MEDICAL APPLICATIONS OF BETA-GLUCAN

Betül Gürünlü

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Authored by

Betül Gürünlü

Üsküdar University,
Bioengineering Department,
Istanbul,
Turkey

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Author: Betül Gürünlü

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PREFACE

Beta glucan has been used in Asia as immunostimulant, adaptogenic and detoxifying medicine. Goro Chihara, from Teikyo University in Kawasaki, Japan, first isolated β -glucan from mushroom shiitake and named it as lentinan in 1969. There are various natural sources of β -glucans such as reishi, maitake and shiitake mushrooms, barley fibers, oats and whole grains, seaweeds, algae; however, they are most frequently prepared from fungal cell walls. Beta glucan are polysaccharides that are composed of linear chains with (1 → 3)-β --glycosidic linkages or branched ones containing additional (1 → 6)-β -d-glycosidic linkages.

Global pandemic diseases such as COVID-19, which have resulted in severe case losses in all over the world, have made us much better understand the importance of health. In this sense, we have seen that keeping our immune system strong is a very important issue. Thanks to beta glucan supplement that strengthens the immune system, it is an important support for the body to cope with many diseases such as cancer, allergic diseases, upper respiratory tract obstruction, ear infections, and diabetes. β-Glucan has been used as an immunoadjuvant therapy for cancer since 1980, primarily in Japan. Yeast β -glucan is able to absorb mycotoxins (such as zearalenon, aflatoxin B1, deoxynivalenol, ochratoxin A, and patulin), probably through hydrogen bonds and van der Waals forces; this β -glucan effect is important particularly for livestock. Certain cereals (barley, oats) and edible mushrooms decreased levels of serum cholesterol and liver low-density lipoproteins, leading to lowering of arteriosclerosis and heart disease hazards. In the central nervous system, β -glucans activate microglial cells. These cells act as scavengers of the brain cell debris and play a positive role in Alzheimer's disease, AIDS, and multiple sclerosis.

Briefly, β-Glucan provides diverse and impinge effects on the immune system. They are natural products useful in preventing various diseases, they have been highly sought after throughout human history. This book is an important source that showing the capabilities of beta glucan as a preventive and therapeutic against many diseases and providing you about the way of contribution of beta glucan for strengthening your immune system.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

Betül Gürünlü
Üsküdar University
Bioengineering Department
Istanbul
Turkey

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I would also like to thank Bentham Science Publishing for their amazing work in preparing this book for publication.

CHAPTER 1

Introduction To β-glucans

INTRODUCTION

Generally, β -glucan is a chemical name of a polymer of β -glucose. The therapeutic effect of β-glucans (beta-glucan) has long been known. Mushrooms are sacred food in ancient Egypt and used for prolonging life three thousand years ago. The medicinal usage of mushrooms that are a major source for β-glucans were mentioned in the texts in India dating back 500 years [1]. US Food and Drug Administration (FDA) recommends an intake of 3 g/day of β-glucan as cholesterol-reducing foodstuffs in 1997 [2]. American Diabetes Association (ADA) pointed that main aim should be kept the LDL-cholesterol (LDL-C) level less than 2.6 mmol/l (100 mg/dl) in individuals without overt cardiovascular disease (CVD). It also has a strong anti-oxidative property which helps in overcoming the problem of oxidative stress of the human body. β-glucan also reduces the chronic fatique syndrome and inhibits the cancer development.

β-glucan is a soluble fiber obtained from the cell walls of bacteria, algae, yeast, fungi, and plants. Also, to a lesser extent in rye and wheat. There are two main types of β-glucan: yeast and mushroom derived type that consisting of 1,3 and 1,6-glucan linkages and oats and barley derived type that including 1,3 and 1,4 linkages [3]. The biological activity of the yeast derived β-1,3/1,6-glucan is greater than the 1,3/1,4 counterparts.

B-glucans have a long history as nonspecific biological modulators. β-1,3-glucan strenghtens the immune system and protect the body against the bacteria, viruses, fungi, and parasites by boosting the fighting ability of macrophages, neutrophils, and natural killer cells [4, 5].

Classification of β-glucans

β-Glucans are glucose polymers that naturally occur in yeasts, molds, algae, mushrooms, bacteria, oats and barleyas shown in Fig. (**1**) [6, 7]. The health benefits associated with consuming β-Glucans-rich foods include lowering blood glucose, insulin, and blood lipids, in particular serum total and low density lipoprotein (LDL) cholesterol. Some of these effects have been shown to depend on the capacity of β-Glucan to increase the viscosity (defined as a measure of re-

sistance to flow) of intestinal contents, which in turn depends on physicochemical characteristics of β-Glucan such as molecular weight (MW) and solubility. In microbial sources, they are a structural component and in grain sources, they are found in the endospermic and aleuronic walls [8 - 10].

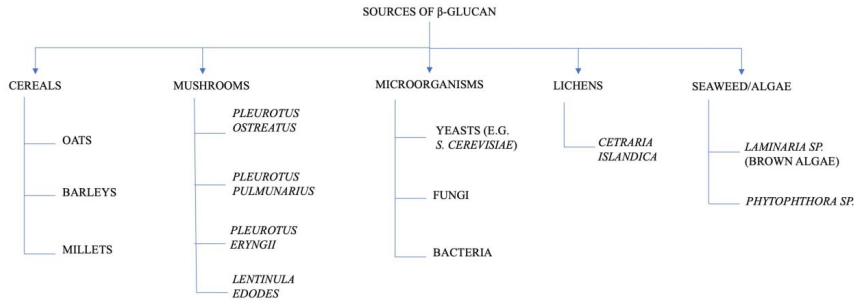

Fig. (1). Classification of sources of β-glucan.

The structural features of β-glucans are important determinants of their physical properties and functionality, including their physiological responses [11]. The molecular size and fine structural features of β-glucans play an important role on the solubility and chain conformation or shape, and hence on their rheological properties in solution. Structural differences, biological sources and molecular masses are presented in Table **1**.

Table 1. Beta-glucan types and structural differences [15].

	Source			
Glucan	Taxon	Species	Linkages	MW (kDa)
Baker's yeast glucan	Yeast	*Saccharomyces cerevisiae*	b-(1,3), b-(1,6)	35–5000
Barley glucan	Plant	*Hordeum vulgare*	b-(1,3), b-(1,4)	23–137
Curdlan	Bacteria	*Alcaligenes faecalis*	b-(1,3), b-(1,6)	53–2000
Laminarin	Algae	*Laminaria digitata*	b-(1,3), b-(1,6)	3.5–7.7
Lichenan	Lichen	*Cetraria islandica*	b-(1,3), b-(1,4)	20–35
Oat glucan	Plant	*Avena sativa*	b-(1,3), b-(1,4)	1–300
Pachyman	Fungi	*Poria cocos*	b-(1,3), b-(1,6)	21–100
Paramylon	Algae	*Euglena gracilis*	b-(1,3)	118
Pullulan	Fungi	*Aureobasidium pulllan*	a-(1,4), a-(1,6)	200
Pustulan	Lichen	*Umbilicaria sp.*	b-(1,6)	20
Schizophyllan	Fungi	*Schizophyllum commune*	b-(1,3), b-(1,6)	76.8–450
Scleroglucan	Fungi	*Sclerotium rolfsii/glucanicum*	b-(1,3), b-(1,6)	1000–5000

(Table 1) cont.....

	Source			
Xyloglucan	Plant	*Tamarind*	b-(1,4)	202

Structurally, β-glucans are comprised of glucose units linked together by several different types of beta-glycosidic linkages (Fig. **2**). In the basic form, the molecule is a polymer of monosaccharide residues. β-glucans are composed of β-D-glucose monomer units, which are held together by glycosidic linkages at differing positions (1,3), (1,4) or (1,6). This structure can be either branched or unbranched [12]. The monosaccharide units interconnect at several points to form a wide variety of different branched and linear structures [13]. The β-glucans source will determine if the molecule has branched structures and to what extent.

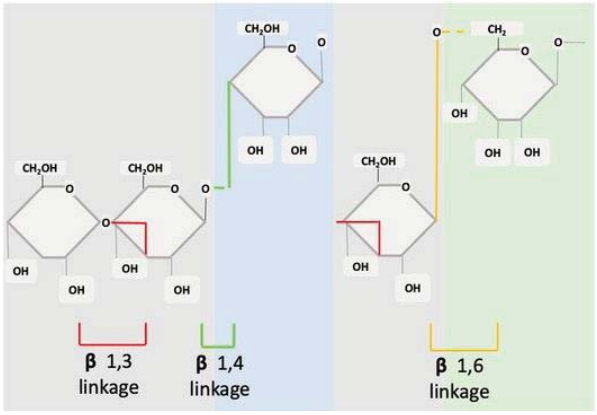

Fig. (2). Structure of cereal β-glucans (1,3 1,4) and non-cereal β-glucans (1,3 1,6).

The fine structure of β-glucans can vary in meaningful ways that modify its effects and mechanisms of action. A variance will occur between glycosidic linkages, molecular weight, branching, degree of polymerization, and solubility. β-glucans from different sources will have different effects or functions [14].

The MW, water retention properties, and solubility of β-glucan have a huge impact on its viscosity and flow behavior [16]. β-glucan is very hydrophilic due to the abundance of hydroxyl groups that participate in hydrogen bonding with water and give the molecule an ability to hold water in both soluble and insoluble forms [17, 18]. Solubility also depends on the MW that influencing by the chain length and degree of branching in the molecule. Two other phenomena that affect the molecular weight of β-glucan, namely self-association and aggregation, are dependent on certain physicochemical properties such as the conformation, the molar ratios of trimers and tetramers in the molecules, and the hydrodynamic radius [19].

CHAPTER 2

Beta Glucan in Cancer Treatments

Abstract: Cancer disease is undoubtedly the plague of today due to the increase in its incidence. The main reasons that make this disease so common are stress, malnutrition, having habits such as alcohol and smoking, and working under unfavorable conditions. Cancer is a disease that destroys blood cells in the body by weakening the immune system. Therefore, it is necessary to keep the immune system strong to cope with this disease. For this purpose, it is very important to take beta glucan support, which is one of the biological response modifiers, into the body. In the treatment of many types of cancer, such as breast cancer, prostate cancer, colon cancer, and lung cancer, the immunotherapy method is used in addition to traditional chemotherapy treatment. Many previous studies showed that beta glucan slows down cancer growth and prevents cancer from spreading to other parts of the body.

Keywords: Beta Glucan, Cancer, Strengthening the Immune System.

INTRODUCTION

β-glucans, which are linked by 1 → 3 linear-glycosidic chain nuclei, are the most plentiful polysaccharides in bacterial and fungal cell walls. β-glucans are distinguished from each other by differences in their lengths and their branching structures, as shown in Fig. (**1**) [1, 2].

