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REVIEW ARTICLE

Beta-glucans is a Potential Inhibitor of Ovarian Cancer: Based on Molecular and Biological Aspects

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Abstract: Ovarian cancer is a lethal type of cancer which is initiated to the ovaries and affects 1 out of every 75 women. Due to the high number of deaths (almost 152,000) related to this cancer, it seems that novel efficient therapeutic methods are required in this field. Beta-glucans are a type of glucose linear polymers which have been proven to have a lot of advantageous activities. Recently, investigations have declared that these polysaccharides have the potential to be used as anti-cancer drugs. These agents are able to affect several mechanisms such as inflammation and apoptosis, and that is how cancers are prone to be affected by them. In this review, we attempt to investigate the role of beta-glucans on ovarian cancer. We hope that this paper would give some novel insights into the field of ovarian cancer treatment.

Keywords: Beta-glucans**,** ovarian cancer, apoptosis, signaling, anti-cancer, ovaries.

1. INTRODUCTION

Ovarian cancer (OC) is one of the most lethal gynecological cancers, which mostly occurs in women at the age of 40 or more [1]. This cancer takes152,000 lives every year and thus, it is acknowledged as the eighth frequent cancer which is causing death among women of the world [2, 3]. It is estimated that the risk of being affected by ovarian cancer is 1 in 75 for every woman and 1 woman patient out of 100 is being killed by this cancer [2]. The survival rate of this cancer does not exceed from 45% and the number of new women diagnosed is augmenting every year [1, 2]. According to evidence, a set of various cancers with diverse origins (cellular and anatomical), pathogenesis, alterations in molecular mechnisms, and expression of oncogenic genes are acknowledged as OC. Between all of these cancers, carcinomas and between the epithelium-related cancers (including serous, endometrioid, clear cell and mucinous), high-grade serous carcinoma are the most common ovarian cancer subtypes [2, 4, 5]; thus, in this paper, our main focus will be on ovarian carcinomas.

Being impacted by this cancer can be more likely in women who have high body mass index (BMI), the habit of smoking and alcohol drinking, and infertility. Furthermore, some other risk factors such as pregnancy, lactation, oophorectomy, consumption of oral contraceptives, and exercise are approved to have a reverse effect on the ovarian cancer risk [2, 6, 7]. After detecting some symptoms in a patient, some procedures are confirmed to be effective for a certain diagnosis. These procedures encompass testing the amounts of serum glycoprotein CA125, computed tomography or CT scan, magnetic resonance imaging or MRI, and ultrasonography [8].

From the treatment perspective, the first step is staging and determining the spread of cancer [8]. In general, four stages account for this cancer which should be managed through different therapeutic strategies [9]. The most common method utilized for the treatment of early stages is surgery [8]. Noteworthy, surgical management relies on the exact stage of the disease and contains hysterectomy and uni or bilateral salpngo-oophorectomy [8]. Nevertheless, using surgery alone is rarely reported to be effective in advanced stages of OC [10]. Intravenous and intraperitoneal chemotherapy are two convenient methods (adjuvant to surgery) in confronting a patient with a stage 2 and above ovarian malignancy [10, 11]. Still and all, platinum-based cytotoxic drugs such as paclitaxel are not being used for patients with recurrent ovarian cancer [8]. Neoadjuvant chemotherapy or NACT is another therapeutic approach which its usage is increased recently [9, 12, 13]. In this method, chemotherapy should be administered

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before operating any surgery [9, 12]. Besides, there are also some other options for OC treatment, including radiation therapy, PARP inhibiting, immunotherapy including PD-1/PD-L1-targeted immune checkpoint inhibitors and VEGFR inhibitors, targeting some antigens and signaling pathways related to OC including PI3K (Phosphatidylinositol 3-Kinase), folate receptor alpha, and Protein tyrosine kinase 7 which are mostly being used in advanced and metastatic stages and the recurrence of this disease [14-19]. All taken together, searching for novel drugs, agents, or methods are needed for enhancing the status of OC patients and reducing the mortality and morbidity rates of this fatal cancer. In such wise, we tend to investigate the advantageous effects of the family of beta-glucans on the cancerous cells especially the ones are located in the ovaries, fallopian tube, uterine ligaments (and adnexa), and the peritoneum and retroperitoneum spaces which all are being known in the name of ovarian cancer [20].

