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An Insight into the Health Benefits of Sodium Alginate and its Derivatives

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ABSTRACT

Owing to safety and unique properties, alginates are widely used in Biomedicine, food industry and pharmaceutics products. The multifaceted properties of alginate make it a captivating topic for extra scientific exploration in the anti-inflammatory and anti-tumoral areas. This paper describes the biological properties including anti-cancer and anti-inflammatory functions of sodium alginate and its components, mannuronic acid and guluronic acid, as alginate derivatives. However, the wide application of alginates as polysaccharides is limited due to their high molecular weight and low solubility; therefore, its degraded monomers, mannuronic acid and guluronic acid as products of alginate hydrolysate can be a solution in this case. In conclusion, these natural non-toxic, biocompatible, biodegradable, and quite cost-effective materials are totally operative for cancer management and control of inflammation, as their important biological effects and health benefits, in addition to their wide applications in food industry.

Introduction

Alginate is a biomaterial with a tremendous utilize in biomedicine and industry due to its beneficial aspects like biocompatibility and easiness of gelation. Fundamentally, alginate is a polysaccharide of linear copolymers consist of sequesters of α-L-guluronate and β-D-mannuronate molecules covalently linked by 1,4-glycosidic bonds [1]. The number and organization of the blocks, alginate source, and extraction procedure led to a specific physicochemical nature [2]. X-ray-based demonstrated that alginate encompasses all 4 probable glycosidic bonds. This property leads to the adaptability of alginate chains due to M and G composition and the arrangement of the chain [3-5].One of the noteworthy particularities of alginates is the ability to form gels by binding multivalent cations or acid precipitation [6]. On the other hand, alginates are mostly extracted from brown seaweed [7-10] but, these polysaccharides can also be extracted from bacterial sources like Pseudomonas aeruginosa and Azotobacter vinelandii [11]. However, the extraction process of alginate is not complex but includes multi stages, ordinarily is started with treating the dried algae with a frail acid. After more fine-tuning it will be changed into soluble sodium alginate [12,13]. Moreover, microbial fermentation is another method to reach additional physicochemical properties [14]. The type, time of year and place of harvesting of algae and extraction circumstances including PH, temperature, and time, considerably modify the chemical properties like pureness, M and G rearrangement and proportion, molecular weight of the extracted alginate [15,16]. Alginates are known as non-immunogenic, non-tox-

ic, and biocompatible constituents [12]; consequently, these natural polymers are used enormously in biomedicine, food, pharmaceutical, and cosmetic productions [17-21].

Application of Alginates in the Pharmaceutical Industry

Alginic acid and its most recognized product, sodium alginate, are utilized in the manufacture of solid drugs. Despite benefits of alginates including richness, low price, safety, and biodegradability, high variability of alginates may possibly limit their function in tablet-making industries [22]. Sodium alginate has been useful as suspending and binder material, flavor improver, and controlled-release medium [21,23-25]. The exploration of natural excipients is a fascinating subject in the pharmaceutical industry. Appropriate drug excipient should be directly condensable and can be mixed with the main ingredient with no effect on the quality of the drug [26-28].

Application of Alginates in the Food Industry

Alginates predominantly are used in the food industries as a forming, thickening, soothing, combining [29], covering [30,31], and pathogen prohibiting materials [32]. Alginate-based films are totally edible and environmentally recyclable products have been used in packing products such as powdered milk and coffee [33]. These foods reduce the non-recyclable wastes and help to control environmental pollution [34,35]. Ca-alginate gel is a famous material for encapsulating polyphenols to keep the benefits of polyphenols in food products. Hydrogel coating of fruit juice preserves its antioxidant function without any interaction between drug constituents and alginate [36]. Calcium-alginate gel microbeads are applied for encapsulating and keeping alive probiotics in the gastrointestinal system [37]. They are also used in dairy products such as ice cream and yogurt to reduce the granular sensation [38]. Ca-alginate gel is used to limited-calorie products such as mayonnaise to reduce fat intake which helps to have a healthy diet [39,40].