There are many studies showing the cytotoxic effects of beta glucan in the literature demonstrating the utilization of raw extracts of herbs having beta glucan and the usage of monocytes prepared from beta glucan. Ganoderma lucidum (lingzhi), which is a herb involving beta glucan, consists of anti-cancer components such as ganoderic acid in its mycelium and triterpenes in its spore [3, 4]. A bacterial β-glucan, Curdlan, has also been shown to adjust tumor-infiltrating dendritic cells (DCs) to stimulate Th1 T cell production. DC adjusting in Dectin-1 medium was demonstrated to stimulate the production of mucosal CD8 (cluster of differentiation 8) T cells naming as a cluster of differentiation 103 (CD103) that collected in the tumors, importantly grown tumor necrosis, and as a result, repressed tumor spreading in laboratory mice having breast cancer [5]. Curdlan was used in 4T1 mouse mammary tumor models in order to show the transformation of regulatory T cells (Tregs) into Th17 effector T cells both *in vitro* and *in vivo* conditions, as given in Fig. (**2**) [6].

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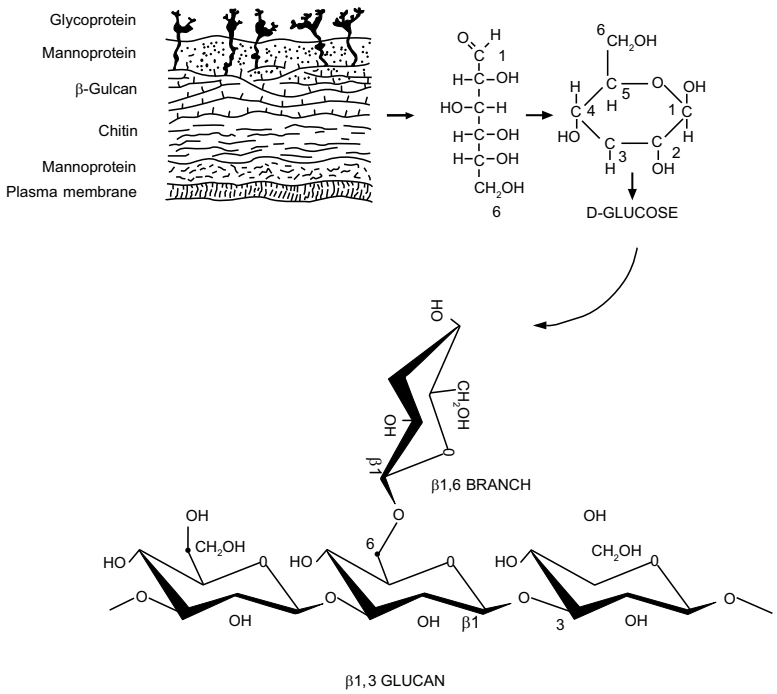

Fig. (1). Fungi cell layers and molecular structure of beta glucan [2].

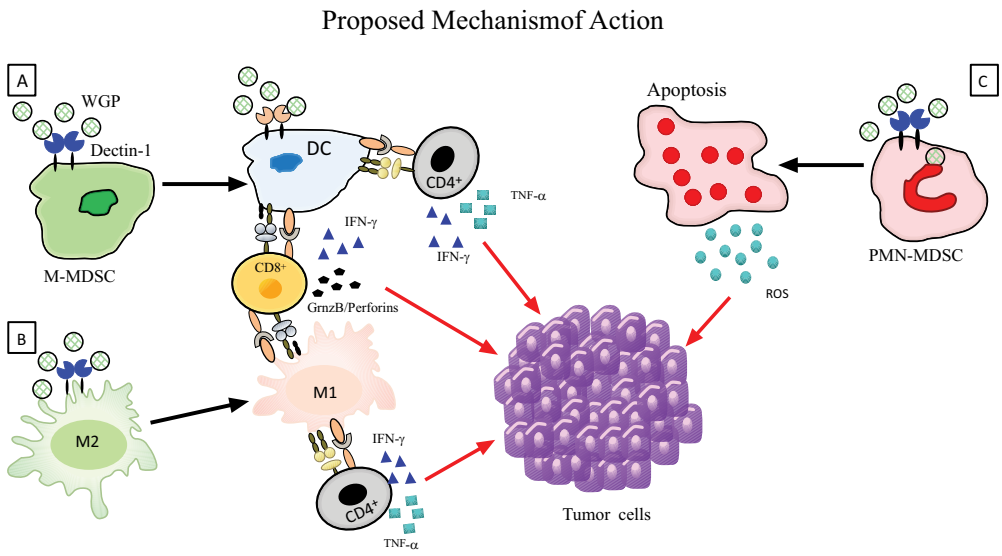

Fig. (2). β-glucan effect on the modulation of the immune cells around the tumor cells [7].

β-glucan, which is attached to the Dectin-1 receptors located on the monocytic - myeloid-derived suppressor cells (M-MDSC) as seen in Fig. (**2a**), is then phagocytosed. The suppressive phenotype of monocytic-myeloid derived suppressor cells (M-MDSC) transforms into the DC phenotype that functions as an Adenomatous polyposis coli (APC) by the Dectin-1 attachment. $CD4^+$ and $CD8^+$ T-cells are activated by DC. While $CD4^+$ T-cells release some pro-inflammatory cytokines such as IFN-γ and TNFα, $CD8^+$ T-cells release perforins, Granzyme B, and IFN-γ. Tumor cells are destructed by releasing these pro-inflammatory cytokines. In Fig. (**2b**), the polarization of suppressive M2 macrophages into inflammatory M1 macrophages is stimulated by β-glucan. Th1 type T-cells are activated by M1 macrophages and cause the removal of tumor cells by the releasement of pro-inflammatory cytokines *via* $CD4^+$ and $CD8^+$ T-cells. In Fig. (**2c**), apoptosis of the cell was occurred by binding of β-glucan to the Dectin-1 receptor founded on polymorphonuclear (PMN)-MDSCs. The cell synthesizes reactive oxygen species (ROS) during apoptosis. The formed ROS enable the death of tumor cells. Thus, a suppressive tumor microenvironment (TME) is converted into the inflammatory TME that providing a convenient medium for stimulating the death of tumors [7].

Beta Glucan Immunotherapy For Different Cancer Types

There are many studies that discussed immunotherapy with beta glucan in the treatment of various cancer types. The tumors of liver, breast, lung cancers were diminished in >60% of patients by using β-glucans of D-Fraction of Grifola frondosa (Maitake mushroom) [8]. Clear results could not be obtained for patients with stomach, leukemia, and brain cancer [9].

On the other hand, there are many studies which support the cytotoxic effect of beta glucan on the different cancer types. For example, the effect of beta glucan on women with breast cancer during chemotherapy was investigated in Ostadrahimi *et al*. study [10]. For this study, thirty people were selected among the suitable candidates, and then they were divided into two groups by the block randomization method as the intervention and placebo groups. During the 21 days between two chemotherapy sessions, two 10 mg soluble 1-3, 1-6, D-beta glucan capsules derived from Saccharomyces cerevisiae were given to the intervention group every day, while the placebo group was given placebo. At the end of the study, it is understood that the global health status (QoL) score was considerably increased ($P=0.023$); on the other hand, the difference between the two groups was not important. Also, they counted white blood cells (WBC), lymphocyte, neutrophil, and monocyte, interleukin 4 (IL-4), and interleukin 12 (IL-12) and understood that the number of WBC in beta glucan group was less decreased than the placebo group [11].

CHAPTER 3

Beta Glucan Against Coronavirus

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new virus that is the source of COVID-19 pandemic and causing great damage all over the world. Among the main accelerating factors of mortality due to COVID-19 are the direct endothelial damage caused by coronaviruses and the defect in the clotting mechanism due to the cytokine storm. These two main destructive factors are deeply related the dysregulation of the immune system. The comorbidities and ethnic variations are also effecting the risk of associated thrombogenic disruption. Beta glucans are gathering a wide range of attention due to their immunostimulating effect, drug potential, and biologically active nature against many diseases by boosting the immune system. In this review, the healing and positive effect of the biological response modifier, beta glucan, on COVID-19's symptoms such as cytokine storm, coagulopathy, lung inflammation causing mortality by modulating the immune system are discussed.

Keywords: Beta Glucan, Coronavirus, COVID-19, Immune System.

INTRODUCTION

The global pandemic coronavirus, which causes various kinds of upper and lower respiratory tract infections in humans, first emerged in Wuhan, Hubei province of China in late 2019. Then, the reason behind this outbreak was reported as a new coronavirus, coded SARS-CoV-2, which is in the same virus family as SARS-CoV by the Chinese Center for Disease Control and Prevention (China CDC) on January 9, 2020 [1]. World Health Organization (WHO) declared a pandemic disease on January 12, 2020 [2]. After that, this life-threatening disease, which was named as COVID-19, spread like greased lightning on all over the world. As of December 29, 2020, 79 million people were diagnosed with COVID-19, and 1.7 million people died of this disease worldwide [3].

Certainly, it is of great importance to keep the immune system strong in order to cope with this inexorable disease causing fatal consequences by seriously affecting the upper and lower respiratory tract. Our immune systems can be vulnerable to external threats such as viruses, bacterias and other infections due to the anxiety, stress, and poor nutrition during the COVID-19 lockdown period.

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Therefore, it is highly important to follow a healthy diet that is rich in Baker's yeast β-glucan supported with vitamins C and D in order to lower the risk of microbial and viral infections by strengthening immune defence [4]. In McCarty and DiNicolantonio's study, β-glucan was described as a natural nutraceutical for improving interferon type 1 (IFN-1) in order to fight against RNA viruses such as influenza, COVID-19, SARS, MERS and Ebola viruses [5]. Also, Bergendiova *et al*. reported the pleuran, which is a type of beta glucans derived from the mushroom *Pleurotus ostreatus*, decreases the risk of upper respiratory tract infection (URTI) symptoms by enhancing the natural killer (NK) cells amount [6].

The Classification and Molecular Structure of Beta Glucan

β-glucans are taking part in the family of glucans which are defined as the polysaccharides consist of glucose [7]. Glucose can be formed from the different kinds of glucans thwith distinct qualifications and functions such as anti-inflammatory, antitumor, anti-allergic, anti-obesity, anti-osteoporotic, and immunotherapeutic activities as a result of glycosidic bonding and branching [8]. Glucans are divided into two main groups named as cellulose and β-glucans as tabulated in Fig. (**1**).

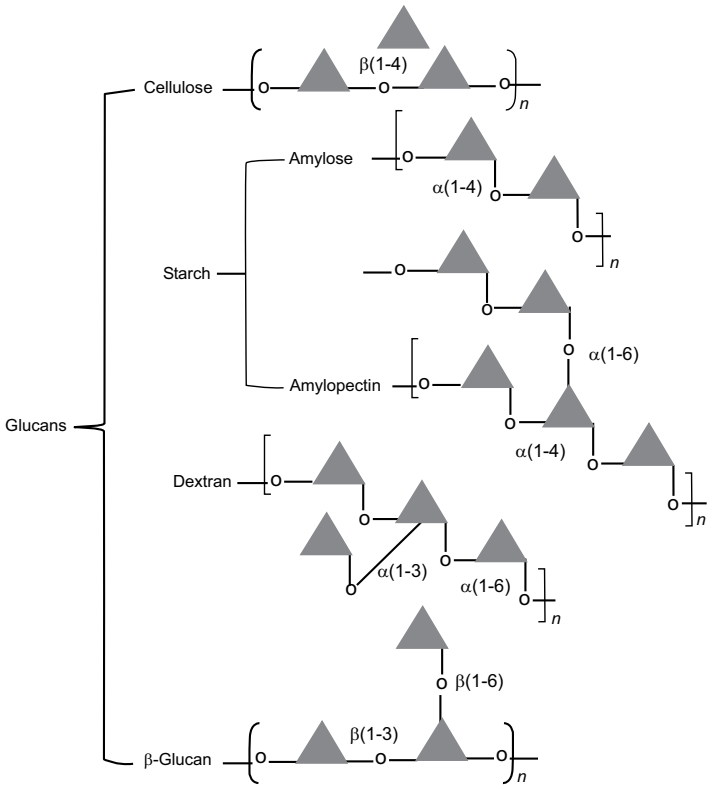

Fig. (1). The classification of glucose-based polysaccharides (glucans) [7].