2. WHAT ARE BETA-GLUCANS?

Glucose molecules are able to bind to each other with diverse kinds of linkages and create various dimers, oligomers, and polymers. When a great number of D-glucose monomers are linked together with several beta-glycosidic bonds, a polymer is established that is called "beta-glucan" [21]. These natural polysaccharides are mainly composed of a linear core chain with β (1→3) bonds and a number of branches which are linked to the core chain by β (1→4) or β (1→6) linkages [22]. Mostly, there are three sources for extraction of beta-glucans: plants such as oat and barley [23, 24], fungi such as yeasts and Shiitake mushrooms [25, 26], and bacteria such as Agrobacterium [27]. These polymers take numerous parts in our body by dint of attaching to their cellular receptors. In our knowledge, four types of receptors are able to provide a connection with these molecules.

Complement receptor 3 or CR3 is one of the most important receptors that allows beta-glucans to function [28]. This receptor is composed of two chains: α and β [29]. The alpha chain is a kind of CD11 that is known to have a, b, and c types, and beta chain is a CD18 protein [22, 28]. This receptor is mostly found in the cellular membrane of myeloid-derived cells such as natural killer cells, macrophages, neutrophils, and dendritic cells as a transmembrane glycoprotein [30]. CR3 has the ability to bind to a beta-glucan by its α_M chain and bind to one of the ingredients of complement (iC3b) from another site [29]. CR3 has the possibility of binding to a great number of endogenous and exogenous ligands and, after creating the connection, it facilitates the complement-associated opsonization and finally triggers the phagocytosis by immunity cells [31, 32]. Dectin-1 is another essential receptor for beta-glucans to act upon [33, 34]. This receptor is a member of C-type lectin family, which comprises extracellular (C-terminal), transmembrane (a single domain), and intracellular (amino-terminal) components [35, 36]. Dectin-1 expression is in similar cells with CR3 receptor which have a myeloid ancestor [37]. Moreover, this receptor is secondarily expressed in T and B lymphocytes [37]. Many functions are attributed to this class of receptors, such as inducing phagocytosis, increasing the release of inflammatory mediators such as cytokines and chemokines, and increasing the oxidative burst conducted by neutrophils [28, 36, 38, 39].

Besides the mentioned receptors, there are also some other additional receptors whose expressions and functions are lesser in amount and number in comparison to CR3 and dectin-1 [36]. Lactosylceramide is one of these receptors that can be found on the surface of the polymorphonuclear leukocytes in humans [40]. Similar to the mentioned tasks of CR3 and dectin-1, this receptor is also able to augment cytokine secretion and oxidative burst after binding to beta-glucans [40, 41]. CD5, which is a scavenger receptor, is another member of the beta-glucan receptor group [42]. The cellular membranes of mature T and B1a cells are where CD5 can be found [42]. The exact tasks and mechanisms of this receptor are not clear yet, but generally, it has the ability to inhibit the activity of B cells signaling, increase the secretion of interleukin-8, and activate ERK and p38 MAP kinase in Jurkat T cells [29, 42, 43].

3. OVARIAN CANCER PATHOGENESIS

According to investigations on the cause of OC, it seems that more than 23% of ovarian cancers are inherited [44]. There are several genetic abnormalities which are known to be responsible for hereditary OC, including BRCA1/2, TP53, BARD1, CHEK2, and RAD51 which BRCA1 and 2 seem to be the most common among them [44]. Carriers of BRCA1 and 2 mutations have a higher chance of getting OC (BRCA1 40%–60% and BRCA2 11%–30%) and in about 65–85% of OC patients, these mutations are detectable [45, 46].

