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Review

The effects of chitosan on glioma: Recent advances in its application for diagnosis and treatment

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ABSTRACT

The most common tumor among adolescents, glioma, is considered as a lethal disease. Despite the improvements in its treating methods, outcomes of glioma patients are not satisfying. Currently-used anticancer therapies against glioma may lead to developing drug resistance as well as cancer recurrence or metastasis. Besides, there are other challenges we are facing today in managing patients with glioma which includes inefficient drug delivery methods, lack of proper cell-culturing microenvironment for drug screening, and incomplete information on glioma biology. Chitosan is a natural product which plays a role in various biological processes. This chitin-derived biopolymer shows biocompatibility and biodegradability without causing toxic effects on normal cells. Since it is shown that chitosan serves as a multipurpose agent in various cancer cells, several studies have been focused on its diagnostic and therapeutic applications. Herein, we provide an insight into chitosan beneficial roles in glioma by covering studies, especially the most recent ones, which are concerned withthe application of chiston.

1. Introduction

Yearly, about 990,000 Patients with gastric cancer are determined entire the world with approximately 738,000 deaths. Gastric cancer is known as the fourth most common cancer and the second main cause of cancer-related deaths (Jemal, Center, DeSantis, & Ward, 2010). The incidence rate of gastric cancer is 2–3 folds higher in males than females (Bray et al., 2018). Gastric antrum cancer and gastric carcinoma are the most common types of gastric cancer while another type of gastric cancer named gastroesophageal junction is dramatically increasing. The rate of gastric cancer incidence is elevating gradually between young age group (Lee et al., 2017). Gastric cancer has some characteristics including high incidence rates of metastasis and mortality as well as low rates of early diagnosis, radical resection and 5-year survival ("Nucleostemin regulates proliferation and migration of gastric cancer and correlates with its malignancy [Retraction]," 2017). Gastric cancer may be determined as sporadic, familial or hereditary disease. Sporadic gastric cancer is initiated from a chronic atrophic gastritis resulting in intestinal metaplasia followed by dysplasia and eventually gastric cancer (Correa, 1988).

Several factors such as high amounts of salt in diet, medication, smoking, alcohol consumption, and H. pylori infection are found as causative agents of chronic gastritis (Correa, 1992). Familial gastric cancer also has some risk factors including infection of H. pylori, diet habits, and gene polymorphisms in pro- and anti-inflammatory cytokine genes. About 1–5 % of gastric cancer patients have hereditary forms (Oliveira, Pinheiro, Figueiredo, Seruca, & Carneiro, 2015). Approximately 30–40 % of hereditary gastric cancer cases have mutations in the CDH1 gene codding E-cadherin. According to the World Health Organization (WHO) classification for the gastrointestinal tumors, gastric cancer is divided into adenocarcinomas, carcinoma with lymphoid stroma and the hepatoid adenocarcinoma. More than 90 % of gastric tumors are adenocarcinoma itself classified to tubular, papillary, mucinous, poorly cohesive, and mixed (Hu et al., 2012). Gastric cancer pathogenesis is multi-step, multi-factorial and complex. Without considering the size of lesions and lymph node metastasis existence, early stage gastric cancer is limited to the mucosa and submucosa. Meanwhile, the advanced-stage gastric cancer metastasize to beyond the

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submocusa, to gastric mascular layer, subserosa and other organs (Berger et al., 2016). Radical surgery and following chemotherapy has been done for patients with early gastric cancer leading to 90 % survival rate in 5-year after operation. Although, due to the lack of specific symptoms in early stage of this cancer, its detection rate in this stage is low. Besides, in advanced stage some cases don't have the chance of surgery as well as the risk of metastasis is high in these patients overally leading to poor prognosis (Song, Wu, Yang, Yang, & Fang, 2017). In recent years, finding a suitable drug delivery system for chemotherapeutic drugs in gastric cancer is an interesting subject for researchers.