β-glucans are formed from glucose polymers that are bonded to each other *via* 1,3 linear β-glycosidic chains, as given in Fig. (**2**) [7]. Fungi is the primary source for β-glucans having side branching at the 1,4 or 1,6 position [9]. Also, apart from mushrooms, β-glucan can be obtained from different organic and nutritional sources such as bacteria, algae, yeast, barley, and oats, *etc* [10].

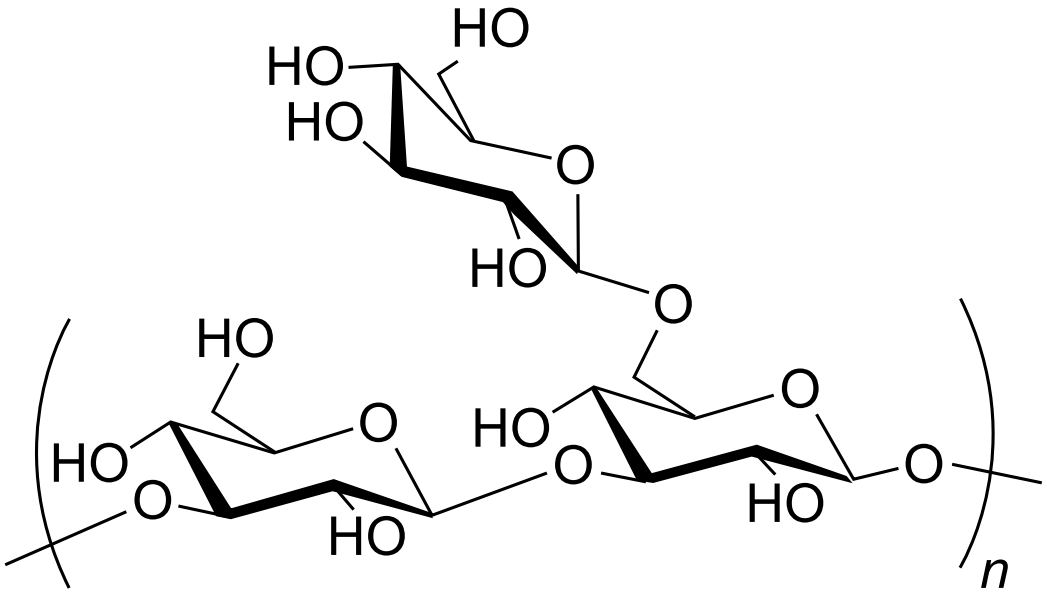

Fig. (2). Chemical structure of β(1,3)-glucan [7].

Beta Glucan Use in Covid-19 Treatment

In ancient times, people were using some specific mushrooms for curing some diseases. In India, a 5000-year-old text on the medical use of mushrooms was found [11]. A mushroom species titled as Lentinula edodes (Fig. **3**), also named as Shiitake in Japanese, which includes carbohydrates (58–60%), proteins (20–23%), fiber (9–10%), lipids (3–4%), and ash (4–5%), has been used in many antifungal/antibacterial, antiviral, immunomodulatory, and antitumor activities for thousands of years [12 - 14]. This edible mushroom, Lentinula edodes produces lentinan, which is a particular type of β-glucans that are consisted of a β-(1-3)-glucose spine including two (1-6)-β-glucose branches of five glucose elements, can be used for declining the bacteria type named *Klebsiella pneumoniae* causing lung infection as a result of multiple antibiotic resistance [15]. Also, bacterial load in arterial blood can be reduced by lentinan intake and white cell amount, causing protein inflammation in the lungs cto decreased by and bronchoalveolar lavage (BAL) in order to cure sepsis in lung injury and develop the physiological variables [16].

CHAPTER 4

Beta Glucan in Allergical Diseases: Rhinitis, Asthma, Eczema

Abstract: Allergic diseases are one of the most common illnesses, and their incidence is gradually increasing. There are a plenty of studies targeting the effect of β-glucan polysaccharides on allergies with symptoms such as rhinitis, post nasal drip, conjunctivitis, cough, fatigue, itchy throat and eyes, and physical pain. Most of the allergic diseases emerged due to the result of disorders of the immune system, primarily deterioration in the balance of the answer of Th1/Th2 lymphocytes towards Th2.

Keywords: β-glucan, Allergy, Allergical Rhinitis, Asthma, Eczema.

INTRODUCTION

Allergic diseases constitute a leading cause of chronic disease in both children and adults. According to the World Health Organization, hundreds of millions of people (10-30% of the population) suffer from rhinitis, and 300 million from asthma, with a negative impact on the quality of life and growing socioeconomic costs. According to many chronic allergy sufferers, these people experience a number of social problems caused by a weak psychological state, such as sleep disorders and emotional problems in their daily lives [1, 2]. Epidemiological research has shown a dramatic increase in allergic disease prevalence, about 30-40%, especially in children [3]. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase III, a 7-year cross-sectional study, reports sharp increases in their prevalence, especially in the 6-to7-year-old age group compared to the 13-to14-year-old age group [4]. Also, studies showed that children who live in moldy houses have a higher risk of developing asthma [5].

Undoubtedly, β-glucan has been defined as an effective biological response regulator and has many immunomodulatory properties such as cytokine propagation, direct activation of natural killer cells, induction of phagocytosis by professional phagocytes. Plenty of environmental reasons are related to asthma and allergic diseases, and allergen exposure plays an important role in accelerating and inducing asthma and allergy symptoms. For instance, alternaria-

sensitivity causes the development of allergic asthma. In this review, β-glucan and its therapeutic effects on the allergical diseases such as allergical rhinitis, asthma, and atopic dermatitis has been discussed.

Allergic Rhinitis

Allergic rhinitis (AR) is a disease characterized by Immunoglobulin E (IgE)-mediated, allergic inflammation of the nasal mucosa [6]. T helper 2 (Th2) cells play an important role in the development of IgE-mediated diseases such as AR, with local overproduction of Th2 cytokines (interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 13 (IL-13)) at the site of allergic inflammation. T helper 1 (Th1) cytokines (interleukin 12 (IL-12) and Interferon-c (IFN-c)) are known to suppress this Th2 immune response, aiding the treatment of these diseases [7]. Pollen from plants of the genus Ambrosia (which includes ragweed) is a primary cause of allergic rhinitis, also known as hay fever, during summer and fall [8]. The airborne concentrations of common ragweed pollen will increase 4-fold in Europe by 2050 [9]. β-1,3-1,6-glucan (Glucan) is an immunomodulator stimulating the antitumor response particularly. An efficient antitumor stimulation can be achieved through a Th1-mediated immune response [7]. Table **1** shows cytokine levels in nasal lavage fluid of the glucan and placebo groups before and after treatment.

Table 1. Mean±SEM cytokine levels in nasal lavage fluid (NLF) of the Glucan and placebo groups before and after treatment [7].

	Pre-Treatment		**Post-Treatment**	
	Glucan	Placebo	Glucan	Placebo
IL-4 (pg/mL)	5.48 ± 0.92	4.63 ± 0.69	3.66 ± 0.64	4.45 ± 0.85
IL-5 (pg/mL)	8.58 ± 1.58	6.78 ± 0.69	5.81 ± 0.83	6.57 ± 0.68
IFN-α (pg/mL)	6.19 ± 1.18	6.13 ± 0.58	7.83 ± 1.22	6.85 ± 0.80
IL-12 (pg/mL)	11.08 ± 2.43	10.48 ± 1.51	17.31 ± 2.75	9.97 ± 1.54

After treatment, IL-4 and IL-5 levels in nasal lavage fluid (NLF) from the Glucan group were found to have decreased significantly ($p = 0.027$, $p = 0.04$; respectively), while IL-12 levels were found to have significantly increased ($p = 0.008$). However, IFN-α levels had not changed. Saito *et al*. have reported that Glucan increases IL-12 levels *in vitro* and decreases Ig-E synthesis *in vivo*, inhibiting the Th2-mediated immune response [10]. Also, the percentage of eosinophils (a type of white blood cell and a type of granulocyte which increases during the infections, allergic reactions, and asthma in the NLF) was found to have decreased significantly after treatment in the Glucan group ($p = 0.01$), while that of the placebo group did not change. 3D rendering of IL4, IL5, IL12, IFN-α,

and eosinophil is given in Fig. (**1**).

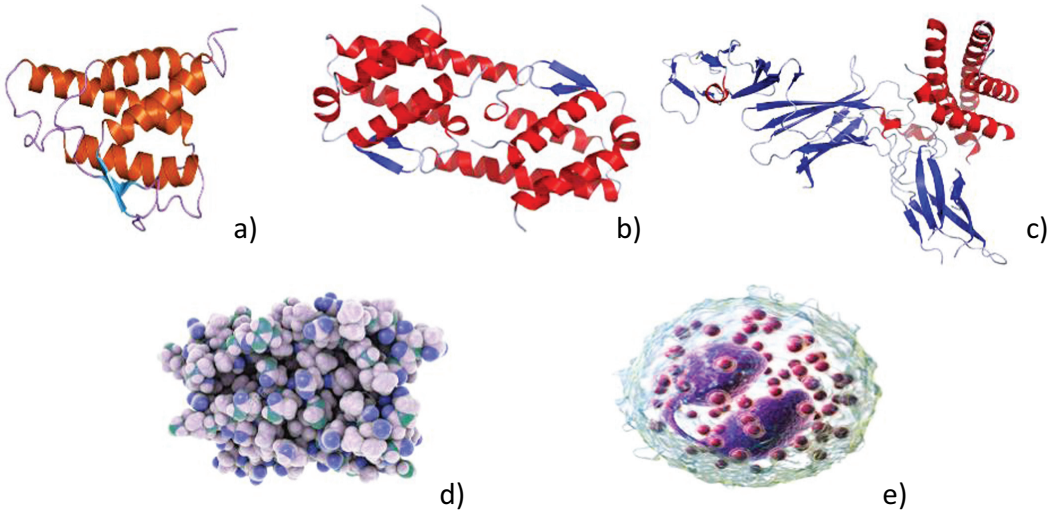

Fig. (1). 3D rendering of a) IL4, b) IL5, c) IL12, d) IFN-α, e) eosinophil.

