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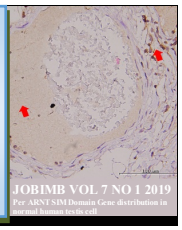

Glycosaminoglycans From Plant Sources and The Potential Uses as Anticoagulant and Anticancer Agents

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ABSTRACT

Glycosaminoglycans (GAGs) are usually found in mammals or invertebrates organisms. Since there are many potential active ingredients in plants that have not been investigated till dates, this review will be discussing the plants' potential to be the alternative for GAGs source. The study will enlighten the correlation between two crucial properties, anticoagulant and anticancer properties. This is because these two properties are usually found in organisms with GAGs presence. GAGs have obviously played an important role to elicit these two properties within an organism's biological system. The study found that based on previous researches investigations, plants have the potential to have GAGs which then act as replacement of anticoagulant carrying anticancer properties.

INTRODUCTION

Plants have been widely known as major sources of anticancer; but, their roles as an anticoagulant are still questionable. On the other hand, animals are the biggest suppliers of anticoagulant of all times; yet, the halal status of the animal-derived products is a major concern for the Muslim community. Glycosaminoglycans (GAGs) are compounds that have medicinal properties such as anticoagulant and anticancer. Currently, the main sources of GAGs are from animals, especially swine. This brings a big issue especially for the Muslim community to consume and use medicinal products with ingredients derived from porcine sources. The good news is that GAGs can also be isolated from plants. However, very few studies have reported the properties of GAGs from plant sources. Thus, this article reviews GAGs isolated from plants as a source of anticoagulant and anticancer.

Medicinal plants as sources for treatments

As they contain therapeutic compounds, plants have long become primary medicinal sources. In fact, humans rely on the effectiveness of plants to cure themselves from many medical conditions such as diarrhoea [1], acne [2], respiratory problem, and wound [3]. Scientists have conducted studies to investigate the biological functions of plants. For example, a study has experimentally proven an antituberculosis potential of Malaysian traditional plants [4]. In the study, tetrazolium microplate assay was carried out, and four plant species were found to have an active component that inhibited tuberculosis, namely *Costus speciosus*, *Piper sarmentosum*, *Pluchea indica* (from leaf and flower, separately), and *Tabernaemontana coronaria*. In another study, *Pereskia bleo* was found to be able to induce apoptosis in breast carcinoma [5]. This result was in agreement with [6], which showed a cytotoxic activity of *P. bleo* on cancer cells.

Other than that, a study has reported that almost 80% of Ethiopian people depended on traditional medicines from plant origins [7]. The study investigated the lifestyle of Zay people in consuming medicines made from plants. Thirty-three types of plants were evaluated as to which ones were the most preferred by the Zay people based on their knowledge on medicinal plants, factors affecting the practice, current status/abundance of medicinal plants, and possible threats in the area. All the plants in the study were reported to have their own functions in healing illnesses such as gastrointestinal problems, febrile ailments, skin diseases, chest pain, and other common illnesses like

haemorrhoids, tonsillitis, and toothache. The study has proven that the plants carried all sorts of healing abilities not only for humans, but for animals as well.

Anticoagulant and anticancer

An anticoagulant, as the name implies, prevents coagulation mechanism. As defined by the American Heart Association, an anticoagulant stops any actions or factors that are required for coagulation to happen by blocking a protein called a cofactor, which is classified into thrombin and fibrin. The cofactor production is controlled by vitamin K in the liver. Warfarin (a type of anticoagulant) also controls the production of the cofactor. Thrombin and fibrin work together to make the blood components to clot. An anticoagulant such as heparin stops the actions of thrombin and fibrin. Therefore, warfarin and heparin play important roles to ensure blood clotting can be regulated. Warfarin and heparin are produced from a single compound named glycosaminoglycans (GAGs), which can be found in diverse forms and sources.

Previous researches have investigated the potential medicinal properties of certain compounds from plant samples. The Western medicinal studies have been focusing on isolation and identification of one compound from a sample. However, this approach has been disapproved by a study that observed the cytoprotective and antioxidant properties of Chinese medicinal herbs [8]. The researchers concluded that the use of only one compound in a treatment might lead to an imbalance between body and environment, which could in turn cause diseases.

