The Improvement of Paclitaxel Cytotoxicity using Nanocellulose based Nature Resources

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Abstract

Paclitaxel is one of the cancer drugs that often used. These drug kills cancer cells by inhibiting mitotic cycle. The efficiency of paclitaxel is increased by the use of nanomaterials as a carrier of paclitaxel. Nanomaterials can enhance encapsulation efficiency, improve the drug release to the target cell following nanomaterial degradation, and improve local accumulation of drug in the cell through endocytosis receptor. Nanomaterial that often used forencapsulation of paclitaxel is a polymer derived from natural resources such as cellulose. The advantages of cellulose as a carrier of paclitaxel are nontoxic, biodegradable, and very abundant from various sources. One of the potential sources of cellulose for drug delivery system is cassava baggase.

Keywords: *Paclitaxel, encapsulation, cell viability, nanocellulose*

I. INTRODUCTION

Paclitaxel is an effective drug to against cancer, such as ovarian breast cancer [1], lung carcinoma, and leukemia [2]. Paclitaxel kills the cells by interfering mitosis cycle [3]. In the G2 and metaphase, paclitaxel prevents microtubule de-polymerization thus disturb microtubule equilibrium [1, 4-5]. Nevertheless, paclitaxel has a pore water solubility, thereby reduce the effectiveness [2]. In addition, the oral administration paclitaxel to patients has several disadvantages, among a small dosage of drug is absorbed, it can be delivered into the liver through veins, gastric acid can restructured drug, and very slow pharmacokinetic response [6].

To improve the pharmacokinetic response of paclitaxel, paclitaxel administration to the patient can be conducted by paclitaxel-nanomaterial conjugating. The conjugation of paclitaxel-nanomaterial can avoid kidney filtration and vascular defects thereby increase its permeability [17]. Nanomaterial is used as carrier by transforming network distribution so-called drug delivery systems [2]. Moreover, nanomaterials are more easily out of the vessels through endothelial [1]. The advantages of nanomaterials are biodegradable, biocompatible, nontoxic [3], increase the permeability [4], and reduce the side effects [2]. Paclitaxel by dose of 30 mg/mm has a good efficiency to overcome carcinoma [5].

Certain polymers have been used as paclitaxel delivery include Poly Vinyl Prolidon-Stearoin Chloride-Chitosan [7]; PEG-Folic Acid [8]; Chitosan - oligosaccharides-Au [9]; and Folate -PLA-TPGS [10]. Recently, there are no research have reported cellulose of cassava baggase as delivery of paclitaxel.

The purpose of this review is to assess the mechanism of nanomaterials affect paclitaxel put to death cancer including encapsulation efficiency, drug release, cell viability, and local accumulation. In addition, this review also examines the potential of cellulose as a paclitaxel delivery.

II. MECHANISM OF PACLITAXEL KILL CANCER CELLS

Paclitaxel has a rigid center ring and flexible side chains [11]. Paclitaxel put to death cancer cells by inhibiting chromosomes separation on metaphase [12]. This inhibition begins from activation of mitotic. Paclitaxel is bounded to the N-terminal 31 amino acid β-tubulin subunit that disrupts tubulin-microtubule equilibrium

[13]. Paclitaxel also attracts several chromosomes that are not tied to microtubule spindle through kinetochore. As a result, at metaphase, the chromosomes do not have symmetrical chromosome lined up the equator, as stem cells. Mitotic cycle is pull up at this phase due to the next phase, anaphase, have to have symmetric chromosome, so generate two symmetric same daughter cell as stem cells [14-15] (see fig 1).

Induction of paclitaxel against cancer cells also causes apoptosis; cell fatality is mediated by caspase (one of cysteine protease). Morphologically, during apoptosis occurs chromatics condensation [9-10]. In the leukemia, paclitaxel induce caspase so causes cell death in the range of 16-36 hours [16]. The paclitaxel structure is presented in Fig. 2.