Talbott *et al*.'s double-blind study compared the effects of daily supplementation for 4 weeks with 250 mg Wellmune WGP® β-1,3/1,6-Glucan (WGP) with placebo 250 mg/day (rice flour) on physical and psychological health attributes of self-described "moderate" ragweed allergy patients [11]. Participants in this study are chosen from two different ages; mean age = 36±9year and range 18-53years) and studies were conducted at the start of ragweed season (September) in Northeastern Ohio. Serum IgE concentration, allergy symptoms [*via* self-report, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Visual Analog Scale (VAS),], psychological well-being [Profile of Mood States (POMS)], and physical function (RAND Corp. Short-Form-36 Medical Outcomes Study (SF-36 MOS)) were estimated directly prior to and after supplement with WGP (n=24) or placebo (n=24) for 4 weeks. Individuals experiencing an allergic response to asthma are supposed to have an overactive Th2 response. β-1,3-glucan can excite macrophages that releasing anti-inflammatory mediators, such as tumor growth factor, prostaglandin E_2, and interleukin 10 (IL-10), and might suppress the Th2 response [12]. Yamada *et al*. proved the beneficial effect of oral intake of β-1,--glucan, produced from shiitake mushroom (*Lentinus edoses*), on the rhinoconjunctivitis symptoms and proved that the particle size of β-glucan affects the efficaciousness. Their placebo-controlled, randomized, double-blind experimental study presented that oral use of overrefined spread β-1,3-glucan (SDG) for 8 weeks improved ongoing symptoms of rhinoconjunctivitis and rhinitis in Japanese patients carrying the symptoms of seasonal cedar pollen and

CHAPTER 5

Beta Glucan And Upper Respiratory Tract Obstruction

Abstract: Every year, during the winter season, 2 out of 4 adults complain of upper respiratory tract infections [1]. The β-glucan has a therapeutic effect on decreasing the symptoms of upper respiratory symptoms of infections such as cold and flu. Talbott *et al*. show that the healing effect of β-1,3/1,6-d-glucan on the psychological well-being of people who are experiencing a moderate levels of physicological stress and upper respiratory tract symptoms [2].

Keywords: β-glucans, Strengthening The Immune System, Upper Respiratory Tract Infections.

INTRODUCTION

Since ancient times, organic polyglucoside food supplements obtained from mushroom and mushroom extracts have played an important role in combating a wide range of diseases from coronavirus, cancer, allergic diseases to diabetes, kidney diseases to celiac disease. Its effects on health have been determined in many in vitro and animal studies. The β-glucans, which are one of these organic polyglucosidic food supplements, are obtained from the bran of oat or barley cereal grains, different kinds of mushrooms, and the cell wall of baker's yeast. Their molecular structure differs from 50 to 2300 kDa, and their biological activities are based on the source that are obtained and prepared.

Each year, adults suffer from upper respiratory tract infections (URTIs), mostly in the winter season (approximately 2–4 episodes), but few effective treatment options are available [3, 4]. URTIs may occur in any part of the respiratory mucosa, sometimes affecting all areas (simultaneously or at different times). URTI symptoms often include sneezing, rhinorrhea (runny nose) or blocked nose, headache, and general malaise. Apart from nasal symptoms, half of the affected individuals suffer from a sore throat, and 40% of URTIs are accompanied by coughing [5]. Common cold infections are mainly caused by viruses (typically rhinovirus, but also coronavirus and respiratory syncytial virus, or metapneumovirus, enterovirus, and others) [6, 7]. However, due to mucus layer disru-

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ption and dysbiosis within the respiratory tract following the virus infection, bacterial colonization may occur, which further leads to the enhancement of the inflammation process and prolonging the recovery.

The Therapeutic Effect of β-glucan on Upper Respiratory Tract Infections

The clinical studies with bakers' yeast β-glucan demonstrated beneficial effects with respect to URTI in different collectives. Previous studies have reported a relationship between chronic stress, URTIs, and raised susceptibility to the common cold. Talbott *et al*. investigated the health-beneficial effect of β-Glucan over both the physical and psychological well-being situation of marathon runners [7]. They conducted a set of self-assessment tests in order to determine the health condition of the patients having URTI. The randomly selected volunteers used 250 mg, 500 mg, β-1,3/1,6-Glucan (which is derived from the yeast *Saccharomyces cerevisiae*) that named as Wellmune whole glucan particles (WGP®) and placebo group are also formed. Placebo capsules consist of 250 mg of rice flour. The most common upper respiratory symptoms reported by subjects were sore throat, stuffy or runny nose, and cough. After 12 weeks, 29% of subjects in the placebo group reported upper respiratory symptoms, but only 11% in the β-glucan group reported symptoms (Fig. **1**) [2].

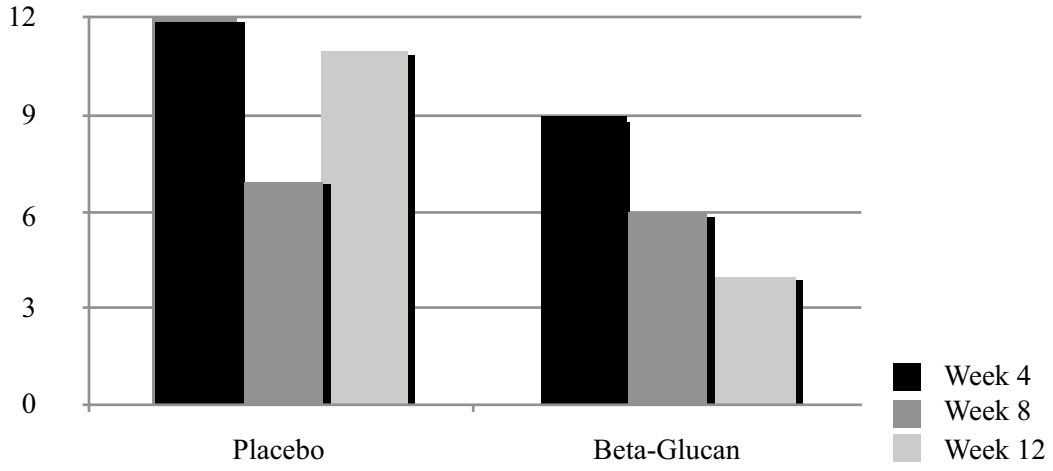

Fig. (1). Upper respiratory symptoms. The total number of subjects reporting any of 11 preselected upper respiratory symptoms at the conclusion of the study. Subjects were orally administered placebo or 250 mg beta-glucan–containing supplement daily for 12 weeks. The β-glucan group reported fewer upper respiratory symptoms at each week (range 4-9 symptoms per week) and across all weeks (19 total) *vs* the placebo group (range 7-12 symptoms per week and 30 total) [2].

Placebo groups showing upper respiratory symptoms entitled as physically felt worse syndrome and this reflects their psychological condition. Reversely, topics

on β-glucan reported lower levels of upper respiratory symptoms and built a felt better that reflects the psychological assessment methods. The people having an impact on certain mood state subscales such as depression, confusion, tension, and anger are not surprising because yeast β-glucan does not show a psychoactive effect.

Toilsome activity like marathon running blocks the mucosal immunity during 24 hours, which might increase the risk of having URTI [8]. In order to investigate the immune system boosting effect of β-glucan on athletes, Niemann *et al*. conducted a study including the administration of β-glucan supplement to male cyclists (N = 19) or placebo (P; N = 17) groups and under double-blind protocols given β-glucan (5.6 g x d(-1)) or P beverage supplements for 2 wk. After an 18 day period, both β-glucan-given and placebo groups did not show a significant change in their immune function or URTI incidence in Table **1** [9]. However, the marathon athletes, which were given two separate doses (250 and 500 mg) of insoluble form of β-glucan derived from yeast, showed developed mood conditions and helped to decrease the symptoms of URTIs.

Table 1. Subject characteristics measured at baseline and performance data averaged during the 3-h cycling about for 3 d [9].

	Cyclists		
Variable	**β-Glucan (N=19)**	**Placebo (N=17)**	**P**
Baseline measures			
Age (yr)	21.8 ± 0.9	25.0 ± 2.2	0.186
Body mass (kg)	70.7 ± 2.1	77.4 ± 1.9	0.026
$\dot{V}O_{2peak}$ ($mL.kg^{-1}.min^{-1}$)	54.9 ± 1.7	52.2 ± 1.1	0.200
$Power_{max}$ (W)	311 ± 10.0	320 ± 8.1	0.495
HR_{max} (bpm)	191 ± 2.9	186 ± 1.9	0.156
Body consumption (% fat)	7.1 ± 0.9	8.5 ± 0.9	0.256
Performance measures			
Mean power (W)	175 ± 5.9	181 ± 4.8	0.494
Power (% W_{max})	56.4 ± 0.3	56.7 ± 0.2	0.801
Mean HR (bpm)	148 ± 2.4	145 ± 1.4	0.352
HR (%HR_{max})	76.3 ± 1.2	78.2 ± 0.9	0.213
Mean $\dot{V}O_2$ ($mL.kg^{-1}.min^{-1}$)	37.1 ± 0.9	35.5 ± 0.6	0.161
$\dot{V}O_2$ (%$\dot{V}O_{2max}$)	68.0 ± 1.4	68.2 ± 1.5	0.916
Cadence (rpm)	86.9 ± 1.8	86.9 ± 1.3	0.996
Values are presented as mean ± SE. $\dot{V}O_2$ = volume of oxygen consumption.			

CHAPTER 6

β-Glucan In Treatment Of Low-density Lipoprotein (ldl) Cholesterol

Abstract: Hypercholesterolemia is one of the most important risk elements of cardiovascular disease causing metabolic syndrome, diabetes, hypertension. Although there is a development in this subject, the studies for finding new ways of preventing and healing dyslipidemia are continuing, and current treatments for cardiovascular diseases are stimulating different side effects. There are two kinds of β-glucans, insoluble and soluble. These supplements directly interact with biliary salts and lipids and in the bowel and decrease the level of cholesterol [1]. The patients having dyslipidemia can be healed by using the therapeutic effect of β-glucans as they do not create any significant side effects. In this review, the healing effect of β-glucans on decreasing cholesterol levels in humans.

Keywords: β-glucans, Hypercholesterolemia, Low-density Lipoprotein Cholesterol.

INTRODUCTION

Cardiovascular diseases threaten human health by building a major risk due to the increased total and low-density lipoprotein (LDL) cholesterol levels. Actually, cholesterol is a vital component of the body that has a significant role in the survival of organisms by building the fundamental structure of the cells and catalyze their biochemical activity. 70% of the cells of intracellular organelles and blood plasma consist of cholesterol and cholesteryl esters. 25% cholesterol of the body are located in brain tissue [2]. The cholesterol, which is formed in the liver, is the main source of steroid, acids, vitamin D, and hormones [3]. Cholesterol is extremely beneficial for adjusting the metabolism energy and overall energy consumption. For instance, cholesterol enhances adaptive thermogenesis chase to disclosing to cold through its transformation to bile acids and forming the gut microbiome [4]. To synthesize chenodeoxycholic and cholic acid, primary bile salts are obtained in the liver through the oxidization of cholesterol. Glycocholic and taurocholic acids, which are synthesized *via* conjugation of chenodeoxycholic and cholic acid with taurine and glycine, are used in adjusting lipid metabolism and energy consumption together with pancreatic lipase [5].