After all, the main question is "how does BRCA mutation result in ovarian cancer?". The answer to this question relies on the DNA damage responses, which get help from these proteins to detect and repair the DNA lesions [47]. Both of these proteins are involved in repairing the double-stranded lesions of DNA, which is mostly possible through non-homologous end-joining (NHEJ) and homologous recombination (HR) repair pathways [47]. In the HR process, BRCA1 is recruited to the damage site by histone H2AX and takes part in DNA end resection by means of CtIP ubiquitination, which initiates the nuclease activities on DNA strands [48, 49].

BRCA2 is also a mediator of HR, aiding the process of RPA removal from the single-stranded DNA, which is established in the DNA end resection stage of HR [48]. Therefore, BRCA2 is participating in the generation of a RAD51-related nucleoprotein filament [49].

Overall, BRCA1/2 mutations or epigenetic inactivation cause the deficiency of HR pathway in ovarian cells and increase their susceptibility to genome defects which is one of the bases of tumor initiation [50].

However, despite all of our improvements in the field of cancer pathogenesis, still, an exact answer is missing for the questions about the pathogenesis of ovarian cancer. Investigators have represented some hypotheses by means of cellular and molecular pathways, which we discuss in this section separately.

3.1. Inflammation

During the process of inflammation, immune cells are recruited at the site of injury or infection due to the secretion of some cytokines and chemokines [51]. Destruction of the injured cells or pathogenic agents is being conducted by some cells such as macrophages, dendritic cells, and neutrophils and some mechanisms such phagocytosis and the release of free radicals, TNF-α, interleukins, serine and cysteine proteases, and interferons [52]. After the binding of inflammatory mediators to a cell, some signaling pathways are triggered, including NF-κB or nuclear factor kappa-light-chain-enhancer of activated B cells, MAPKs or p38 mitogen-activated protein kinases, and JNK or c-Jun *N*-terminal kinase [53-55]. Recently, a great body of evidence has revealed the role of different components of this process in the initiation of many diseases such as cancer [56]. Mutating cellular DNA and triggering NF-κB pathway are two main known reasons why inflammation leads to cancer [57]. In ovarian cancer perspective, inflammation is reported to be one of the main pathogenesis-related mechanisms by many researchers [58]. One of the most reliable hypotheses in this field is "incessant ovulation" [58]. It is believed that every month during ovulation, ovarian epithelium undergoes a bunch of injuries which is being repeated in the entire life of a woman, and this occurrence results in induced inflammatory responses [57, 58].

The role of inflammation in each step of ovulation is confirmed; for instance, Luteinizing hormones are causing an augmentation in the number of neutrophils in the ovaries before the ovulation [57]. Moreover, there are several macrophages in the thecal layer of ovaries which are responsible for secreting epidermal growth factor (EGF), reactive oxygen species or ROS, tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β). Increased amounts of these mediators manage some alterations in the expression of some inflammatory genes and induce cyclooxygenase-2 (COX-2) and IL-8 expression [57, 59, 60]. In addition to the ovulation process itself, there are also some other factors that are able to boost the risk of OC through inflammation. These factors include infection in the reproductive system, overweight, endometriosis, and polycystic ovarian syndrome (PCOS) [61-65]. Overall, evidence demonstrates that inflammation is able to help ovarian cancer initiation by two mechanisms: secreting cytokines, chemokines, and growth factors and releasing free radicals such as ROS and providing oxidative stress.

3.2. Apoptosis

The lack of apoptosis or programmed cell death is one of the fundamental parts of cancer pathogenesis [66]. There are two main pathways that provoke the process of apoptosis: intrinsic and extrinsic [67]. The former pathway is conducted by mitochondria and their released agents and the latter pathway is conducted through the binding of some ligands such as FasL to their receptors on the cell surface [67]. Both of these pathways have the task of activating some cysteine proteases named caspases [68]. These proteases are responsible for most of the alterations happening in an apoptotic cell [68]. Additionally, there are some genes and their related proteins like Bc1-2 and p53, which are regulating apoptosis by triggering or inhibiting it in times of need [67]. Overall, any disturbance in any ingredient of this process is able to establish a disease like malignancies.