Biological Properties of Sodium Alginate

Anti-Cancer Effects of Sodium Alginate and its Molecular Mechanisms

Cancer is the leading reason for death in developed countries and the second most common cause of death in other countries [41]. Chemotherapy is a critical modality of cancer management [42] but is often followed by serious side effects [43]. Despite of effectiveness of agents such as cisplatin, carboplatin, and oxaliplatin, their use is restricted due to their severe, dose-limiting adverse effects [44]. Avoiding unwanted effects of chemotherapeutic drugs, many researchers are searching to find non-toxic natural anti-cancer materials in the ocean. Between these materials, sodium alginate is an attractive and hopeful product because of its non-toxic, non-immunogenic, and biodegradable nature [45]. Sodium alginate is a non-toxic, and quite cost-effective natural polysaccharide that is used act of a drug delivery vehicle for cancer therapy. It encapsulates anti-tumor agents and carries them to tumor cells, decreasing the adverse effects and improving the efficiency of the treatment.

To administer anti-tumor agents, alginate-based medicine delivery techniques can be used with passive and active targeted methods. Therapeutic and diagnostic uses of alginate-based nanomedicine were also studied recently [46,47]. Moreover, alginate-based hydrogels are considered for drug-delivery vehicles in cancer management. Hydrogels are hydrophilic polymers with three-dimensional patterns that make them absorptive for large quantities of liquids such as water or biological fluids which is a superiority for drug delivery. Alginate-based hydrogels are applied to transport a range of chemotherapy drugs, including cisplatin, paclitaxel, and Doxorubicin. Alginate hydrogels have also been used to deliver drugs to specific sites in the body, such as the liver and the brain. Alginate hydrogels have been shown to be effective in decreasing tumor development and improving the survival rate of animals with malignancy [48].

Remarkably, the anti-inflammatory and antioxidant features of sodium alginate can protect the cells against cellular and DNA impairment evolved by oxidative stress. Interestingly, sodium alginate has been shown in some investigations that prevent the development and invasion of tumor cells by promoting apoptosis and modifying the immune system. The anti-cancer effects of alginate oligosaccharide consist of several mechanisms such as inhibition of growth and invasion of tumor cells, directing defense immune responses, and enforcement of anti-inflammatory and antioxidant processes. For example, alginate oligosaccharide has been confirmed to reduce the proliferation and invasion of prostate cancer cells by suppressing the Hippo/YAP/c-Jun signaling cascade [49]. Cancer-associated inflammation plays a key role in cancer development, angiogenesis, and metastasis. Fujihara et al. reported in 1992 that sodium alginate which is extracted from Sargassum fulvellum has significant anticancer function against several murine tumors, such as IMC carcinoma, sarcoma180, and Ehrlich ascites carcinoma. Alginate has the capability to enhance the chemotactic and cytolytic activities of macrophages; therefore, the antitumor property of alginate may be indirectly due to the triggering of macrophages [50]. Notably, the anticancer function of alginate oligosaccharide can be influenced by several factors such as the greater levels of MM-blocks allied with a higher antitumor effect [50,51].

Anti-Inflammatory Effects of Sodium Alginate and its Molecular Mechanisms

There is growing data that confirms the association of inflammation with the progress of a variety of pathologic conditions, like cancer, cardiovascular disorders, and obesity [52,53]. It is established that Toll-like receptors, and TLR4 chiefly, have a central role in the molecular mechanisms of inflammation [54]. The triggering of TLR4 downstream signaling by lipopolysaccharide (LPS) activates cellular events leading to the activation of several kinases such as MAPK, Akt, and PI3K, transcription factor NF– κ B, and eventually augmented production of inflammation-related mediators, comprising ROS, NO,