The environment of seas contains a considerable supply of small molecules and macromolecules. The main compounds of marine materials contain polysaccharides, lipids and proteins. Chitin is one of the major polysaccharides found in marine. This compound is outstanding due to its high availability (Ruocco, Costantini, Guariniello, & Costantini, 2016). Chitin is produced by some marine organisms such as crustaceans, mollusks, insects, and fungi. The chemical structure of chitin consists of *N*-acetyl-D-glucosamine units with a high production rate and biodegradability (Tharanathan & Kittur, 2003). Chitin is known due to its biocompatibility, bioactivity, biodegradability and high mechanical strength. However, its utilization has been limited because of its low solubility. Thus, the attention of researchers has changed into chitosan which is the major derivative of chitin (Zhao et al., 2018). Chitosan is produced from chitin by enzymatic or chemical mechanisms. Chitin treatment with hydroxides at high temperature leads to its chemical deacetylation (Younes & Rinaudo, 2015). During this process the deacetylation is done very quickly and chitosan is produced. Chitosan consists of D-glucosamine and *N*-acetyl-dglucosamine units bonded by 1,4-glycosidic linkages, 50 % of deacetylation leads to production of a soluble chitosan in aqueous acidic media (Elieh-Ali-Komi & Hamblin, 2016).

The solubility of chitosan in acidic environment results in protonation of its amino groups making chitosan as a cationic polymer which allows it to interact with several molecules. Chitosan is known as the only cationic marine polysaccharide. This feature of chitosan accounts for its antimicrobial function through the interaction with cell membranes of microorganisms which have negative charge (Ferreira, Alves, & Coelhoso, 2016). Another biomedical attribute of chitosan is selective chelation function especially for iron, copper, cadmium or magnesium. Due to its solubility, this compound is found in several forms such as films, nanofibers, hydrogels or pastes (Ardila, Daigle, Heuzey, & Ajji, 2017; Dai, Tanaka, Huang, & Hamblin, 2011). Recently, chitosan and its derivatives have been considered as vehicles for drug delivery in order to controlled release for drugs, improve the stability of drugs, reduce adverse drug reactions, and enhance bioavailability of drugs in various diseases such as many cancers (Huang, Liu, & Chen, 2017). In addition, a large amount of experimental evidence has reported the efficacy of chitosan for drug delivery in gastric cancer. Thus, the aim of this article is to review this evidence as well as new chitosan-based drug delivery systems investigated in gastric cancer.

1.1. Chitosan, drug delivery and cancer

Chitosan is known as an appropriate compound for deliverying chemothepeutic agents in cancer treatment. Moreover, trans-mucosal drug delivery is facilitated by chitosan *via* its mucoadhesive and cationic features enhancing interaction with mucous membrane (Jeong et al., 2010). Chitosan nanoparticles are able to be utilized for delivering both hydrophilic drugs and hydrophobic drugs (Kim et al., 2006). In conjugation of chemotherapeutic drugs its several free amine groups are involved. For instance, recently a study has shown that chitosan was conjugated to doxorubicin, a hydrophilic drug, by utilizing a succinic ahydride spacer (Yousefpour, Atyabi, Vasheghani-Farahani, Movahedi, & Dinarvand, 2011). This spacer interacted to amine groups of soxorubicine producing a carboxylic acid form of doxorubicine. Then, this carboxylic acid of doxorubicine was conjugated with free amine groups of chitosan. In the next step, the chitosan-doxorubicine complex transformed to nanoparticles in aqaueous solution. Also, The Her2+ (human epidermal growth factor receptor 2+) targeting monoclonal antibody named trastuzumab was added to chitosan-doxorubicine nanoparticles. This compound had a considerable more uptake in comparison with free drug. In another study, chitosan-pluronic micelle was another strategy for encapsulation of doxorubicine. The results indicated that chitosan-pluronic micelle carrying doxorubicine has better therapeutic function than free doxorubicine (Fu, Xia, & Wu, 2016).