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Oat β-glucan, which is included in the endosperm cell walls of oats, gathers the significant amount of interest due to its cholesterol-lowering benefits [6]. Oat β-glucan (OBG), which is basic soluble ingredient included in oats, is the primary active substance that lowers the total blood and LDL cholesterol. In 1997, β-glucan soluble fibers obtained from oats were approved as a reducing supplement for plasma cholesterol levels and risk heart disease by The United States Food and Drug Administration (FDA). In 2004, the United Kingdom Joint Health Claims Initiative (JHCI) agreed that oat β-glucan could reduce the risk of Coronary heart disease (CHD) by means of its total blood cholesterol and LDL cholesterol-lowering effect [7]. A commercial product, Oatrim, including saturated amounts of soluble fiber, β-glucan, was invented by Dr. George Inglett, ARS, USDA, Peoria, IL [8, 9] to use instead of fat in foods. Human studies show that oat fiber extract is used to lower the plasma lipids which are related to increase of the risk heart crisis. Today, various health authorities and agencies worldwide [United States: U.S. Food and Drug Administration [10]; Canada: Health Canada [11]; Europe: European Food Safety Authority [12]; Australia and New Zealand: Food Standards Australia New Zealand [13]; Malaysia: Ministry of Health Malaysia [14]] approve the cholesterol lowering effect of β-glucan. Except for Malaysia, the diets are based on a meal containing at least 3 g OBG/d, that changing according to the particular conditions, for instance, the Food and Drug Administration [15] permits individual meals, including 0.75 g OBG, whereas the European Food Safety Authority [16] allows 1-g amounts.

Othman *et al*. proved that 5% and 7% reductions in total and LDL cholesterol levels were observed by oat consumption, respectively. The chemical molecular structure of β-glucan, which is consisted of glucose molecules with mixed β-(1→4) and β-(1→3) bonds, was given in Fig. (**1**) [6].

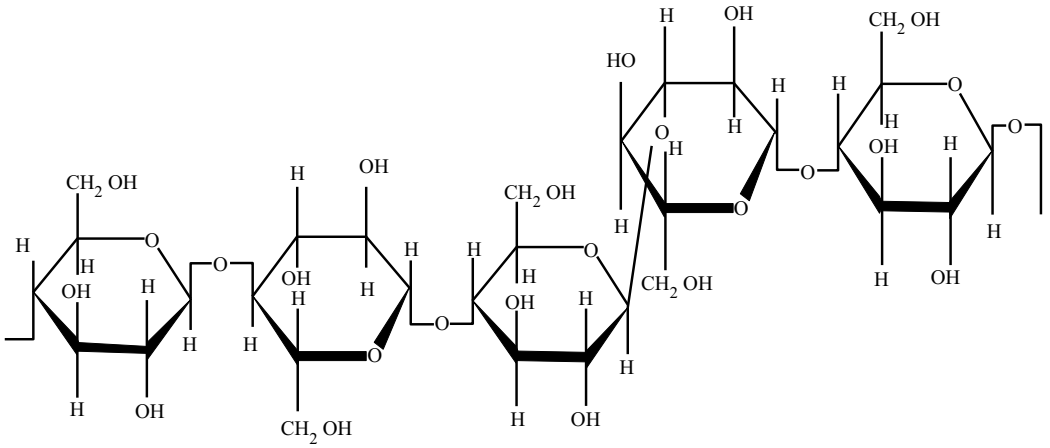

Fig. (1). Chemical structure of oat β-glucan [6].

Wolever *et al*. conducted a post-hoc analysis in order to examine the decreasing effect of oat-based-β-glucan in low density lipoprotein – cholesterol (LDL-C) level in Caucasians and non-Caucasians by evaluating the results of a randomized, controlled, double-blind, multi-center clinical trial whose primary aim was to determine if molecular-weight (MW) influenced the LDL-C-lowering effect of oat β-glucan [17]. On the other hand, β-glucan derived from yeast seems to have a similar effect on blood lipids and is more concentrated so that lesser calories need to be ingested. The yeast-derived β-glucan is substantially more adaptable than oat products because it can be agreeably integrated into a wide range of food products [18].

Previous Studies On β-glucan's Cholesterol Lowering Effect

It has been shown that β-glucans decrease non-high-density lipoprotein-cholesterol (non-HDL-C) level which includes low density lipoprotein-cholesterol (LDL-C) that having an effect on triglyceride and HDL-C levels [19 - 22]. Since the 1960s, β-glucans have benefited in decreasinig the blood cholesterol levels and boosting the immune system [23 - 25].

The soluble fiber (β-glucan) in oats appears to be one of the components responsible for lowering plasma lipids [26 - 31]. Behall *et al*.'s study, twenty-three of the volunteers, seven men and sixteen women, selected for the study based on their cholesterol levels after consuming self-selected diets completed the study. Initial subject characteristics are listed in Table **1**.

Table 1. Mean plasma lipids after controlled lipids [26].

	Maintenance mmol/L	Diet Low (β-glucan mmol/L	High β-glucan mmol/L	Analysis of covariance
Total cholestrol	5.470.19[a*]	4.950.19[b]	4.67 0.19[c]	p < 0.0001
HDLC	1.290.09[a]	1.340.10 [a]	1.190.09[a]	p <0.226
HDL2-C	0.58 0.08[a]	0.700.09 [a]	0.570.08[a]	p < 0.280
HDL3-C	0.72 0.03[a]	0.650.04[ab]	0.620.03[b]	p < 0.022
LDL-C	3.65 0.16[a]	3.11 0.16[b]	2.89 0.16[b]	p < 0.0001
VLDL-C	0.55 0.05[a]	0.54 0.05[a]	0.590.05[a]	p < 0.361
Triglycerides	1.18 0.11[a]	1.15 0.11[a]	1.28 0.11[a]	p < 0.288

***** Weight adjusted Least Square Means ± SEM from analysis of covariance. Mean weight (kg) for each diet was 76.1 ± 3.9 (maintenance), 73.8 ± 3.9 (low Il-glucan), and 73.9 ± 3.9 (high Il-glucan) (sex, $p < 0.04$; diet, $p < 0.001$). t Means with different superscripts within a row are significantly different at $p < 0.05$ (LSD)

Total cholesterol levels were not significantly different by sex at screening Table **1**, p <0.27). The men had obviously higher triglyceride levels than either group of

CHAPTER 7

Beta Glucan In Diabetes Treatments

Abstract: Soluble fibers are more effective for the management of diabetes, obesity, dyslipidemia, hypertension, and different cancers when compared with insoluble fibers. The ingestion of foods with a low glycaemic index is a helpful alternative in controlling diabetes. The hypocholesterolemic and hypoglycemic effects of β-glucan are due to its high viscosity and high molecular weight. For this reason, β-glucan is chosen by the food industry to manufacture various types of functional foods. β-glucans, which are also having form as Oat β-glucan (OβG), including primarily of the linear polysaccharide (1→ 3), (1→ 4)-β-D-glucan is a vital food supplement for achieving insulin responses and decreasing postprandial glucose. Also, β-glucans accelerate wound healing and prevent ischemic heart injury disease. Dose, physicochemical properties, and processing techniques are important factors in controlling glycaemia by emerging the effects of β-glucans.

Keywords: β-glucans, Diabetes, Hyperglycemia, Oat, Soluble Fiber.

INTRODUCTION

Diabetes mellitus is an important metabolic disease developed from a dysregulation in releasing insulin leading to chronic hyperglycaemia, and other deficiencies such as myocardial infarction, nephropathies, neuropathies, vascular alterations, and retinopathies [1].

According to the International Diabetes Federation (IDF), the number of people suffering from Type-2 Diabetes (T2D) will be 578 million, and it will be equal to 10.2% of the worlḋs population by 2030. If the increasing trend continues at this velocity, it will be 10.9% (700 million people) by 2045 [2].

The rate of having diabetes is higher in men than women; however, the number of women having diabetes is larger than men [3]. Table **1** summarizes the calculated numbers of people with diabetes by region for 2000 and 2030 according to the population changes.

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Table 1. Estimated numbers of people with diabetes by region for 2000 and 2030 and summary of population changes [3].

	2000	2030	2000–2030			
Region (all ages)	Number of people with diabetes	Number of people with diabetes	Percentage of change in number of people with diabetes*	Percentage of change in total population*	Percentage of change in population 65 years of age*	Percentage of change in urban population*
Established market economies	44,268	68,156	54	9	80	N/A
Former socialist economies	11,665	13,960	20	-14	42	N/A
India	31,705	79,441	151	40	168	101
China	20,757	42,321	104	16	168	115
Other Asia and Islands	22,328	58,109	148	42	198	91
Sub-Saharan Africa	7,146	18,645	161	97	147	192
Latin America and the Caribbean	13,307	32,959	148	40	194	56
Middle Eastern Crescent	20,051	52,794	163	67	194	94
World	171,228	366,212	114	37	134	61

* A positive value indicates an increase, a negative value indicates a decrease.

Dietary fibers are planting that resist digestion against gut enzymes in human beings. They consist of heteropolysaccharides, homopolysaccharides, oligosaccharides, resistant starches gums, lignin, and mucilages. Unlike other fibers, a smaller amount of β-glucan is sufficient enough in order to obtain a decline in postprandial glucose and insulin responses in healthy volunteers and type 2 diabetic patients [3, 4]. Dietary fibers can be divided into two sub-groups: soluble and insoluble dietary fibers (SDF and IDF), as shown in Fig. (**1**) [5].

In this review, the therapeutical effect of β-Glucan on diabetes, glycaemia, insulin resistance and glycolised hemoglobin levels are discussed.

β-Glucans and Diabetes

β-glucans provides many benefits for preventing, treating, and managing diabetes, obesity, hyperlipidemia, cancer, cardiovascular diseases, and many infectious and parasitic diseases by boosting the immune system through the activation of

monocyte/macrophage, the rise of immunoglobulin, T cell and natural killer cells (NK) (Fig. **2**) [7].

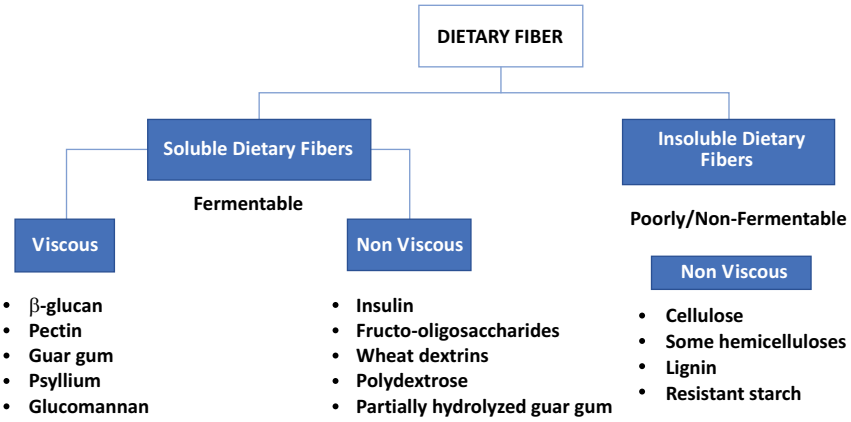

Fig. (1). Classification of dietary fiber according to chemical properties [6].