Such a conclusion is in line with another study on traditional Chinese medicine for cancer treatments [9]. The researchers investigated 50 types of plant that were proven to carry an anticancer property. They found a high amount of phenolic compound in these plants, which also exhibited a high antioxidant activity. Not only that, a phenolic compound named coumarin (vitamin K antagonist) that reduces blood clotting by preventing vitamin K production, was also found in these plants. The researchers concluded that the total phenol content in the plants reflected their antioxidant activity, and reflected the role of these plants as an anticancer and anticoagulant. Therefore, it is possible to test multiple medicinal properties of plants, as one property might be caused or supported by another property.

GAGs as anticancer and anticoagulant

Glycosaminoglycans are divided into several classes such as heparan sulphate, chondroitin sulphate, keratan sulphate, and hyaluronic acid (see **Fig. 1**). These classes have different functions [10-13]. Of all these classes, heparan sulphate is said to have numerous anticoagulant contents. The structure of heparin and chondroitin are completely identical, but their anticoagulant abilities are different [14].

A previous study has discussed the action of heparin to avert tumour cells. According to the study, chondroitin sulphate carries much lower anticoagulant than heparin [15]. Heparin sulphate contains heparin (highly negative charge than heparan sulphate) in human body in heparan sulphate proteoglycan. Fibrin is a component responsible for coagulation to occur. It protects tumour cells by surrounding them. This so-called heparin, on the other hand, carries a predominant role in atherogenesis. It helps to break open the tumour cells' protective zone by inducing them to be susceptible to natural killer cells. This is how an anticoagulant affects cancer activity.

Moreover, heparin affects cancer progression in many ways [14]. Heparin-treated rats were found to be able to inhibit a metastatic process after administered with Walker carcinoma cells [16]. Heparin was also found to reduce tumour growth in induced rats [14, 17]. Another study has proven heparin was capable to alter the distribution patterns of cancer cells [18]. Heparin has also been demonstrated to have the capacity to affect the development of primary tumours and metastases and to prevent the development of thromboembolic events [19].

GAGs as an anticoagulant

Studies have been conducted to investigate the ability of GAGs as an anticoagulant agent from various sources. For example, shrimp heparin from *Penaeus brasiliensis* was found to exhibit a similar antithrombotic activity like that of low molecular weight heparins. The shrimp species was found to be rich in glucuronic acid and non-sulphated iduronic acid residue [20]. Another example is an algae species as a source of anticoagulant. From a metachromatic assay, the algae species yielded 2.3g/50g yield of heparin, making the species a new anticoagulant agent. The algae species was found to resemble a heparin activity [21].

Moreover, GAGs have also been extracted from snail. However, previously the method was tedious, thus researchers have come out with a novel and practical way to obtain a high and readily available yield. These acharan sulphate-like GAGs are highly effective at low concentrations such as 1 mg/mL and 2 mg/mL. Other than that, GAGs have also been found in sea cucumber for thrombosis prevention by fucosylated chondroitin sulphate (FCS) [22]. At 1.5 mg/kg dose, FCS may reduce thrombosis rate. The anticoagulant activity is influenced by GAGs by intervening the venous thrombosis.

Plants are highly believed to possess an anticoagulant property as they also contain anticancer agents. For example, *Erigeron canadensis L.* was found to act as an anticoagulant and antiplatelet due to its polyphenolic-polysaccharide activity [23]. The plant showed a higher anticoagulant activity than *Porana volubilis* [24]. Next, an anticoagulant from the plant *Bauhinia forficata* was reported to be the next cure for snake venom [25]. Other than that, GAGs in aloe vera such as *Portulaca oleracea L.* were found to be highly potential in healing wounds [26-28].

GAGs as an anticancer

Glycosaminoglycans have been proven to have an anticancer activity. For example, a study on ovary cancer reported that GAGs were able to surpass a major obstacle in chemotherapy namely drug resistance by providing resistance towards mediators like P-glycoprotein and ATP-binding cassette [29]. Another study involving GAGs proposed heparosan-DOX conjugate in their attempt to investigate endocytosis pathway of heparosan on HeLa and A549 cells [30]. Other than that, there was also a new discovery on a methodology to mediate antiangiogenic acharan sulphate-like GAGs from one of its classes, heparin for cancer treatment. About 60% of clinical anticancer drugs originate from natural sources, mostly derived from plants [31]. Plants have long been used in the treatment of cancers [31,32]. Plants such as vegetables, fruits, and herbs are also used to treat cancer patients undergoing chemotherapy [33]. Remedies derived from natural products have been reported to help patients to endure their pain much better. Herbal preparations for treating cancers are more practical than conventional medicine especially for rural and poor people as they could get the medication at an affordable price