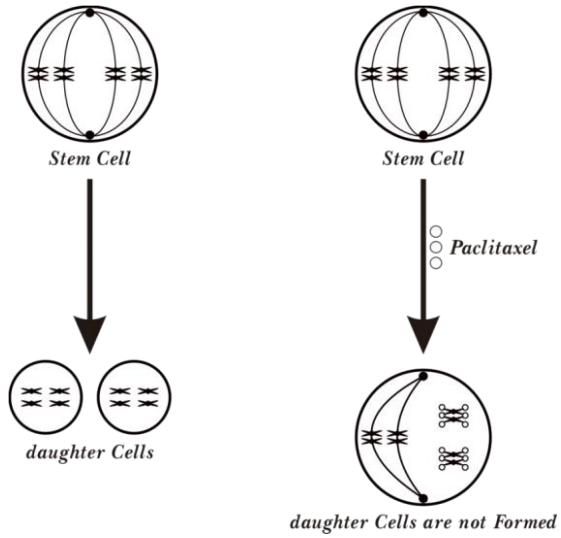

Figure 1. Mechanisms of paclitaxel kill cancer cells [14]

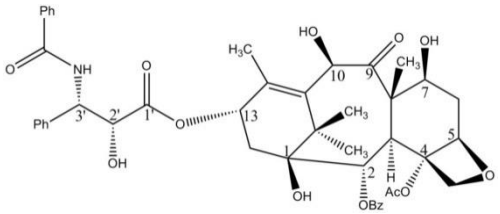

Figure 2. Structure of paclitaxel [11, 16]

Based on Structure activities relationships OH group at C-1 and C-2 benzoloksi are vital groups on anticancer activity of paclitaxel. Additionally,the Flexible of C-2 and C-3 also affect paclitaxel activity. On the other hand, the OH group at C-2 is binding site between paclitaxel and microtubules. Although C-7 to C-10 do not interacted directly, but affects the affinity of P-glycoprotein [11].

One of paclitaxel barrier kills cancer cells is multidrug resistance (MDR). P-glycoprotein (Pgp), one of the ATP-binding cassettes (ABC), causes resistance paclitaxel. These proteins are located at cell membrane that has energy of ATP. These energies are used to push paclitaxel out of the cell so cannot inhibit mitotic cycle [15]. Therefore, nonmaterial is needed as delivery agent to reduce resistance of paclitaxel.

III. AGENTS

Cellulose is very potential on the drug encapsulation, one of which paclitaxel. One of mean used on encapsulation of paclitaxel is conjugation polymer with paclitaxel. Chain side of the polymer is interacted with the existing paclitaxel so it will be trapped in the polymer (see fig 3) [17].

There are several advantages of cellulose as delivery agent. First, cellulose has a good biocompatibility, meaning that the much number of hydroxyl groups, it interacts easily with other molecules, chemically or by hydrogen bonds. Secondly, cellulose is nontoxic so it is safe for humans. Third, the long carbon chains cause cellulose hydrophobic that prevent drug degradation during delivery. Fourth, cellulose is biodegradable, when it reach cell, it rupture easily caused by cell environment so the drug more easily released by following cellulose degradation [18]. The use of cellulose for encapsulation of ACN increase release rate. Within 24 hours, more than 90% of the drugs are released toward target cells. This suggests that cellulose degradation is very easy to increase drug release rate [19]. Additionally, cellulose also has good thermal stability. Microcrystalline cellulose is depredated at temperatures of 296-344oC. This means that the cellulose resistant to temperature changes. During encapsulation process, there is no cellulose degraded so the risk of drug degradation before use can be avoided [20].

Figure 3. Paclitaxel encapsulation scheme [17]

From terms of resources, cellulose has highly abundant availability. Cellulose can be obtained from nature resources, for example from waste wood and biomass (bagasse sugarcane, oil palm empty fruit bunches, and cassava) [18]. Availability of cellulose derived from cassava baggase is one distinct advantage. Cassava products in Indonesia at 2013 reached 23,936,921 tons [21]. It is predicted cassava products in Indonesia will

increase continuously to supply the needs of starch in Indonesia. The increase of cassava production will increase the amount of cassava baggase product. Cellulose content in cassava is the second greatest after the starch, namely 34% [22]. Unfortunately, until now there is no study that reported the use of cellulose from cassava baggase as encapsulation materials of paclitaxel.