Regarding to delivery of hydrophobic drugs chitosan has been also applied. Paclitaxel is an example of poor water soluble chemotherapeutic drug which has been encapsulated in a glyceryl monooleate-chitosan core-shell nanoparticle. A remarkable reduction in toxicity of paclitaxel was seen with this core-shell nanosystem when was used for the treatment of human breast cancer cells (Trickler, Nagvekar, & Dash, 2008). In another study, glycol chitosan nanparticles with paclitaxel had a higher significant anticancer effect than free drug (Kim et al., 2006). Encapsulation of 5-flurouracil, a hydrophobic chemotherapeutic drug, with chitosan-PEG-gelatin polymer nanocomposite led to less toxicity than free drug with better physiochemical properties including particle size, homogenous distribution, morphology, and drug loading capacity (Rajan, Raj, Al-Arfaj, & Murugan, 2013). In human colorectal adenocarcinoma, 5-flurouracil which was encapculated with chitosan nanospheres could decrease tumor cells proliferation and inhibit their adhesion to human umbilical vein endothelial cells (Cavalli, Leone, Minelli, Fantozzi, & Dianzani, 2014). Recently, chitosan nanoparticles have been used to be conjugated with tumor-specific ligands (Ghaz-Jahanian, Abbaspour-Aghdam, Anarjan, Berenjian, & Jafarizadeh-Malmiri, 2015). Specific ligands in nanoparticles are able to interact with specific cell surface receptors leading to endocytosis nanoparticles. Some of the most common receptors used for drug delivery in cancers are including transferring, folate receptor, CD44 receptor, epidermal growth factor receptor (EGFR), low density lipoprotein receptors, and integrins (Sirsi & Borden, 2014). In cells, endo-lysosome cannot degrade drug-loaded chitosan nanoparticle; thus, its intracellular concentrations are increased. Over time, the drugs are gradually released from nanoparticles. In the design of this drug delivery system, the amounts of the expression of the receptors in each types of cancer cells should be considered (Petrovsky & Cooper, 2011).

1.2. Chitosan, drug delivery and H. pylori infection

The treatment of H. pylori infection which is one of the main causes of gastric cancer should be considered as a potential strategy for gastric cancer prevention. Recently, many strategies have been utilized for antibiotic drugs delivery in the way of H. pylori infection. Chitosan nanoparticles have been widely explored for encapsulation of antibiotic drugs for H. pylori treatment due to its high mucoadhesive properties (Gong et al., 2015). Moreover, chitosan nanoparticles improve remaining time of the drugs in stomach by protecting them from acidic and enzymatic breakdown through bonding to mucus barrier of gastric. Thus, drugs are allowed to diffuse into the mucus barrier leading to be more effective in the infection sites (Arora et al., 2012). In a recent study, chitosan nanoparticles were used to improve the effect of amoxicillin for the treatment of H. pylori infection. Chitosan nanoparticles were observed to directly bind to the infection site *via* some ligands specified for gastric mucosa or bacteria. Lectin is one of these legands binding specificly to carbohydrate resides of glycoproteins of gastric mucosa. In addition, lectin could improve the drug absorption and reduce the digestion in the stomach environment (Adebisi & Conway, 2011). In an *in vivo* study, adding lectin to clarithromycin-carried chitosan microspheres elevated their adhesion to the gastric mucosa by 73 % (Jain & Jangdey, 2009).

Liposomes consisting of phospholipid bilayers have attracted researchers' attention as potential systems of drug delivery suitable for

both hydrophobic and hydrophilic drugs. Despite of their potential in delivering into intracellular places, their application has been limited because of their spontaneous fusion (Akbarzadeh et al., 2013). Chitosan can also be utilized as coating for liposome system leading to inhibition of liposome fusion at acidic pH. In physiological pH, chitosan nanoparticles release liposome allowing it to diffuse into target bacteria membrane in order to release drugs (Thamphiwatana et al., 2013). Besides, chitosan is also used in another way as an H. pylori-binding system (Fernandes et al., 2013). Chitosan microspheres can adhere H. pylori bacteria in gastric environment leading to their eradication. Moreover, these chitosan microspheres have been found not to be cytotoxic as well as to be able to eliminate and inhibit H. pylori attachment to gastric cells (Goncalves et al., 2013). These strategies of using chitosan microsphere or nanoparticles for H. pyori medication are widely promising for designing future treatment.