prostaglandin E2 (PGE2), iNOS, COX-2, as well as pro-inflammatory cytokines [55,56]. However, in most cases, extreme inflammatory responses are accompanied by adverse effects. And so, the anti-inflammatory action of natural polysaccharides has been intensively explored to find anti-inflammatory agents suppressing the production of NO and PGE2 and decreasing the expression of iNOS and COX-2. However, the wide application of these polysaccharides is limited due to their high molecular weight and low solubility [57-59]. Therefore, degrading the polysaccharide molecule can be a solution in this case [60]. Sodium alginate has been approved to exert a variety of favorable biological functions such as anti-inflammatory effects [61]. Niu, et al. in 2022 suggested that the use of sodium alginate accompanied by chlorogenic acid enhances therapeutic effect on ulcerative colitis by controlling inflammatory factors, oxidative stress, and the intestine microbita [62].

Sodium alginate has been extensively used in the biomedical field as an accepted biomass material. Because of exceptional hydrophilicity and biocompatibility, sodium alginate hydrogels are considered wound dressing materials that provide a suitable healing milieu for damaged tissue and control the inflammation in the course of healing and treatment [63]. It has been proved by Zhou and colleagues in 2015 that guluronate oligosaccharide extracted by oxidative degradation method decreases the production of inflammatory moderators ROS, NO, PGE2 as well as inflammatory proteins COX-2 and, iNOS, as well as pro-inflammatory cytokines IL-1 β , IL-6, and TNF-α in RAW264.7 macrophages that were triggered by LPS. Guluronate oligosaccharides can inhibit the binding of LPS to cell membrane and decrease the LPS-induced up-regulation of TLR4 and CD14 and subsequent inhibition of MAPK and NF- κ B signaling pathways [64]. These researchers in another study showed that the curing of BV2 cells, a well-characterized cell line of microglia, with guluronate oligosaccharide significantly reduced the LPS-stimulated production of IL-1 β , IL-6, and TNF-α and similarly the amyloid β -protein-stimulated secretion of IL-1 β , IL-6, and TNF-α. The findings are hopeful for developing a potential management for neuro-inflammatory diseases by decreasing the inflammatory mediators in the nervous system [65].

Biological Properties of Alginate Hydrolysate, as an Alginate Derivative

Anti-Cancer Effect of Mannuronic Acid and its Molecular Mechanisms

The significance of chronic inflammation has been established for cancer progression such as prostate cancer. According to the potential capacity of β-d-mannuronic acid to inhibit the molecules involved in inflammation. Mohsenzadegan, et al. investigate the anti-inflammatory function of mannuronic acid in prostate cancer. To find the optimal concentration, they initially detected the cytotoxicity of mannuronic acid in PC3 cell line and showed that doses of ≤200 μg/ml did not show any cytotoxicity consequence on the cell line Subsequently, PC3 cells were cultured and cured with low (25 μg/ml) and high (50 μg/ml) doses of mannuronic acid. The expressions of Myd-88, NF- κ B, MMP-2 MMP-9, IL-8, and COX-2 molecules were evaluated using zymography, flow cytometry and real-time PCR. As result, they revealed that Myd-88 gene expression was decreased significantly in both assessed concentrations of mannuronic acid compared to the control group. Also, the nuclear factor of NF-kB was decreased at both gene and protein levels. Treated cells with high concentration of mannuronic acid showed lower gene expression of COX-2 and IL-8 and decreased expression of the MMP-9 gene was observed at both doses. These authors concluded that mannuronic acid in both high and low concentrations are able to down-regulate the inflammatory molecules in the PCa cells [66].

