yang et al. 2020; Xu et al. 2021).

Polymerosomes:

Polymerosomes are special types of liposomes, produced by self-assembly of amphiphilic diblock copolymers and have higher membrane stability and low membrane permeability (Zhang et al. 2018; Shahriari et al. 2019). HA-polymerosomes can carry both hydrophilic and lipophilic drugs, do not react with blood components and do not harm non-target cells. Hyaluronic Acid-Shelled Disulfide-Cross-Linked polymersomes have shown high drug loading capability, very negligible amount of drug leakage under physiological conditions, nontoxicity to non-target cells and very prompt glutathione-triggered release of drug in the target organ (Zhang et al. 2018). Hyaluronic acid-based polymersomes containing doxorubicin was also applied against murine 4T1 and human MCF-7 breast cancer cell lines. It was observed that the polymerosomes improved the biodistribution of the drug, increased tumor necrosis, and *in vivo* antitumor efficacy (Shahriari et al. 2019).

HA-based polymerosomes have been successfully used against MDA-MB-231 tumor-bearing nude mice (Zhang et al. 2018) and murine 4T1, human MCF-7 cancer cell lines (Shahriari et al. 2019).

Dendrimers:

Dendrimers are branched synthetic polymeric compounds. They have many branches emerging from a core. HA can be used as a terminal group in synthetic dendrimer. Hyaluronic acid-modified manganese chelated dendrimer with entrapped gold nanoparticles have been successfully used in the CT/MR imaging of hepatocellular carcinoma (Wang et al. 2016). The dendrimers also showed improved water solubility, colloidal stability and biocompatibility (Xu et al. 2021).

Hyaluronic acid conjugated polyamidoamine dendrimers containing 3, 4-difluorobenzylidene curcumin (CDF) have been used against human pancreatic cancer cells (MiaPaCa-2 & AsPC-1) which improved specific delivery of the CDF and reduced toxicity (Kesharwani et al. 2015).

Inorganic nanoparticles coated with HA:

Different inorganic nanomaterials such as silver nanoparticle, gold nanoparticle, iron oxide, quantum dot, ceramic nanoparticle, and carbon-based nanoparticle (graphene oxide) have been proven effective against cancer in various studies. However, the use of these inorganic nanoparticles against cancer has some limitations as they themselves are somewhat toxic in nature and do not exhibit cell specificity. But if these inorganic nanoparticles can be coated with hyaluronic acid, their effectiveness increases with increased cell specificity and biocompatibility (Kim et al. 2018).

HA-Coated Ag NPs:

Silver nanoparticles are well known for their remarkable anti-microbial properties. However, various studies have shown that silver nanoparticles are also effective against various cancers. Experiment showed that if hyaluronic acid is used as a reducing agent during the synthesis of silver nanoparticles in the reducing method, then a coating of hyaluronic acid is formed on the nano-silver core, thereby reducing the toxicity of the silver nanoparticles to a large extent. Such hyaluronic acid coated silver nanoparticles have been successfully used against leukemia(Zhang et al. 2019). The study showed how HA coated Ag-NPs have selectively targeted CD44 enrich leukemic cells with improved apoptosis of the cancer cells (Shahriari et al. 2019).

HA-Coated Au NPs:

Due to their surface plasmon effect, gold nanoparticles have proven effective against different types of cancer in photothermal therapies. To improve their efficacy, cell specificity and prevention of protein adsorption, and opsonization, HA coating of AuNPs is done (Kim et al. 2018). Hyaluronic acid-coated cisplatin conjugated gold NPs have been found effective against Human breast adenocarcinoma MCF-7 cells, human primary glioblastoma U-87 cells and murine fibroblast NIH/3T3 cell lines (Gotov et al. 2018). The nanoparticles entered specifically into the cancer cells due to recognition by CD44 receptors and then by endosome formation. Then 670 nm near infra-red laser was applied, which reduces and releases cisplatin from the conjugate. Cisplatin then works specifically on cancer cells, thereby improving its efficiency and reducing its side effects (Wang et al. 2016). HA functionalized gold nanoparticles carrying metformin have been successfully used against HepG2 liver cancer cells (Kumar et al. 2015). In this study HA-Coated Au NPs not only improved targeting of drug to the cancer site, but also significantly blocked the cancer cells in G2/M phase and increased apoptosis of the cancer cells (Kesharwani et al. 2015).

HA-Coated Iron Oxide NPs:

Superparamagnetic iron oxide nanoparticles are primarily used in MRI, but they can be used effectively in hyperthermia therapies. If HA is conjugated with iron oxide nanoparticles, then it will specifically target CD44+ cancer cells and those cells can be killed by hyperthermia therapies. Hyaluronic acid (HA) coated superparamagnetic iron oxide nanoparticles have been successfully used against SCC7 and NIH3T3 cell lines (Thomas et al. 2015). The CD44+ cancer cells readily uptake the nanoparticles and produce heat when alternating magnetic field (AMF) is applied over a time period of 3 h. The specific absorption rate (SAR) was also calculated and it was found that these nanoparticles kill cancer cells by hyperthermia (Zhang et al. 2019). Similar type of effects was observed when superparamagnetic iron oxide nanoparticles was used against KB and CT-26 cell lines. The nanoparticles show good dispersibility and improved cytotoxicity due to high amount of ROS generation (Ryong Lee et al. 2021).