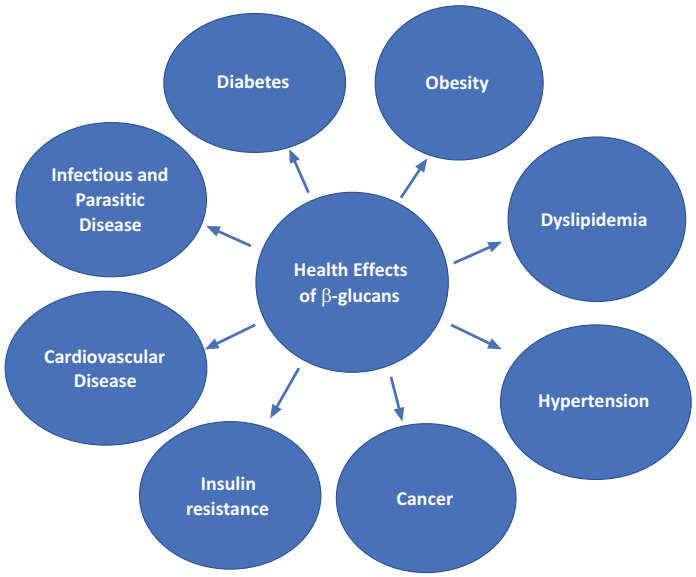

Fig. (2). Health effects of β-Glucans [8].

They are formed from non-starch polysaccharides consisting of D-glucose monomers that bondwith β-glucosidic bonds found in grains such as oats, wheat, barley, rye, yeast, some grasses, and mushrooms [9]. Their polysaccharide structures consist of short and medium chains as (1 → 3)/(1 → 6) and (1 → 3)/(1 → 4) bonds, relying on the used carbon source [10]. β-glucans are a rare form of dietary fibers that can be synthesized from various types of sources such as

CHAPTER 8

Beta Glucan For Treatment Of Ear Infections: Acute Otitis Media

Abstract: β-glucans offer a unique chance to explore new therapeutic agents. They have gathered huge amıunt of attention for plenty of health advantages such as immune system modulator, cardioprotective, anticancer, antioxidative, hepatoprotective, and antimicrobial functions. β-glucans have the capacity to develop a congenital and cell-mediated immune response. They demonstrate changing degrees of antitumor function in humans due to differences in their structure, size, water solubility, and molecular mass; these differences in turn provide its therapeutic characteristics.

Keywords: Acute Otitis Media, Antiinflammatory, Antioxidant Activity, Ear Infections, Glucan.

INTRODUCTION

2400 years ago, Hippocrates said, “Let your food be your medicine, and your medicine be your food” [1]. In addition to meeting the basic nutritional needs, functional foods developed on the basis of this view have potentially many positive effects on health in today's world where diseases such as cancer, cardiovascular diseases and diabetes are incrementally increasing [2].

Acute otitis media (AOM) disease, which is common in childhood, catches 75% of preschool children at least once a year. Among the complications that they will develop is the spread of intracranial infection. AOM mechanisms in the middle ear cavity (MEC) that can make the person susceptible to the development of inflammation are partially known [3, 4]. *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*s, *Haemophilus influenzae*, *Streptococcus pyogenes* are among the five most common bacterial species that cause AOM [5]. Human rhinovirus, respiratory syncytial virus, adenovirus, influenza viruses and enteroviruses are among the most common viruses that can contribute to the formation of AOM [5]. In patients with AOM, there are many disorders that will adversely affect their quality of life, such as cognitive impairment, headache, pain, and hearing loss [6, 7]. Finding the appropriate treatment is difficult due to

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the resistance of AOM pathogens to antibiotics of choice [8]. For this reason, some AOM patients can be prescribed alternative therapies derived from herbs in addition to traditional treatment methods.

β-glucan provides a wide variety of healing effects on the body and immune system by building and strengthening immune cells. It is an approved and proven biological defense modifier [5]. It triggers the development of many immune cells such as macrophages, monocytes, natural killer cells, neutrophils, and dendritic cells, as well as inhibits the development of tumors in the growth phase [9]. β-Glucans are soluble fibers that have many physiological functions, such as interfering with sugar absorption and lowering serum lipid levels. β-glucans can be obtained from different types of food sources such as *Grifola frondosa, Tremella aurantia, Lentinus edodes, Tremella mesenterica, Rhynchelytrum repens, Phellinus baummi, Zea may, Agaricus blazei, Saccharomyces cerevisae* (yeast) and Agaricus blazei murell (mushroom) [10]. Also, it is used in the treatment of many diseases such as common cold (cold), flu (flu), H1N1 (swine) flu, fibromyalgia, rheumatoid arthritis, multiple sclerosis, ulcerative colitis, Crohn's disease, Lyme disease, hepatitis, asthma, allergies, ear infections, aging, so on [10].

In this review, the effect of β-glucan as well as its antiinflammatory, antioxidant and cytotoxic activities were investigated for the alternative treatment of ear infections in acute otitis media.

Previous Studies on Therapeutic Effect of β-glucan For Acute Otitis Media

There are many studies on proving the therapeutic effect of β-glucan for ear infections and AOM. In the study of Çetinkaya *et al*., 35 adult rats were randomly divided into 5 groups as Group 1 (control), Group 2 (acute otitis media, no treatment), Group 3 (acute otitis media + antibiotic), Group 4 (acute otitis media + β-glucan) and Group 5 (acute otitis media + beta-glucan + antibiotic). In this study, the results of immunology and histopathology examinations were analyzed in terms of epithelial damage, thickening of the tympanic membrane, inflammation and sclerosis. Serum levels of TNF-α, IL-4, IL-6 and IL-1β were evaluated for all experimental groups [5].

As a result, the serum cytokine levels of the β-glucan and antibiotic treatment group were lower than those of the acute otitis media group. Again, significant differences were observed between the acute otitis media + antibiotic group and the acute otitis media + β-glucan group in terms of criteria such as tympanic membrane thickness, epithelial damage, sclerosis and inflammation. According to these criteria, the best results were obtained for the acute otitis media + antibiotic + β-glucan group. A significant difference was observed in the acute otitis media

+ antibiotic + β-glucan group compared to the acute otitis media group ($p < 0.001$) [5].

In the study conducted by Dore *et al.*, The simultaneous application of N(gamma)-nitro-L-arginine methyl ester (LNAME), diclofenac, and glucan extract in the treatment of ear edema caused by croton oil showed a supra-additive anti-inflammatory effect. These results revealed a synergistic interaction between iNOS or COX inhibitors and glucan extract, which led us to suggest that the anti-inflammatory effect of the glucan extract from the mushroom Geastrum saccatum is mediated by inhibition of both NOS and COX. Thus, it was concluded that the anti-inflammatory effect of the glucan extract obtained from the mushroom Geastrum saccatum appeared through the inhibition of both NOS and COX [11]. Ear edema caused by croton oil was inhibited thanks to the combination of Glucan (60.4% at 10 mg/kg), L-NAME (86.23% at 60 mg/kg) or diclofenac (89.2% at 5 mg/kg). Histological analyzes of ear edema caused by croton oil in the presence of Glucan (10, 30 or 50 mg/kg) demonstrated a reduced degree of polymorphonuclear cell migration. Hence, it can be concluded that Glucan contains antioxidants, and it can be said that besides its anti-inflammatory properties, its anti-inflammatory effect is mediated by the inhibition of both nitric oxide synthase (NOS) and cyclooxygenase (COX). The preparation protocol of β-glucan extract from *G. saccatum* fruiting bodies of *G. Saccatum* was given in Fig. (**1**) [11].

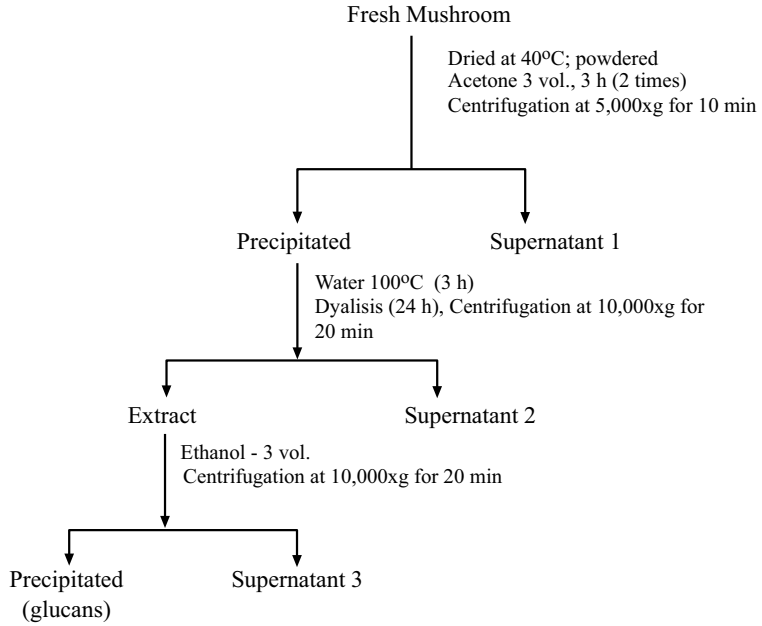

Fig. (1). Extraction procedure for glucans from *Geastrum Saccatum* [11].

CHAPTER 9

Beta Glucan in Treatment of Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Diseases (IBD): Ulcerative Colitis (UC) and Crohn's Disease (CD)

Abstract: Since ancient times, the healing properties of fungi have been used in the treatment of many health problems such as hypertension, diabetes, allergies, cancer, atherosclerosis, digestive system disorders and inflammation. Inflammatory bowel diseases are a very serious health problem that significantly reduces a person's quality of life. Regarding immune-mediated inflammatory diseases, two of the most common types of inflammatory bowel disease are Crohn's disease (CD) and ulcerative colitis (UC). Levels of C reactive protein (CRP), neutrophil elastase, leukocyte esterase, interleukin 1ß (IL-1ß), interleukin receptor 1 antagonist, tumor necrosis factor (TNF), and eosinophilic cationic protein (ECP) biomarkers observed in the body in inflammatory bowel diseases. It is reduced by giving the body β-glucan. At the same time, the percentage of lymphocytes was decreased, and pathways for cytokine and chemokine marking were developed. This review focuses on the therapeutic effect and mechanism of β-glucan content derived from fungi, yeasts, and other organic sources on inflammatory bowel disease (IBD) such as CD and UC, and irritable bowel syndrome (IBS).

Keywords: β-glucan, Crohn's Disease, Irritable Bowel Syndrome, Inflammatory Bowel Diseases, Ulcerative Colitis.