Free radicals like oxygen or nitrogen reactive species are one of the factors that have the ability to activate some signaling pathways, such as HIF-1α and thus, disturb the balance between apoptosis and proliferation in a cell. Some cellular mechanisms exist which have the duty of inhibiting free radicals; for instance, N(G)-nitro-L-arginine methyl ester or L-NAME is an inhibitor of nitric oxide (NO) synthesis and prevents the accumulation of NOS in cells [69].

In the case of OC, investigations express that apoptosis helps the cancer progression in two ways: promoting apoptosis in lymphocytes, which is the cause of IL-6 secretion, and the suppression of immune system [70]. Although the main mechanism happens in the cancerous cells: in these cells, L-NAME (N(G)-nitro-L-arginine methyl ester) inhibits iNOS and therefore, apoptosis is down-regulated in these cells because of NO/iNOS pathways [71].

3.3. Uncontrolled Cell Proliferation

Uncontrolled cell proliferation is one of the most essential cancer hallmarks, which is mostly triggered in cancerous ovarian cells by inflammation-associated signaling pathways. PI3K/AKT/mTOR is one of these pathways which aids tumor formation through a diversity of mechanisms, including increasing cellular proliferation [72]. Targeting ingredients of this signaling pathway by specific siRNAs has shown that the proliferation of cancerous cells of ovaries can be suppressed [73, 74]. On the other hand, NF-κB is also an essential part of OC pathogenesis which affects the cell cycle by regulating its checkpoints, activating mitogen-activated protein kinase (MAPK) phosphorylation, and regulating mortalin [75-77]. On the other hand, it might also be related to uncontrolled proliferation of OC cells. Guan *et al*., [78] found out that higher levels of PUM1 gene (pumilio RNA binding family member 1 in these cells is involved in cancer initiation). This gene is associated with chromosomal mutations [78].

Additionally, there are some other genes whose abnormal expression is observed to be related to increased proliferation of OC cells and their effect is approved after observing the suppressed proliferation when they are targeted by non-coding RNAs. PTEN, PLXNB2, YWHAZ, hTERT, FOXA1, SNHG17, S100A10, PTCH1, and ZEB1 are some of these genes [79-86].

4. DIVERSE FUNCTIONS OF BETA-GLUCANS IN CANCER

In general, a wide range of functions are attributed to beta-glucans but what is orienting many researchers towards them is their anti-cancer and immunologic effects. Inflammation, oxidative stress, and apoptosis are three main mechanisms that are being affected by these polysaccharides (summarized in Fig. **1**), but before discussing these mechanisms, we would take a brief look at beta-glucan's cellular effects.

The cellular impact of these polymers is mediated by different types of membrane receptors containing Dectin-1,complement receptor 3 or CR3, lactosylceramide, and Toll-like receptors [87]. Dectin-1 receptor is mostly expressed at

the surface of inflammatory cells, including neutrophils, macrophages, and dendritic cells. Dectin-1/Syk/NF-κB signaling is one of the most important axes through which this receptor works [88]. NF-kB activation is the share point of Dectin-1 and lactosylceramide receptor which participates in pro-inflammatory responses [89]. Similar to Dectin-1, CR3 is also broadly expressed on macrophages and natural killer cells and, when activated by beta-glucans, binds to a variety of cells encompassing antibody-coated cancer cells [90].

4.1. Inflammation

With respect to researches, beta-glucans are affecting both innate and adaptive immunities and thereby modulate the inflammatory response [91]. The influence of beta-glucans on inflammation is possible in two ways: affecting the production of cytokines/chemokines and impacting the proliferation and activation of immune cells. Some studies have approved the former mechanism; for example, Olson *et al*., showed that beta-glucans are increasing the release of TNF-α by neutrophils [92]. Increasing the production of TNF-α by macrophages is also detected due to the binding of beta-glucans to CR3, Dectin-1, and TLR-2 [91]. In addition to TNF-α, serum levels of some other cytokines such as IL-1a, IL-2, IL-4, IL-8, IL-10, and IFN-gamma are investigated after beta-glucan administration [93-95].