IV. Effect of Nanomaterial on Cytotoxicity Paslitalsel

A. Improvement of Encapsulation Efficiency

Surfactant is used for the synthesis of nanomaterials to improve encapsulation efficiency of paclitaxel. [23]. surfactant stabilizes paclitaxel in nanomaterial thus inhibiting drug disintegration from nanomaterial during delivery process. Vitamin E as surfactant of paclitaxel, approximately 81.6% paclitaxel remain in nanomaterials for delivery process to the target cell. Whereas, in the absence of vitamin E amount paclitaxel that reaches the target cells only about 71.7% [24]. Meanwhile, the encapsulation efficiency value of paclitaxel in nano-Poly Vinyl Chloride Prolidon-Stearoin-Chitosan was about 92.8% [7]. On the other hand, paclitaxel which remain in nano-PEG-folic acid during delivery process is by 13.1%. The low encapsulation efficiency is due to repolymerization reaction of PEG-nanomaterial [8]. In addition, paclitaxel solubility in water increases with increasing surfactant concentration which increase the diffusion paclitaxel of the nanomaterial heading out during delivery process [3]

B. Drug Release Rate

Nanomaterial is used for encapsulation paclitaxel to speed up the release of the drug brush [25]. Within the duration of 24 hours, at pH of 5.6 about 11.2% from 13.1% paclitaxel that was delivered by nano-PEG-folic acid has reached the target cell. Paclitaxel nonspecific bonding in nano-PEG-folic acid a network significantly increase release rate [8]. On the other hand, the high release rates paclitaxel in nano-PEG-Cyclodextrin occurs in 6-12 hours, where about 60% paclitaxel been released. PEG result nanomaterial that has more slippery surface to facilitate penetration through the mucous lining in gut [25-26]. Additionally, paclitaxel encapsulated chitosan-oligosaccharides nano-Au released to target cells after three hours. After 48 hours approximately 96% of paclitaxel has released from nanomaterial [3,9] (see Fig 4).

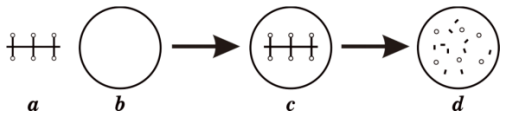

Figure 4. (a). Paclitaxel in nanomaterial, (b) cancer cells, (c) paclitaxel has entered into cancer cell, (d) degradation paclitaxel follows nanomaterial degradation [3,9]

High drug burst rate in the first day caused by several mechanisms, first, diffusion through a channel formed during nanomaterial preparation. Second, drug release followed the nanomaterial degradation. The strong explosion is caused by local diffusion of paclitaxel which is entrapped weakly in polymer matrix. Terminal carboxylic acid increases release rate. The functional groups accelerate water absorption so accelerate swelling and degradation of nanomaterial. Small molecular weight also improves nanomaterials degradation because of low hydrophobic that facilitates pores formation [3]. It showed continuously paclitaxel release rates after 24 hours. After 48 hours paclitaxel that is released from nano-PEG-Chitosan-Transferin about to 67.14% and 69.64% at pH 7.4 and 4.0. Continuous release is resulted from paclitaxel diffusion through polymer pores as polymer degradation [26]. Third, the small particles have a large surface so produce high brush in a short time [3]. Additionally, paclitaxel which was released by nano-chitosan-oligosaccharides-Au to target cells by 96%, 68%, and 56% at pH 5.5; 6.8; and 7.4. This means that drug brush of nanomaterial more easily under acidic conditions [9]. The environmental of cancer cells have an acidic condition. Endosome has pH of 5-6, while lysosomes have pH of 4-5. The positive charge of nanomaterial will be exchanged with protons in acidic media. Consequently, nanomaterial less stable and easily degraded under acidic and drugs were released from the nanomaterial to target cells. Therefore, drug release was better under acidic than neutral or alkaline condition [27].

C. Cell Viability

Nanomaterial significantly decreased cell viability [3]. This is due to the positive charge of the nanomaterial. The positive charge of nanomaterials cause cellular interactions with negative charged of plasma membrane stronger than the negative charge [26,28]. Pure paclitaxel with a concentration of 0.28 ug / ml reduce cell viability CT26-CEA; while paclitaxel was released by nano-polyelectrolyte-PEG reduce cell viability CT26-CEA at a concentration of 0.014 µg / ml. This indicates that the nano-encapsulation paclitaxel-PEG

polyelectrolyte decreased the cell viability significantly by proliferative activities [28].