1.3. Chitosan-based drug delivery systems in gastric cancer

1.3.1. Chitosan nanoparticles

Despite of recent advancement of the treatment of gastric cancer, several issues such as local recurrence, hematogenous metastasis and drug resistance remains yet resulting in treatment failure (Peng, Guo, Liu, & Wu, 2014). One of the main issues of chemotherapeutic drugs application is finding a desirable drug delivery to overcome some problems exist such as low water solubility, gastric pH tolerance, and intracellular diffusion. Thus, the development of drug delivery systems may contribute to the treatment and prognosis of gastric cancer. Recently, chitosan as a suitable polymer for designing drag delivery systems have approached in several types of cancer studies including gastric cancer. In a recent study, norcantharidin, an anticancer compound, was conjugated with carboxymethyl chitosan through amidation reaction and its antitumor effects on gastric tumors were investigated and compared with free form of the drug. The results showed that drug conjugated with carboxymethyl chitosan remarkably suppressed the proliferation, migration, and tube formation of gastric cancer cells. Compared to free drug, the carboxymethyl chitosan conjugated form was more successful in inducing apoptosis of gastric tumor cells. In addition, carboxymethyl chitosan significantly decreased systemic toxicity and improved the anticancer effects of norcantharidin. This study reported that carboxymethyl chitosan could increase the gene expression of TNF-α and Bax as well as decrease the gene expression of VEGF, Bcl-2, MMP-2 and MMP-9 suggesting that carboxymethyl chitosan may be a promising conjugative agent for gastric cancer treatment (Chi et al., 2019).

In another study, ligand-based strategy was evaluated for gastric cancer treatment *via* using chitosan nanoparticles. In this study, docetaxel, a chemotherapeutic drug, was conjugated to N-deoxycholic acid glycol chitosan nanoparticles and GX1, a suitable ligand for anti-angiogeneous drugs for gastric cancer treatment, was used. This new strategy of drug delivery showed more efficient cytotoxicity against gastric cancer cells than free drug in gastric cancer cells (Zhang et al., 2019). The aim of an investigation was to evaluate an encapculating method for cytolethal distending toxin (CdtB) in gastric cancer therapy using chitosan/heparin nanoparticles. This method potentially suppressed the proliferation of gastric tumor cells, increased cell cycle arrest at G2/M phase and apoptosis (Lai et al., 2014). Li et al. evaluated the function of N-((2-hydroxy-3-trimethylammonium) propyl) chitosan chloride (HTCC)/alginate-encapsulated Fe3O4 magnetic NPs (HTCC-MNPs) on multidrug resistance (MDR) gastric cancer cells. The (HTCC-MNPs) represented high water solubility and biocompatibility as well as decreased tumors viability. Autophagy, apoptosis, mitochondrial membrane potential loss and reduced ROS generation were found as the main mechanisms involving in these observed effects (Li et al., 2016). An investigation explored the effect of chitosan nanoparticles on drug delivery of green tea polyphenol extract, epigallocatechin-3-gallate, in gastric cancer. A complex of fucose-conjugated chitosan and polyethylene glycol-conjugated chitosan was used for encapsulating of this herbal compound. The nanoparticles was shown to potentially decreased drug release within stomach acids leading to a controlled epigallocatechin-3-gallate release suppressed gastric cancer proliferation, increased apoptosis, and downregulated vascular endothelial growth factor protein expression (Lin, Chen, Lai, Hsieh, & Feng, 2015).

Another derivative of chitosan named trimethyl chitosan was used for encapsulation of paclitaxel, a classical microtubule inhibitor, in order to gastric cancer therapy. Paclitaxel-loaded trimethyl chitosan nanoparticles were observed to increase cell cycle arrest in G2/M phase and apoptosis in gastric tumors. This drug formulation decreased the tumor growth without significant systemic side effects suggesting being a promising and safe drug delivery for gastric cancer treatment (Song et al., 2014). Also, recently, chitosan-encapsulated BRAF siRNA nanoparticles were utilized for gastric cancer treatment. Chitosan nanoparticles were observed to reduce cell invasion, decreased BRAF expression in gastric tumors and suppressed their invasion (Huo, 2016). Similarly, in another study the effect of PIK3CA/siRNA chitosan nanoparticle were observed on gastric cancer cells. Results showed that PIK3CA/siRNA chitosan nanoparticle could remarkably reduced the expression of PIK3CA/siRNA and the invasive capacity of gastric cancer cells (Zhou, He, Liang, & Liu, 2014). Overall, this evidence has suggested that chitosan and its derivatives may be applied as suitable drug delivery in form of nanoparticles and microspheres conjugated to chemotherapeutic drugs for improvement of the efficiency of anti cancer drugs in order to treatment of gastric cancer. (Table 1)