Angiogenesis (new formation of vessels in a tissue) is strongly associated to the development of cancer and chronic inflammation. The β-D-mannuronic acid has been verified as a matrix metalloproteinase (MMP) inhibitor. Rastegari-Pouyani, et al. carried out in vivo and in vitro studies to assess the anti-angiogenesis property of mannuronic acid via a 3D collagen-cytodex model and the chick chorioallantoic membrane (CAM) assay. They showed that mannuronic acid is an anti-angiogenic molecule that indirectly affects endothelial cells; however, its anti-inflammatory property may partially advance the anti-angiogenic role [67]. Myelodysplastic syndromes (MDS) are a collection of cancers that precursor blood cells in the bone marrow do not mature or develop into normal blood cells. Treatments based on the anti-inflammation agents are standard methods for MDS management. Bakhtiari et al. assessed the outcome of β-d-Mannuronic acid on peripheral blood mononuclear cells (PBMCs) of MDS patients. These cells were cured with low, moderate, and high doses of mannuronic acid. The gene expression of IL-6, IL-3, TNF-α, G-CSF (granulocyte colony-stimulating factor) as well as serum Levels of IL-6 and TNF-α were measured by real-time PCR and ELISA, respectively. A significant reduction in the secretion of IL-6 and TNF-α was found, and in opposition' gene expression of G-CSF was considerably augmented. These findings suggest the anti-cancer effect of mannuronic acid [68].

Metastasis is the key reason for death in patients with breast cancer. Crosstalk between tumor cells and tumor microenvironment is a key player in the progression and metastasis of cancer. Hosseini, et al. in 2017 investigated the effects of β-D mannuronic acid in 4T1 breast cancer cell lines and a murine model. In a dose-dependent manner mannuronic acid leads to lower activity of MMP-2 and MMP-9 and subsequently the lower connection of 4T1 cells to the extracellular matrix. The findings showed that mannuronic acid significantly prevents tumor progression and survival in comparison with control mice. The tumor size reduction was associated with lower metastasis, and the number of inflammatory cells in the tumor microenvironment [69]. After the hopeful result of the Hosseini, et al. study, Kashefi, et al. in 2019 decided to test the oral administration of mannuronic acid in 24 pre-surgical women with breast cancer. Patients received 500 mg of mannuronic acid twice a day for 6-8 weeks. Blood samples were collected at baseline and at the end of the study period. The results

of real-time PCR showed a significant reduction in the gene expression of MMP-2, MMP-9, and CCL22. Moreover, flowcytometry demonstrated a significant reduction in the frequency of Tregs population which are key players in the advance of angiogenesis, metastasis, and inflammation [70].

Anti-Cancer Effects of Guluronic Acid and its Molecular Mechanisms

Cancer-associated inflammation is allied with the malignant development of a number of cancers. Hosseini and colleagues in 2018 assessed the function of α-l-guluronic acid on breast cancer-associated inflammation both in vitro and in vivo studies. The results confirmed that α-l-guluronic acid can successfully inhibit inflammation and tumor-promoting molecules such as proinflammatory cytokines, VEGF, MMP2, MMP9, and COX-2 lacking cytotoxicity. Besides, α-l-guluronic can efficiently prevent the tumor cell adhesion to extracellular matrix which is related to diminished tumor growth, angiogenesis, metastasis, and extended mice survival [71]. Bagherian, et al. in 2022 evaluated the inflammatory molecules involved in tumorigenesis of prostate cancer. Gene expression of IL-8, NF-κB, Myd-88, COX-2, MMP-2, and MMP-9 were investigated in the PC-3 cells cured with 25 and 50 μg/mL of α-l-guluronic acid using real-time PCR. NF-κB protein expression and activities of MMP-2 and MMP-9 were examined using flow cytometry and zymography, respectively. Interestingly, the gene expression of COX-2, MMP-2, NF-κB, IL-8, NF-κB protein, and MMP-2 activity were expressively decreased after treatment with α-l-guluronic acid for 24 hours in comparison to the control group. PC-3 cells proliferation was also stopped by adding10-500 μg/mL of α-l-guluronic acid. The researchers concluded that α-l-guluronic acid has the capacity to inhibit the proliferation of PC-3 cells and diminish the expression of progression and metastasis mediators of prostate cancer like NF-κB, IL-8, COX-2, and MMP-2 [72]. Apoptosis is an intrinsic mechanism for controlling the creation of cancer cells and its defect leads to a longer life of malignant cells which enhances the progression of tumors. Hassani, et al. in 2020 Evaluated the safety feature as well as the apoptotic function of α-L-Guluronic Acid in vitro condition in the Hepatocellular Carcinoma Cell Line (HepG2) and the mouse fibroblast cell line L929, as a control. Their results showed that 72 hours of treatment with high concentration (400μg/mL) of guluronic acid significantly cause a decline in cell viability of HepG2 cells. Interestingly, this effect considerably increased by the dose of 200μg/mL, suggestive of dose- and time-dependence of guluronic acid in the induction of apoptosis in HepG2 cells which can promote its anticancer effect [73].