Moreover, nanomaterials also increase cell death in tumor tissue by generating hyperthermia [5] and change cell morphology [9,28]. Nano-Folate-Paclitaxel-PLA-TPGS with concentration of 3 mg / ml can damage HeLa cells. This means that the encapsulation paclitaxel in nanomaterial effectively destroy target cells by increasing cell internalization. Folic acid damage target cells that are internalized by the cell-folate receptor endocytosis [10]. Paclitaxel encapsulated by nano-PEG-folic acid with a concentration of 4.9 nM provide a 50% growth inhibition of MDA-MB231 cells [8,23,27]. The nanomaterials penetrate cells exclusively through receptor endocytosis. When gamma carbonyl of folic acid bound to the PEG, FR binding affinity cannot be measured accurately and absorption messages by receptor endocytosis via receptor endocytosis cannot be detained.

D. Local accumulation Paclitaxel in Cells

In vivo, after 24 hours paclitaxel accumulation in the tumor tissue of mice was higher than in other peritoneal tissue [29]. Effectiveness paclitaxel local accumulation in cells [23] occur through several mechanisms, the first, increase in permeability. Second, is effect of retention [7, 10]. Third, is redistribution of drug from the peritoneal cavity through the circulatory system. Fourth, is drug diffusion through liquid which was collected in the tumor tissue [29]. After seven days of Nano-Folate-Paclitaxel-PLA-TPGS more effectively inhibit tumor tissue than pure paclitaxel [10]. Certain compounds such as tetrandrin (TET) can also weaken Pgp functions in cell membrane, making it easier entry into cells. TET with a concentration of 5 μM affects the cytotoxicity of MCF-7 and MCF-7 / ADR [27]. Tumor inhibition ratio values of nano-Poly Vinyl Chloride Prolidon-Stearoin-Chitosan-Paclitaxel about to 76.1% while the tumor inhibition ratio value of pure paclitaxel about to 52.9%. It is attesting that nano-Poly Vinyl Chloride Prolidon-Stearoin-Chitosan-Paclitaxel inhibit tumor cells more effective in mice than pure paclitaxel [7]. In cancer cells, nanomaterials maintain therapeutic concentrations so reduce reactivity of phase G2 and M that is radiosensitive phase in mitotic cycle [2,5]. Paclitaxel concentration survives in cancer cells for 48 hours by using nano-PEG-cyclodextrin as a carrier. This is due to increased residence time of a nanomaterial that is close to the absorption, as presented on Fig. 5 [29-30].

Nowadays, research topic that is study by researchers in various countries is a nanomaterial. This is due to the nanomaterial has physical and chemical properties are uniquely different with the amount of material. The properties include the volume ratio and high surface, high reactivity, and high electron conductivity. Some of scopes that have use nanomaterials are including electronics, biomedical, pharmaceutical, photography, and the energy [29-30].

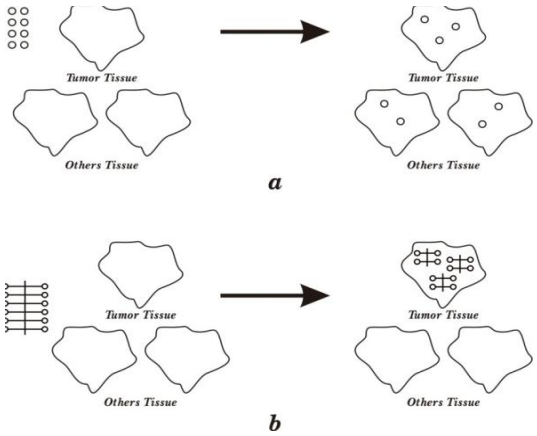

Figure 5. Paclitaxel accumulation in the tissues (a) without nanomaterial, (b) with nanomaterial [29-30]

V. CONCLUSION

Oral administration paclitaxel to the patient is less effective because degraded easily during delivery. On the other hand, the encapsulation of paclitaxel can improve the effectiveness of the drug. Nanomaterial increase the drug explosion rate followed nanomaterial degradation and through the process of diffusion. High release rates occurred in the first day. Moreover, nanomaterials also significantly decrease cell viability through changes in cell morphology. Local Accumulation paclitaxel in tumor cells also increase by using nanomaterial as delivery agent of paclitaxel. One of nanomaterials that are used for encapsulation of paclitaxel is cellulose as easily degraded, non-toxic, and the abundant availability materials from various resources. The authors suggest research encapsulation of paclitaxel using cellulose derived from cassava baggase.

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