HA-Coated quantum dots:

Quantum dots are colloidal fluorescent nanocrystals. Their core is made up of semiconductor materials such as grapheme, Cadmium selenide, Cadmium sulfide, Lead Selenide, Zinc Selenide, Gallium arsenide etc. They are mainly used for imaging purpose. HA-Graphene quantum dots have been successfully used against HeLa and L929 cell lines (Kumar et al. 2015). It was found that the HA-Coated quantum dots are completely biocompatible and reduce the number of HeLa and L929 cells significantly (Vahedi et al. 2022).

Hyaluronic acid and bovine serum albumin coated $CuInS_2$-ZnS quantum dots have been successfully used against HeLa cells (Yang et al. 2020). Due to its CD44 receptor/magnetic dual targeting ability high accumulation of the quantum dots have been observed by near infrared (NIR) fluorescence and magnetic resonance (MR) imaging. About 90% reduction of tumors have been observed when NIR laser irradiation was applied on the nude mice (Thomas et al. 2015).

HA-Coated ceramic NPs:

Ceramic nanoparticles are inorganic, heat-resistant, solids of both metallic and nonmetallic compounds. They are synthesized by heating at high temperature and then cooling rapidly. They are amorphous, crystalline, dense, porous or hollow in structure. Their small size, biocompatibility, stability make them a good choice for cancer drug delivery. Addition of HA to the surface of ceramic nanoparticles increases tissue specificity. 5-fluorouracil-loaded hyaluronic acid-conjugated silica nanoparticles have been successfully used against colon cancer cell bearing xenograft tumor mice model and Colo-205 colon cancer cells (Liu et al. 2015). It was observed that 5-fluorouracil-loaded hyaluronic acid-conjugated silica nanoparticles showed ~45% cell apoptosis whereas 5-fluorouracil-silica nanoparticles displayed only 20% apoptosis. This difference in result is due to CD44 recognition by the hyaluronic acid of the former nanocarrier (Ryong Lee et al. 2021). Hyaluronic acid functionalized mesoporous hollow alumina nanoparticles were used successfully in liver cancer therapy (Gao et al. 2019). The hyaluronic acid coated mesoporous hollow alumina nanoparticles sustained drug release, increased cellular uptake, increased the level of drug in tumor tissues, and promoted apoptosis (Vahedi et al. 2022).

HA-Coated Carbon NPs:

HA conjugated carbon-based nanoparticles such as single walled carbon nanotube, multi walled carbon nanotube, fullerene, grapheme oxide nanosheets showed promising results in cancer drug delivery. Gemcitabine loaded hyaluronic acid conjugated PEGylated multi-walled carbon nanotubes (GEM/HA-PEG-MWCNTs) were used successfully against HT-29 colon cancer cell line (Prajapati et al. 2019). GEM/HA-PEG-MWCNTs produced less hemolytic toxicity ($7.73 \pm 0.4\%$) when compared to free Gemcitabine ($18.71 \pm 0.44\%$). At the same time GEM/HA-PEG-MWCNTs showed higher cytotoxicity, reduced tumor volume and increased survival rate without loss in body weight when compared with free Gemcitabine (Prajapati et al. 2019). HA-modified single-walled carbon nanotubes (SWCNTs-DOX-HA) were used successfully to deliver doxorubicin (DOX) against breast cancer (Liu # et al. 2019). SWCNTs-

DOX-HA improved delivery of Doxorubicin in CD44+ MDA-MB-231 breast cancer cell line blocking migration of MDA-MB-231 cells, inhibiting proliferation and inducing apoptosis of cells (Liu et al. 2019).

Conclusion and Prospective Outlook:

From the above discussion it is clearly demonstrated that hyaluronic acid can be successfully used in targeted cancer therapy. The use of HA in cancer drug delivery has added another dimension as it can easily identify CD 44 RHAMM, LYVE-1 over expressing cancer cells. Various studies have observed that hyaluronic acid has increased the solubility, bioavailability, stability, targeting efficiency and reduced toxicity of various anti-cancer drugs. Also, because HA is a natural polymer (which is present in our body cells), it is itself non-toxic, biodegradable, non-immunogenic, and non-inflammatory. This makes it an excellent anticancer-drug delivery system agent. In this review, we have described how HA can be easily modified and combined with various anti-cancer drugs (such as doxorubicin, paclitaxel, cisplatin, gemcitabine etc.) to be used against cancer. Also, we have described how can we make various nano-drug carriers (such as liposomes, micelle, dendrimers, hydrogel, polymerosome etc.) using HA that are able to deliver drugs to specific cancer cells very successfully. Further, we have discussed how various inorganic nanoparticles can be used against cancer by combining them with hyaluronic acid. According to the data available so far, the use of hyaluronic acid for drug delivery against cancer has been quite successful, although some areas still need research. As the exact relationship between hyaluronic acid and protein corona formation is not yet known, further research is needed in this field. Sometimes HA receptors located in the liver and spleen can attract cancer drugs and cause side effects there. More research is needed to solve this problem. Another disadvantage of using HA is that it is degraded by HA-degrading enzymes present in the body, such as hyaluronidases. So how can this HA be chemically modified to act as a long-lasting carrier and to serve as a better drug delivery system? More research is needed. It can be expected that the above problems will be resolved through research in the near future and that HA can be used more successfully as a drug delivery system against cancer in a better regulated way.

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Conflict of Interest:

The author declares that there is no conflict of interest.

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