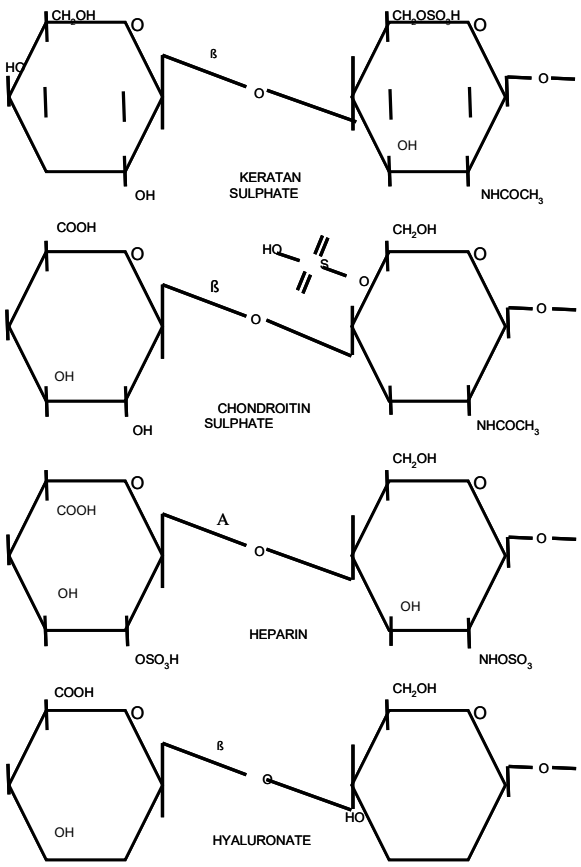

Fig. 1. Structure of different GAGs classes. Unlabelled sections indicate Hydrogen group.

Plants are the best anticancer due to the presence of secondary metabolites that effectively block metabolic pathways and hormones that are direct or indirectly involved with cancer [34]. Ancient people believed plants were the best source of anticancer to prevent cancer diseases in many ways. However, their claims have not been proven scientifically. Thus, many clinical studies have been conducted by the reputable scientists to prove the claims. For example, *Pouzolzia indica* was found to exhibit the highest cytotoxic activity and to prevent cell mitochondrial activity of cancer cells [35]. Another study focusing on plant secondary metabolite reported many anticancer agents were derived from plant secondary metabolites [35]. Anticancer agents such as vinca alkaloids have been identified from *Catharanthus roseus, Podophyllum* sp., *Taxus brevifolia, Camptotheca acuminate, Betula alba, Cephalotaxus sp., Erythroxylum pervillei, Curcuma longa, Ipomoea batatas, and Centaurea schischkinii.*

Many other clinical studies have proven the capability of plants in fighting against cancers. Examples are *Ailanthus altissima* and *Pyrus malus* against intestinal cancer, *Chelidonium majus* var. asiaticum against stomach cancer, *Chimaphila umbellata* against breast cancer, *Lonicera japonica* against ascites cancer, *Nidus vespae* against gastric and liver cancers, *Oldenlandia diffusa* against leukaemia, *Phaleria macrocarpa* against oesophageal cancer, *Pygeum africanum* against prostate cancer, and *Vitex rotundifolia* against lung tumour [23-25, 36-40].

Anticancer property has been studied from diverse sources such as microorganisms, seafood, seafood waste, and animals. Such a property has also been studied on plants mostly from their secondary metabolite compounds. In most cases, the compounds have been tested on mammals for anticancer their effect. For example, the effect of heparin in an anticancer therapy on animal tumour model was investigated. The anticoagulant activity was found to show a good sign of inhibition in blood coagulation [41]. Cancer proliferation on cell lines was also observed to be inhibited by GAGs in osteoblasts and human osteosarcoma cells [42]. Heparin has also been identified as one of the GAGs for cancer therapy [43]. The activity of heparin on breast cancer was monitored. It was used as a biomarker for invasive ductal carcinoma. Other than that, GAGs are promising compounds to be modified. The effects of modified and pure chondroitin sulphates were compared, and it was found that they showed different effect on anticancer activity [44]. For example, heparin and chondroitin sulphate were mixed to secrete neoglycans, which were surprisingly effective to cause apoptosis to myeloma cells [45].

CONCLUSION

Many studies have been carried out to investigate the potential of plants as a source of anticoagulant and anticancer. More investigations must be conducted to support previous pre-clinical studies, as plants could be a new source of anticoagulant carrying anticancer property, a potential that could replace animal-derived medications.

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