INTRODUCTION

Irritable bowel syndrome is a disorder related to the functionality of the digestive system and manifests itself with changes in bowel order and abdominal pain [1]. It has a multifactorial etiology, including inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) [2]. IBD is a disease of the gastrointestinal system that causes chronic recurrent inflammation and activation of the immune system. Inflammation caused by the pathogens damages cells and tissues while also stimulating the body to create a protective response [3]. The prevalence and incidence of IBD is approximately 0.2% of the European population [4]. In the case of such gastrointestinal diseases, there is an increase in the levels of cytokines such as Tumor necrosis factor-alpha (TNF-α), Interferon

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gamma (IFN-γ), Interleukin 17 (IL-17), and Interleukin 12 (IL12), which are formed before inflammation in the intestinal lumen, intestinal mucosal barrier, and intestinal flora [5]. As a result of the high inflammation that occurs due to this disease, the main symptoms such as abdominal pain, bloody stools, weight loss, diarrhea occur throughout the disease. The symptoms of CD include chronic inflammation in all parts of the digestive system. In addition, this inflammation covers the thickness of the entire intestinal wall. UC is seen in the mucosa and submucosa of the large intestine.

Thanks to its immune system regulating effects, the consumption of nutritious fibers such as β-glucan helps treat and prevent acute and chronic inflammations in the intestine [6]. β-glucan plays a key role in the formation of the innate immune response as a result of the interaction of dendritic cells and macrophages, as well as in the formation of T cells and natural killer cells and adaptive immune response as a result of cytokine release [7]. To our knowledge, previous studies on the effects of β-glucan during human inflammation are limited. However, in recent years, it has been observed that Saccharomyces cerevisiae yeast and its derivatives prevent adherent invasive E. coli-induced colitis seen in a mouse with CD disease [8]. In addition, intestinal health and the occurrence of intestinal diseases depend on various factors such as diet, lifestyle, or the occurrence of infections [9].

β-glucan and Crohn's Disease

Crohn's disease (CD) is an inflammatory bowel disease and is defined as inflammation mediated by the chronic wall from the oral cavity to the anus, which can result from stimulation of the mucosal immune system that is overstated by both normal and dysbiotic common bacterial intestinal flora [10].

In individuals with CD and increased gut permeability, an increase in luminal bacteria, parts of endotoxin and antigenic is observed, which will have negative effects on barrier function [11]. CD disease involves a gradual treatment with 5-amino-salicylic acid, glucocorticoids, or antibacterial drugs followed by the use of immunomodulators and ultimately biological drugs.

β-glucan is used to develop the barrier function of the intestinal and build a positive effect on inflammation due to UC [12]. In the studies conducted by Ganda Mall *et al*., it was observed that yeast-derived β-glucan was able to reduce excessive paracellular and transcellular permeability caused by mast cell-degranulation [12]. *In vitro* studies have observed a higher passage of β-glucan from the follicle-associated epithelium (FAE) compared to villus epithelium (VE). In addition, in the same study, it was found that the condensation compound of N-methyl p-methoxy phenethylamine and formaldehyde (C48/80) did not

significantly reduce the level of TNF-α compared to that, β-glucan intake provided a significant decrease in the level of TNF-α. The effects of yeast-derived β-glucan on C48/80-stimulated paracellular hyperpermeability in FAE and VE of 8 control subjects mounted in Ussing chambers are summarized in Fig. (**1**).

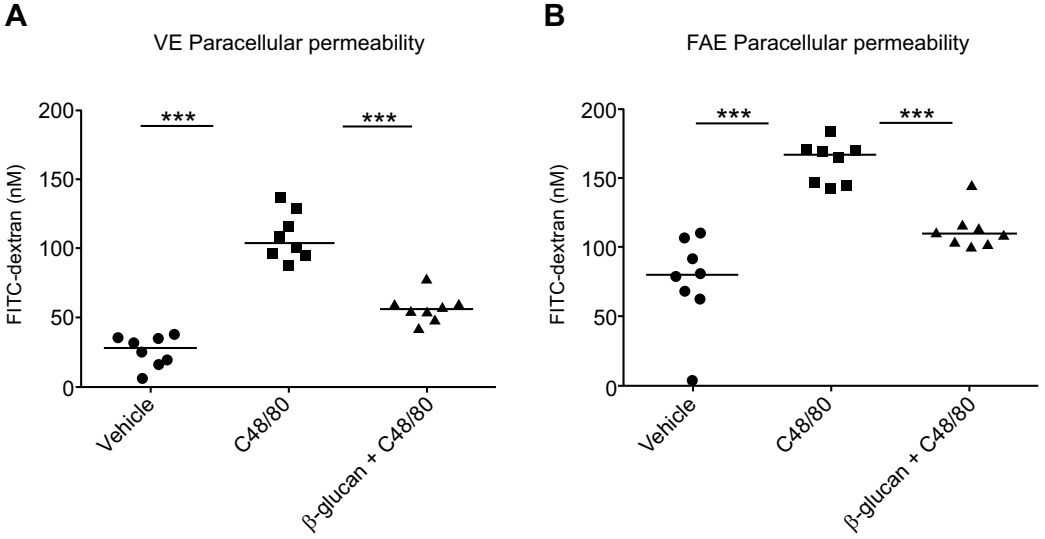

Fig. (1). Effects of yeast-derived β-glucan on compound 48/80 (C48/80)-induced paracellular hyper-permeability in a) VE and b) FAE of 8 control subjects mounted in Ussing chambers [12].

In addition, since the percentage of macrophages is close to β-glucan, it is importantly higher in the FAE of both CD and the control group compared to VE. There was no significant difference in the percentage of MCs in close proximity to β-glucan, between CD and controls, neither in VE nor in FAE, and no difference between the epithelial types within the groups. In addition, there was no significant difference in the percentage of mast cells (MCs) close to β-glucan between the control group and the CD group, neither in terms of VE nor in terms of FAE, and there was no difference between epithelial types within these groups [12].

In another study conducted by Notararigo *et al*., it was determined that the oxygen-added-(1–3) -β-D-glucan polymer had an anti-inflammatory effect and reduced the level of Interleukin 8 (IL-8) [13].

Table **1** shows the quantification of immune cells and proximity to uptaken β-glucan. For building Table **1**, 5 volunteers with CD and control group were mounted in Ussing chambers, and their VE and FAE were examined. Alexa Fluor 594-conjugated β-glucan was given to the mucosal section for 20 min. The tested

CHAPTER 10

Beta Glucan For The Treatment Of Recurrent Aphthous Stomatitis And Diabetic Ulcers

Abstract: Recurrent Aphthous Stomatitis (RAS), which has symptoms like pain while eating, speaking, or swallowing, is one of the most hurtful oral mucosal inflammatory ulcerative diseases [1]. Tumor necrosis factor α (TNF α), has a main role in predominantly cell-mediated immune response due to the pathogenesis of RAS. The aim of this study was to investigate the therapeutic effects of Beta-glucan on the response of lymphocytes with and without phytohemagglutinin (PHA), a T lymphocyte mitogen, in treatment of RAS. RAS, estimated by the Ulcer Severity Score (USS), shows ulcer characteristics (number, size, duration, ulcer-free period, site, and pain).

Keywords: Beta Glucan, Diabetic Ulcers, Recurrent Aphthous Stomatitis.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a disorder characterized by recurrent ulcers confined to the oral mucosa in patients [1]. RAS is a very common but not fully understood mucosal disorder [2]. It has a prevalence of 10% to 30% of the population and is among the most common oral mucosal lesions [3]. Its incidence in children is 39%, and it is more common [4]. In the epithelium of the pre-ulcerative step, a mononuclear (lymphocytic) cell infiltration is followed by a localized papular swelling because of keratinocyte vacuolations encircled by a reactive erythematous halo demonstrating vasculitis. The papule, which becomes painful, then becomes an ulcer and a fibrinous membrane begins to cover the ulcer infiltrated principally by lymphocytes, neutrophils, and plasma cells [5, 6]. Minor aphthae are the most general type and appear clinically as regular, painful, circular ulcers 3-6 mm in diameter, covered with a whitish-yellow membrane and circled by a thin red halo as given in Fig. (**1**). These lesions are single and multiple, and they can be treated by not scarring in 7-12 days.

Various predisposing reasons such as allergy genetic predisposition, trauma, hematological inadequacy, endocrine disorders, emotional stress, and AIDS have been examined. The rate of occurrence of human leukocyte antigen (HLA) A33,

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HLA-B35, HLA-B51, HLA-B12, HLA-DR7, and HLADR5 is more than in patients having RAS comparing to healthy control groups [7]. Also, genetic heritage are effecting of the having RAS. The DNA polymorphisms throughout the human genome, such as Interleukins (IL) (*e.g.*, IL-ß, IL-2, IL-4, IL-5, IL6, IL-10, and IL-12), interferon, and tumor necrosis factor (TNF)-á also occurs [8].

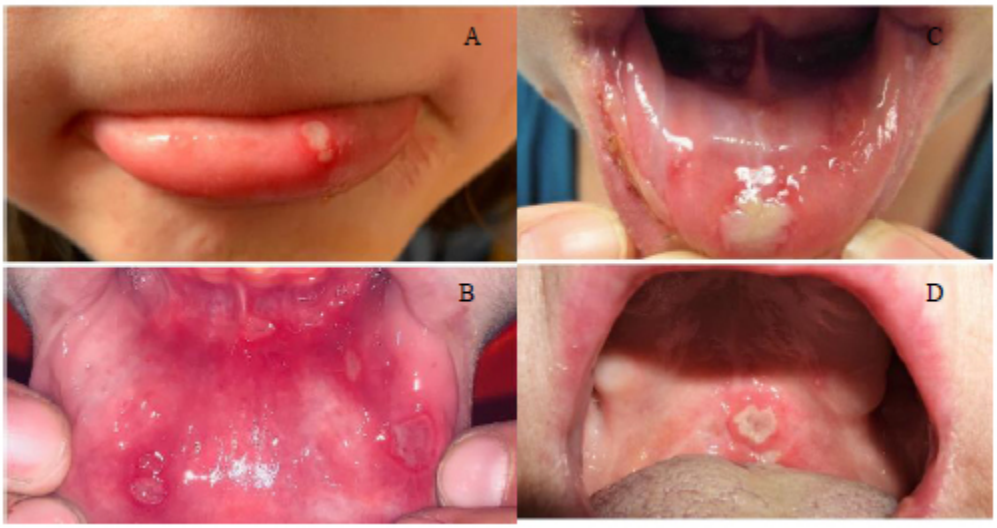

Fig. (1). Minor ulcers on the a) lip and b) mucous membrane of the lower lip and c) major ulcers on the mucous membrane of the lower lip d) ulcer on the soft palate.

There are many remedies for healing patients having RAS. In order to control the disease, in some situations, local therapy can be enough. Also, topical steroids are used for the healing of RAS. In order to diminish the treatment time of the lesions, the usage of topical corticosteroids can be useful in more serious situations. The use of fluocinolone or triamcinolone three or four times a day presents an efficient treatment for the topical lesions [9].

In literature, there are some publications about the effectuality of β-glucans for healing minor aphthous stomatitis [3, 10]. Ikuzowa *et al*. reported that the oral intake of β-glucans had an inducing effect on host immune defense mechanisms, predominantly including NK cells, neutrophils, and macrophages [11]. Taking 10 mg beta glucan on daily basis demonstrates a therapeutic effect on ulcers compared with the placebo groups [12, 13].