1.3.2. Chitosan based hydrogels

Recently, hydrogels based drug delivery systems have been highly used due to their high thermal stability, biocompability, and other mechanical features (Lovett et al., 2015). Hydrogels are polymeric networks with three-dimensional feature and some physical and chemical interactions. Their polymer chains are mostly hydrophilic therefore, hydrogels are able to absorb and keep high amounts of water (Ahmed, 2015). Other advantages of these compounds are their good biodegradability and controlled drug release ability. Due to these features, hydrogels have been recently used as drug delivery in treatment of cancers (Chai, Jiao, & Yu, 2017).

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been employed for early gastric cancer surgery, super-facial cancer in the stomach, colon, and esophagus. EMR is a method by which large superficial lesions of the gastrointestinal tract can be removed by saline injection into the submucosal layer. Suitable submucosal injection under the tumor which is vital for formation a submucosal fluid cushion facilitating a clean dissection and resection of tumors is a key factor for these endoscopic techniques. Several agents for submucosal injection have been developed in EMR such as dextrose, glycerol, normal physiological and hypertonic saline, and *etc.* each of which has some advantages and disadvantages (Feitoza et al., 2003). Although, solutions with high viscosity such as 50 % dextrose, glycerol, and hypertonic saline with epinephrine decrease quick dissipation of submucosal fluid cushion, they can damage tissues and cause local inflammation at the injection place. Until now, various techniques have been utilized for EMR using some natural, synthetic and semisyntethic compounds of macromolecules, proteins, and polysaccharides like chitosan (Fujishiro et al., 2005; Ishizuka et al., 2009). Photo-cross-linked chitosan hydrogel has been employed as a drug delivery materials for several cancer treatments (Ishihara et al., 2006; Obara et al., 2005). In a recent study, Hayashi et al., (Hayashi et al., 2004) used photo-cross-linked chitosan hydrogel as an injection agent in EMR method. Photo-cross-linked chitosan hydrogel or normal saline was injected into the submucosal layer of the stomach of rat. At several time points, the thickness of that layer was assessed. The histological results showed that chitosan retained from the submucosal layer, was able to fill the base of ulcer and totally surrounded the bleeding site. Thus, the results of this study indicated that chitosan based hydrogel could be

Table 1
Experimental studies that investigated the chitosan-based drug delivery systems in gastric cancer.

Chitosan form	Drug	Nanoparticle/microsphere	Model	year	Ref
Carboxymethyl chitosan	Norcantharidin	–	*In vitro/In vivo*	2019	Chi et al. (2019)
N-deoxycholic acid glycol chitosan	Docetaxel- GX1-PEG-deoxycholic acid	Nanoparticle	*In vitro/In vivo*	2019	Zhang et al. (2019)
Chitosan/heparin	Cytolethal distending toxin	Nanoparticle	*In vitro*	2014	Lai et al. (2014)
N-((2-hydroxy-3-trimethylammonium) propyl) chitosan chloride (HTCC)/alginate	Fe3O4 magnetic NPs	Nanoparticle	*In vitro/In vivo*	2016	Li et al. (2016)
Fucose-conjugated chitosan and polyethylene glycol-conjugated chitosan complex	Green tea polyphenol extract epigallocatechin-3-gallate	Nanoparticle	*In vitro/In vivo*	2015	Lin et al. (2015)
Trimethyl chitosan	Paclitaxel	Nanoparticle	*In vitro/In vivo*	2014	Song et al. (2014)
Chitosan	BRAF siRNA	Nanoparticle	*In vitro*	2016	Huo (2016)
Chitosan	PIK3CA/siRNA	Nanoparticle	*In vitro*	2014	Zhou et al. (2014)

suitable for utilize in EMR technique as a submucosal injection material that prevent complications.