Anti-Inflammatory Effects of Mannuronic Acid and its Molecular Mechanisms

Inflammation is a vital reaction of the immune system against dangerous stimuli, such as toxins, pathogens, injured cells as well as heat and radiation. Inflammation has a dual function, and acts by eliminating adverse stimuli and beginning the healing mechanism [74]. Matrix metalloproteinases (MMPs) are crucial for extracellular matrix remodeling by degrading the components of extracellular matrix also they play a role in the inflammatory response by regulating the pro-inflammatory cytokines TNF-α and IL-1β [75]. Farahani, et al. [76] in 2017 aimed to evaluate the effect of mannuronic acid on MMP-2, MMP-9, and extracellular matrix metalloproteinase inducer (CD147/EMMPRIN) using real-time quantitative PCR and flow cytometry and zymography. They showed that Mannuronic Acid can lessen inflammation by cellular surface down-regulation of CD147 and reduction of the gene expression and gelatinolytic action of MMP-2 and MMP-9 in phorbol myristate acetate (PMA)-differentiated THP-1 cells. Also, Mirshafiey, et al. in 2007 used The fibrosarcoma cell line to examine the influence of mannuronic acid on the MMP-2 activity using zymography and established the higher inhibitory effect of mannuronic acid in MMP-2 activity compared to famous anti-inflammatory molecules such as dexamethasone and of piroxicam [77].

Innate immune cells express Toll-like receptors (TLRs) responsible for the identification of pathogen-associated molecular patterns (PAMPs) and introduce an inflammatory immune response in response to them [78]. Sharifi and colleagues in 2019 showed a significant reduction in gene expression of TLR2 and TLR4 in an intestine cell-line, HT29, under an inflammatory condition and after curing the cells with mannuronic acid [79]. In the same year, Aletaha, et al. showed that mannuronic acid can effectively prevent mRNA expression of TLR signaling molecules including MyD88 and NF-κB, in HEK293 cells triggered by a TLR2 agonist (LTA) and a TLR4 agonist (LPS); also, they showed that mannuronic acid decreased LTA and LPS-activated production of TNF-α and IL-6 inflammatory cytokines [80]. Moreover, Pourgholi, et al. in 2017 aimed to assess the effects of mannuronic acid on Suppressor of Cytokine Signaling-1 (SOCS-1) and Src Homology-2 domain-containing inositol-5'-phosphatase 1 (SHIP1) proteins via Toll-Like Receptor (TLR) 2/microRNA-155 pathway in Peripheral Blood Mononuclear Cells (PBMCs) and HEK293 TLR2 cell line. These researchers showed that mannuronic acid can significantly increase the expression of SOCS1 and SHIP-1 and decrease miR-155. They concluded that mannuronic acid indirectly can decrease inflammatory cytokines secretion by limiting the expression of SOCS1, SHIP1, and miR-155 [81]. Khalatbari, et al. in 2020 evaluated the anti-inflammatory properties of mannuronic acid in PBMCs of healthy individual's ex vivo. They demonstrated that a high dosage of mannuronic acid can meaningfully diminish the expression of NF-κB gene [82]. Mohammed, et al. in 2017 and 2018 showed that 10μg/ml and 50μg/ml of β-D Mannuronic acid incubation of PBMC with 1μg/ml of LPS significantly down-regulated gene expression of RORC, IL-17, and TNF-α, whereas the IL-4, GATA3, and FOXP3 gene was considerably up-regulated [83,84]. Seyed Shahabeddin Mortazavi-Jahromi in 2017 carried out research aimed at investigating the outcome of β-d-mannuronic acid on the expression of miR-146a and its two targets (IRAK1 and TRAF6), and NF-κB in the HEK-Blue hTLR2 cell line. They showed that mannuronic acid could alter TLR signaling via in-

hibiting the adaptor molecules IRAK1 and TRAF6, the transcription factor NF-κB and miR-146a [85].