The latter mechanism or affecting immune cells such as dendritic cells, Myeloid-derived suppressor cells, macrophages, neutrophils, and leukocytes are also explored by a great body of research [40, 95-98]. In macrophages, regulating Phospholipase A2 and increasing the cyclo-oxygenase 2 expression is achievable after the adminis-tration of zymosan [99]. Zymosan increases arachidonic acid and leukotriene C4 through Dectin-1 and increases COX2 expression and prostaglandin through TLR2 [99]. Zymosan also affects leukocytes in a direct manner and, after activating them, stimulates phagocytosis and the amounts of ROS secreting from them [100]. In view of leukocyte, "β-glucans shift the tumor microenvironment toward a T cell-sensitive environment" [101].

4.2. Oxidative Stress

Wakshull *et al*. revealed that beta-glucans are able to improve the oxidative burst response of neutrophils by binding to one of their receptors: lactosylceramide [40]. Furthermore, the interaction between beta-glucans and C-type lectin receptors (CLRs) is widely reviewed by Goyal *et al*. [102]. CLRs are known for their ability to bind to carbohydrates and include several receptors like Dectin-1 and Dectin-2. It seems that in addition to immune cells, pulmonary epithelial cells are also prone to be affected by beta-glucans *via* Dectin-1 and afterward, generate ROS [103]. Liang *et al*. [104] also observed an augmentation in oxidative burst response conducted by neutrophils in rats after PGG-Glucan treatment. They also revealed that this effect is not dependent on the expression of TNF-α and IL-1β in rats [104]. Bose *et al*. tried to reveal the exact receptor which mediates this function of beta-glucans in monocytes [105]. They used GE2 antibody for blocking Dectin-1 and a combination of antibodies for different subunits of CR3. They concluded that Dectin-1 inhibition effectively decreases the SO production in these cells while CR3 inhibition doesn't affect oxidative burst [105].

4.3. Apoptosis

There are not many papers directly mentioning apoptosis as an important influence of beta-glucans, but beta-glucans can indirectly affect apoptosis in cancer cells. For instance, affecting NF-κB pathway by these agents is related to apoptosis alterations [106, 107]. Another way of inducing apoptosis is by increasing oxidative stress [108], which we have declared before. Sensitizing cancerous cells to apoptosis by means of caspase 8 and 3 activation is one of the mechanisms by which these agents work [109, 110]. In addition, transferring BID into the mitochondria is also stimulated by beta-glucans which results in apoptosis [109]. Beta-glucans are also capable of regulating apoptosis-related genes, such as decreasing the expression of Bcl-2 and increasing the expression of Bax [110, 111]. On the other hand, β-*D*-glucans also induce necrosis along with apoptosis which inhibits the progression of cancer cells [112].

5. HAVE BETA-GLUCANS EVER BEEN USED IN CANCER TREATMENT?

A great body of evidence has shown how beta-glucans have the potential to help overcoming cancer. For instance, Thomas *et al.* used PGG in combination with chemotherapy for the treatment of advanced lung cancer [113]. Furthermore, there is also some other evidence for lung cancer [114]. Ostadrahimi *et al.* [115] revealed that using beta-glucans adjuvant to chemotherapy is useful for breast cancer treatment. Kataoka *et al*. revealed the roles of lentinan on the life quality of gastric cancer patients [116]. Tari and colleagues also worked on lentinan and found that it is useful for the treatment of metastatic prostate carcinoma [117]. Overall, these evidence (and a great number of others that we have not mentioned) demonstrate that beta-glucans have the potential for being administered adjuvant to chemotherapy in order to enhance their efficacy and decrease their side effects on the patients of different cancers.

6. BETA-GLUCANS AND OVARIAN CANCER: MECHANISMS

In regard to the many roles that beta-glucans have in cancer treatment, they might have some advantages in ovarian cancer treatment, as well. Therefore, we gathered some evidence to investigate the exact functions of these natural polymers in OC (Fig. **1**).