ESD is another potential method for the treatment of early gastric tumors by enhancing the resection of tumors (Gotoda, Yamamoto, & Soetikno, 2006; Park, Cho, Kang, & Kim, 2011). Due to the relatively high bleeding after the ESD, the wide utilization of this method has been limited (Pissas, Ypsilantis, Papagrigoriadis, Hayee, & Haji, 2015). Thus, using a material which is able to adhere the wound, isolate the contents of gastrin, and enhance the ulcer healing could be effective for decreasing the complications of ESD leading to its extensive use without limitation. Various biomaterials have been employed in this way such as polyethylene glycol membrane, fibrin glue, polylactic acid and others (Tsuji et al., 2015). chitosan/β-glycerophosphate (CS/GP) based thermo-sensitive hydrogel is a proper candidate to satisfy the requirements for endoscopic methods. The CS/GP is solution at low temperature which converts into hydrogel by heating making a soluble injectable thermos-sensitive hydrogel. However, this system has also some disadvantages such as low mechanical resistance, cytotoxicity due to its β-glycerophosphate and its slow gelation (Assaad, Maire, & Lerouge, 2015). In a recent study, a thermo-sensitive hydrogel of chitosan/β-glycerophosphate/collagen (CS/GP/Col) was developed for ESD. The results showed that the CS/GP/Col hydrogel is suitable for using through catheter reaching the gastric ulcer formed during ESD operation. The more concentrations of collagen led to better biocompability. In addition, the high-collagen hydrogels could protect gastric cells from acidic condition and increase some growth factors such as EGF, FGF, and VEGF as well as enhance coagulation. Therefore, these results indicated that CS/GP/Col hydrogel could be a potential agent for the endoscopic treatment of ESD by healing the ESD-induced ulcer (Shan et al., 2019). Taken together, these results have shown that chitosan based hydrogels is another drug delivery system which can be also used as a potential agent for the treatment of gastric cancer.

2. Conclusions

Currently, gastric cancer is known as one of the most common aggressive malignancies with high rates of metastasis and local recurrence. Due to some problems in chemotherapeutic drug applications in gastric cancer treatment such as low water solubility, gastric pH tolerance, and intracellular diffusion attention to find new drug delivery systems are required. One of the compounds in designing drug delivery systems is chitosan. Several studies designed drug delivery systems based on chitosan aiming to improve antitumor efficiency of chemotherapeutic drugs of gastric cancer in clinical application. This evidence suggested that the conjugation of chitosan with various drugs could significantly inhibit cell proliferation *via* different mechanisms such as increasing apoptosis, cell cycle arrests, and decreasing angiogenesis and metastasis (Fig. 1). Taken together, chitosan may be used as a promising polymer therapeutics for gastric cancer treatment.

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Author contributions

JH and RSh contributed in the conception, design and drafting of the manuscript. BY and MAM contributed in reviewing relevant

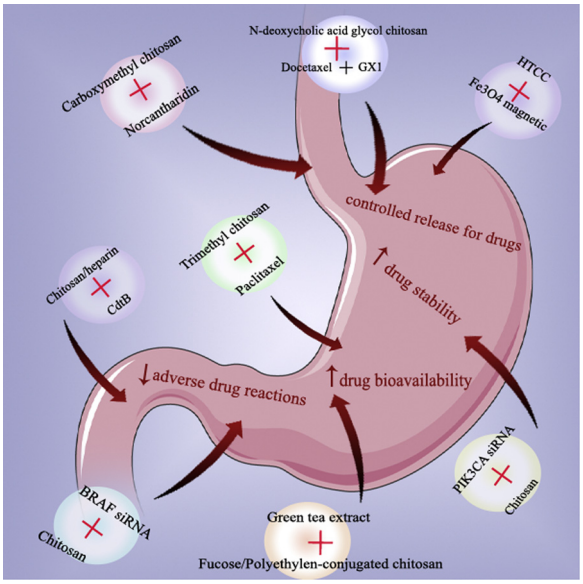

Fig. 1. Chitosan and its derivatives used in gastric cancer treatment.

literature. All authors approved the final version for submission.

Declaration of Competing Interest

The authors declare no conflict of interest.

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