Gaafar, et al. in 2020 enrolled a study to find the influence of mannuronic acid on the gene expression of STAT1, STAT3, STAT4, and STAT6 in the PBMC using the real-time PCR method. They found that can cause the reduction of STAT1, STAT3, and STAT4 gene expression in PBMC of rheumatoid arthritis (RA) patients [86]. Omidian, et al. in 2022 investigated the anti-inflammatory effects of B-D-Mannuronic acid expression of inflammatory markers such as TNF-α, IL-6, IL-22, MYD88, and TLR2 in PBMCs of RA patients. The cells were cultured with, low (5 μg/mL), moderate (25 μg/mL), and high (50 μg/mL) doses of mannuronic acid accompanied by 1 μg/mL LPS. RT PCR analysis revealed that all three doses of mannuronic acid are able to considerably decrease the gene expression of inflammatory molecules of TNF-α, IL-6, MYD88, and TLR2 in the PBMCs. Also, flowcytometry technique showed that surface expression of TLR2 was significantly downregulated by moderate and high doses of mannuronic acid [87]. Rouzbehkia et al. in 2017 studied the genes of the TLR/NF-kB signaling cascade in patients with ankylosing spondylitis (AS). Orally intake of mannuronic acid significantly decreases the expression level of Myd88, IKB-α, MAPK14, and NF-kB in AS patients in comparison to controls [88].

Mirshafiey, et al. in 2005 examined the effect of mannuronic acid on an animal model of multiple sclerosis (EAE). The outcomes of that research displayed that the treatment of EAE with mannuronic acid can overwhelm inflammation in a prophylactic or therapeutic manner. Interestingly, clinical improvement was along with an obvious reduction of specific T-cell reactivity and decreased vessels with perivascular cellular invasion in mice who received mannuronic acid [89]. In 2022, Najafi et al. studied the effects of mannuronic acid on IL-1β, IL-17A, STAT1, and STAT3 gene TLR2 and TLR4 receptors in patients with secondary progressive MS. Results showed that the gene expressions of IL-17A, STAT1, and STAT3 were reduced after 6 months of receiving mannuronic acid. Also, the gene expression of IL-1β decreased numerically after 6 months. Additionally, expressions of TLR2 and TLR4 on the cell membrane of PBMCs declined significantly [90]. In 2004, Mirshafiey, et al. assessed the anti-inflammatory effect of mannuronic acid ($C_6H_{10}O_7$) molecule was evaluated in Adriamycin-induced nephropathy. This research team revealed that rats who was received mannuronic acid had a significant decrease in serum levels of IL-6, BUN, creatinine, cholesterol, and also had a lower level of proteinuria [91]. Robat-Jazi. et al. in an ex vivo study investigated the anti-inflammatory property of mannuronic acid on the PBMC of patients with COVID-19 who progress acute respiratory distress syndrome. Remarkably, gene expression and supernatant levels of IL 6, IL-17, IFN γ, and TNF-α were decreased in PBMCs co-cultured with mannuronic acid in comparison with the control group [92] .