6.1. Lentinan

Lentinan is a β-(1 → 3)-d-glucan that can be excreted from a common edible mushroom, *Lentinus edodes* [118]. A case-control trial on an OC patient with recurrent cancer in the lymph nodes declared that Adoptive immunotherapy with lentinan without using any chemotherapeutic drugs is useful for the treatment of lymph node metastases from ovarian cancer [119]. Another case-control study also revealed that utilizing intravenous lentinan with IA 5FU increases the production of IL-6 and, overall, inhibits cancer recurrence [120]. Another paper also confirmed the anti-cancer effects of

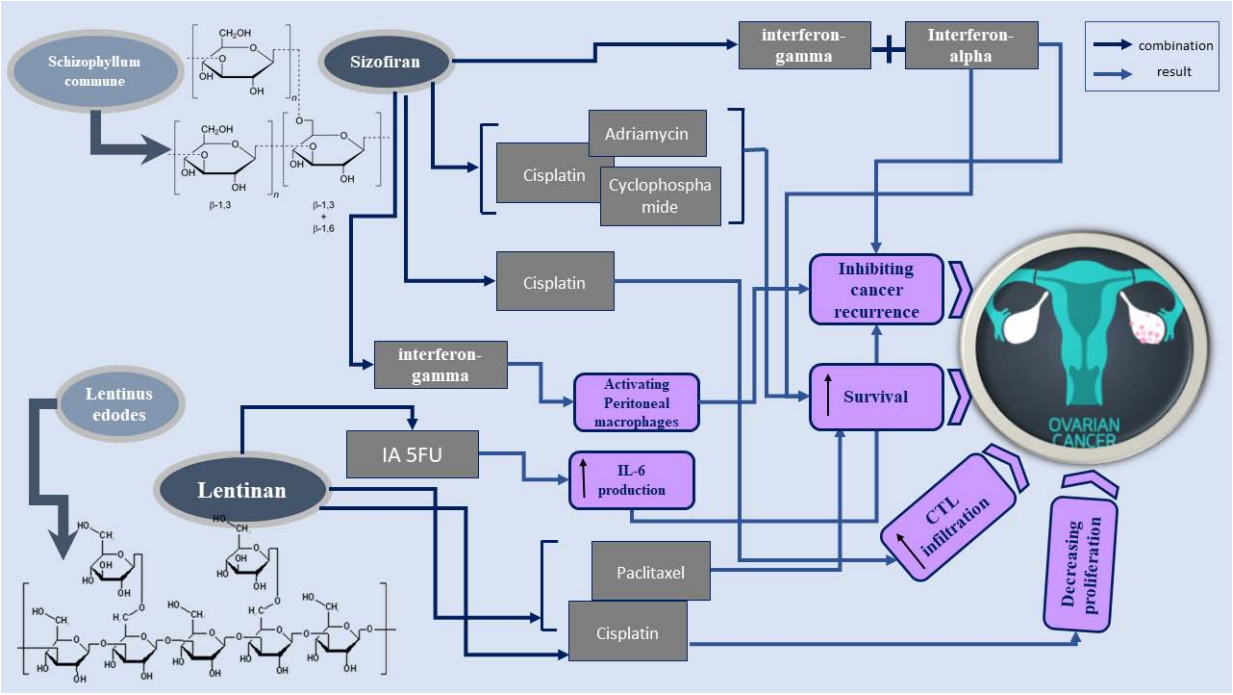

Fig. (1). Schematic representation of how beta-glucans exerts its functions in ovarian cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

lentinan on advanced ovarian cancer patients by combining this beta-glucan with cisplatin and paclitaxel [121, 122].

Furthermore, using the combination of lentinan and cisplatin on Hey ovarian cancer cells inhibited these cells by decreasing their proliferation [123] (Fig. **1**).

6.2. Sizofiran

Schizophyllan or SPG is produced by the fungus *Schizophyllum commune*. Schizophyllan is a *β*-1, 3 beta-glucan with *β*-1, 6 branching. Schizophyllan is also known as sizofiran [124]. Chen *et al*. [125] used combined immunotherapy on 12 ovarian cancer patients and found that the combination of sizofiran with Interferon-alpha and interferon-gamma is helping the survival of OC patients and no recurrence was observed in these patients. Hoshino and colleagues used another combination (sizofiran and rG-CSF) on OC patients who are going through chemotherapy. They revealed that this combination could be useful for myelosuppression by chemotherapy for ovarian cancer [126]. Another group of investigators also worked on this beta-glucan and revealed that utilizing sizofiran or SPG in patients undergoing chemotherapy with cisplatin, adriamycin and cyclophosphamide can enhance the prognosis in these patients [127]. Sugiyama *et al.* used this agent with cisplatin on OC rats and demonstrated that this combination improves the survival rate and cytotoxic T-lymphocyte (CTL) infiltration [128]. Chen *et al.* conducted an *in vivo* trial on 19 patients and expressed that sizofiran and recombinant interferon-*γ* prevent the recurrence of gynecological cancers especially ovarian cancers, by activating peritoneal macrophages [129] (Fig. **1**).

6.3. Cellulose

Cellulose is another beta-glucan that has been used for designing nanoparticles in the field of drug delivery. There are some studies confirming the efficacy of cellulose-nanoparticles in OC patients, but there is no evidence of direct impacts of this beta-glucan on ovarian cancer cells [130, 131]. However, there is one study using cellulose as a delivery system for cisplatin. Using conjugates of cellulose, 2, 3-dicarboxycellulose (DCC) increases the time of drug release in the cancer site and thus, increases the efficacy of this drug [132].

6.4. Laminarin

Laminarin is beta-1,3-glucan, which can be extracted from brown algae [133]. A recent study has shown some benefits of this beta-glucan against OC cells. *In vitro* investigation of laminarin indicates that it decreases the proliferation of OC cells dose-dependently [134]. Increasing ROS generation, cleaved caspase-3, and caspase 9 are the pro-apoptotic effects of this agent. Furthermore, it is able to trigger mitochondrial apoptosis by increasing the concentration of Ca [134]. More importantly, "laminarin significantly decreased the phosphorylation of PI3K/MAPK signaling proteins in OC cells." All these results suggest that further investigations on this beta-glucan might be useful for providing more therapeutic options for advanced OC [134].

CONCLUSION

Ovarian cancer is one of the most lethal and important health problems among women in the world. The most common treatment used for this cancer is chemotherapy which has a great number of disadvantages on patients. For instance, Chemotherapy-induced peripheral neuropathy (CIPN), Chemotherapy-induced nausea and vomiting (CINV), cognitive dysfunction, mood disorders, fatigue, and cytopenias are the most frequent side-effects between OC patients undergoing chemotherapy (as reviewed by Gockely

[135]). Thus, despite all the improvements in diagnosis and treatment of this cancer, still, more methods and strategies are required for reducing the burden of this disease, increasing its survival rate, and enhancing the life quality of survived patients. Beta-glucans are a kind of glucose polymers that have attracted a lot of attention for their anti-cancer effects and non-toxicity. The role of these linear polysaccharides is investigated in several types of cancers. In this paper, we gathered some evidence on the efficacy of these agents on ovarian cancer. We found that lentinan and sizofiran are useful for enhancing the treatment, preventing recurrence, and decreasing the cytotoxic effects of chemotherapeutic drugs. Although, still more investigations are needed. We suggest that other beta-glucans such as curdlan might also be useful for ovarian cancer treatment (Fig. **1**). Moreover, recently some explorations have shown the effectiveness of oral administration of beta-glucans with monoclonal antibodies in the field of cancer treatment [136]. However, there is no evidence for the effectiveness of this method on ovarian cancer. Therefore, we think that working on this subject might give us new insights for OC treatment.

AUTHORS' CONTRIBUTIONS

FS, ZA and JH contributed to the conception, design and drafting of the manuscript. MAM, BY contributed to reviewing relevant literature. All authors approved the final version for submission.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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