Anti-Inflammatory Effects of Guluronic Acid and its Molecular Mechanisms

In 2018, Sharifi, et al. reported the results of their research on the influence of guluronic acid on the expression of TLR2 and TLR4 proteins, the related signaling molecules, and subsequent pro-inflammatory cytokines in human PBMCs. The researcher reported that 25 μg/mL guluronic acid significantly inhibited mRNA expression of signaling molecules of IκB, MyD88, transcription factor of NF-κB, and IL-1β secretion by PBMCs while having no significant effect on the protein expression of TLR2 and TLR4 [93]. However, these researchers in 2019 again verified the relation between the immunosuppressive effect of guluronic acid and TLR2, TLR4 signaling downstream by way of the concentrations of 5 and 25μg/ml could suppress the mRNA expression of MyD88, Tollip, and NF-κB in HEK293 TLR2 and TLR4 cell lines [94]. Farhang, et al. in 2019 endorsed the anti-inflammatory effect of guluronic acid using quantitative RT-PCR to test the expression of TLR2 and TLR4 mRNA in HT29 cell line. They found that guluronic acid can significantly decrease TLR2 and TLR4 gene expression compared with the untreated HT29 cells [95]. In 2016, Hajvalili, et al. aimed to evaluate guluronic acid efficacy on the IRAK1 and TRAF6 as inflammatory and miR-146a as an anti-inflammatory component of TLR4 signaling downstream in HEK-TLR4 cells and PBMCs. The results showed that IRAK1and TRAF6 expression reduced 5-8-fold and 3-10 folds, in a dose-dependent manner but, miR-146a expression did not alter after treating guluronic acid [96]. Mortazavi-Jahromi, et al. in 2018 reported that guluronic acid could meaningfully diminish the gene expression of TLR4 and MyD88, NF-κB as well as IL-1β production in in HEK-Blue hTLR4 cell line and conversely, rise the gene expression of SHIP1 and SOCS1. The authors concluded that guluronic acid can be suggested for reducing inflammatory responses [97].

Afraei, et al. in 2015 tested the anti-inflammatory property of guluronic acid in an animal model of multiple sclerosis (MS). Pathology reports confirmed that inflammation measures such as the number of inflammatory cells, plaques, and demyelination were lesser in guluronic acid-treated mice [98]. Nourbakhsh et al. in 2019 carried out an in vitro study to assess the effect of guluronic acid on mRNA expression of TLR2, TLR4, MyD88, TNF-α, and CD52 in PBMCs of patients with MS. They found that guluronic acid could considerably reduce the gene expression of TLR2, TLR4 and TNF-α compared to untreated cells and may be used to manage the inflammatory processes in MS [99]. Bakhtiari, et al. in 2019 showed that guluronic acid could reduce pro-inflammatory cytokine and their transcription factors in the blood sample of RA patients who received a dose of 500 mg twice daily for 12 weeks. They found that guluronic acid could diminish pro-inflammatory cytokines and their transcription factors and increase the anti-inflammatory cytokine and its associated transcription factor [100]. High production of pro-inflammatory factors is the cause of hyperinflammation in Nonalcoholic Steatohepatitis (NASH).

The baseline expression levels of TLR4 and NF-κB, TNF-α, and IL-6 were significantly elevated in NASH patients compared to healthy individuals. Treating the PBMCs of NASH patients with the suitable amount of guluronic acid leads to significantly lower gene expression of TLR4 and NF-κB and lesser secretion of IL-6 and TNF-α [101].

Conclusion

The multifunctional properties of alginate make it a captivating topic for extra scientific exploration in the anti-inflammatory and anti-tumoral fields. Sodium alginate and its components, mannuronic acid and guluronic acid, as alginate derivatives extracted from alginate hydrolysate exert their anti-inflammatory effect by suppressing matrix metalloproteinases (MMPs), Toll-like receptors (TLRs), TLR signaling molecules, nuclear transcription factors, inflammatory cytokines and their mediators. Also, they prevent the development and invasion of tumor cells by promoting apoptosis and enforcement of anti-inflammatory and antioxidant processes. In conclusion, the outcomes of anti-cancer and anti-inflammatory studies on sodium alginate and its derivatives indicate their high capacity in controlling the inflammation and cancer development, as the important health benefits of these safe agents.

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