POSSIBLE CAUSES OF RECURRENT APHTHOUS STOMATITIS

There are many reasons that are affecting the severity of having Recurrent Aphthous Stomatitis (RAS). Among these causes, drugs, immunologic reasons,

hormonal situation, food allergy, bacterial and viral factors, local injuries, and stimulative systemic diseases are main reasons of RAS as summarized in Fig. (**2**).

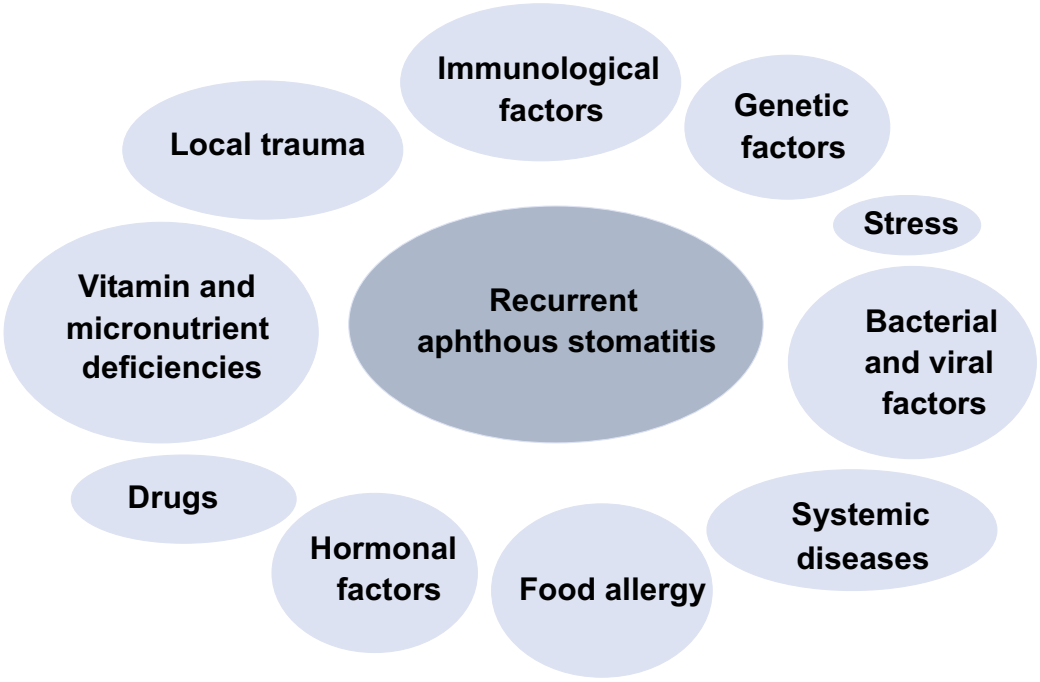

Fig. (2). Factors affecting the pathogenesis of recurrent aphthous stomatitis.

Bacterial And Viral Factors

There is a relation between RAS and different microorganisms, involving bacteria of the genus Streptococcus, especially Streptococcus sanguinis 2A, Epstein-Barr virus, Lactobacillus, *Helicobacter pylori*, and Epstein-Barr virus.

Local Injury

Local injury is one of the casual agents in genetically predisposed patients with RAS, including edema, increased viscosity of the extracellular matrix of oral submucosa, and early cellular inflammation. Sawair reported that smoking has a time- and dose-dependent "protective effect" on RAS. When lesions appeared, smoking showed no effect on RAS severity [14].

Food Allergy

Allergy is considered as one of the main causes of RAS. Being hypersensitive to some substances such as heat shock proteins and oral microorganisms (S sanguinis) can be reported as the other causes of RAS.

CHAPTER 11

Beta Glucan for Healing of Bedsores, Wounds, Burns

Abstract: Highly purified yeast-derived insoluble β-(1 → 3)-d-glucan efficiently inhibited adipogenic differentiation, promoted wound healing, and significantly reduced skin irritation [1,2]. β-glucans can be used on the skin for dermatitis, bed sores, wrinkles, wounds, eczema, burns, radiation burns, and diabetic ulcers. β-glucan wound dressings show a suitable wound therapeutic agent with superior stability and demonstrate resistance to wound proteases. This review explains new developments and progression on identifying the healing properties of β-glucans for wounds *in vitro* and *in vivo* and their safety and effectiveness remedy for non-healing wounds or other chronic dermatological diseases.

Keywords: Beta Glucan, Bedsores, Burns, Wounds.

INTRODUCTION

Polysaccharides such as β-glucan, cellulose, pullulan, chitosan, starch, hyaluronic acid, collagen, and alginate are often used as wound dressing materials used in many medical applications such as bedsores scar, wrinkles repairment. Among these polysaccharides, β-glucan, derived from many sources such as yeasts, lichens, algae, fungi, plants, oats, bacteria, and barley, was first discovered by Leibovich and Danon in 1980 [3]. β-glucan presents faster re-epithelialization, increased macrophage activity and fewer polymorphonuclear neutrophils in the wound bed during the inflammatory step of recovery. β-glucan removes cellular debris due to oxidative stress by activating macrophages and thus accelerates the recovery of damaged tissues [4].

Dietary fiber has usually included β-D-glucan component. Natural oat β-glucan is a linear polysaccharide consists of 1-3-O-linked (30%) and 1-4-O-linked (70%) β-D-glucopyranosyl units (Fig. **1**) [5].

β-glucan which demonstrating high viscosities at low concentrations, has conspicuous nutritionary and functional properties. β-glucan solutions, having concentration at 1%, also have low flow behavior and high consistency indexes in the power law model [6].

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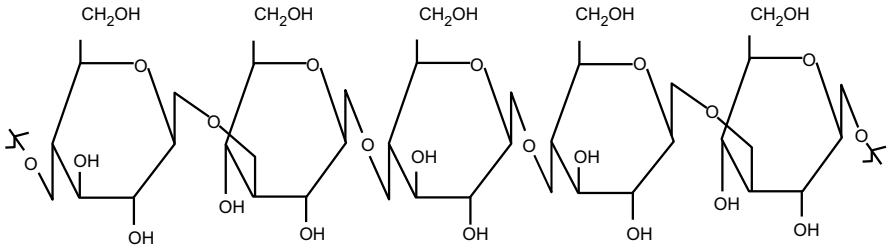

Fig. (1). Molecular structure of oat β-glucan [5].

Working Mechanism of β-glucan

Healing time of chronic and acute wounds can be decreased by the use of β-glucans [7]. Several receptors such as the Dectin-1 receptor, Toll-like receptors (TLR-2, 4, 6), complement receptor 3 (CR3), scavenger receptor, and lactosylceramide intervened in the working mechanism in the organism [8]. There are two action modes of β-glucan for wound healing by immune system boosting activity. One action mode of β-glucan reveals indirect activation *via* different cytokines of macrophages, and another action mode works by directly influencing fibroblasts and keratinocytes [9]. The highly efficient Dectin-1 receptor is found in many immunocompetent cells such as eosinophils, neutrophils, monocytes, several T lymphocytes, macrophages, cutaneous cells (fibroblasts and keratinocytes), and dendritic cells (DC) [9]. β-Glucans show many biological functions such as anti-inflammatory and immunomodulatory that are used for wound healing. Different kinds of skin diseases can be healed by the pluripotent properties of β-glucans such as anti-inflammatory, antioxidant, moisturising, immunomodulative, radioprotective, rejuvenative and regenerative effects [10 - 12]. Plenty of studies show the wound healing function of different kinds of β-glucan are summarized in Table **1**.

Table 1. β-glucan types from various source and their respective wound healing activity.

Name of the β-glucan	Target cell type/ animal model	Inference	Ref
Baker's yeast Glucan	Human Dermal Fibroblasts (HDF)	increased the nuclear factor-1 binding capacity and enhanced collagen biosynthesis	[13]
	Porcine keratinocytes	enhanced the keratinocyte proliferation	[14]
	3T3 fibroblast	nanofibrous membranes enhanced the adhesion and proliferation of fibroblasts and keratinocytes	[15]
	Venous ulcer biopsy	enhanced the healing in venous ulcer	[16]
Barley Glucan	Adult Human dermal fibroblast (HDFa) / Mice	induces an early response in HDF cell favouring movement *versus* proliferation	[17]

(Table 1) cont.....

Name of the β-glucan	Target cell type/ animal model	Inference	Ref
Oat Glucan	Rats	increased anti microbial activity, reduction of cholesterol and blood pressure	[6]
Xyloglucan	Wister rats	exerted good healing effect in rats with a severe wound	[18]
	Normal Human Epidermal Keratinocyte (NHEK), HaCaT and Normal Human Dermal Fibroblasts (NHDF)	promoted skin regeneration	[19]
Laminarin	Human corneal epithelial cells	improved the epithelial migration	[20]
Paramylon	Mice	accompanied with a modest increase of inflammatory cytokines	[21]
	Human embryonic kidney (HEK) 293 T cells	acts as a bioactive supplement by boosting the cell proliferation capacity	[22]
Curdlan	Human Keratinocytes	induced the cell proliferation and migration in a Dectin-1 dependent manner	[23]
	Swiss 3T3 fibroblast & wister rats	Nanofibrous dressing of PVA/curdlan incorporated with Ag has fast healing of wound in rats	[24]
β-(1,3–1,6)-D-Glucan from *Aureobasidium pullulans*	BALB / cnude mouse	Membrane containing 50% β-glucan and Poly-(lactic co glycolic acid), accelerated the wound interactions	[25]
	ddY mouse Human dermal fibroblasts	Beta-glucan and chitosan complex enhanced the wound repair by activation macrophages and cytokine release	[26]
	Human dermal fibroblasts	enhanced the dermal fibroblast migration and proliferation that modulated the effect of transforming growth factors	[27]
	Human dermal fibroblasts, adipose tissue-derived stem cells	boosted up the cellular response, migration, and proliferation of both the cells	[28]
Schizophyllan (SPG)	L292 Fibroblast	SPG based nanofibrous scaffolds showed cell proliferation and cell migration	[29]
		Polyvinyl alcohol (PVA)/ Schizophyllan (SPG)/Silver nanoparticles (AgNPs) nanofibers showed anti-microbial activity, thereby helping in reducing the infection in the wound	[30]
Lichenan	NHEK and HaCaT keratinocytes	stimulated human keratinocytes by specific mechanism into the terminal differentiation	[31]

CHAPTER 12

Beta Glucan and Lyme Disease (lD)

Abstract: Lyme disease (LD) is an insect-borne infectious disease caused by spirochetes-spiral shaped-flexible bacteria titled as Borrelia burgdorferi, has been rapidly growing in United States, Europe, and Asia. During Lyme disease, Borrelia burgdorferi causes the release of pro-inflammatory type cytokines such as interleukin (IL-1), and T-helper cell-derived cytokines stimulating inflammation. Lyme disease causes a wide scale of disorders on the human body *i.e.* skin, heart. It builds a broad scale of problems such as arthritic symptoms at joints, nervous system problems, bacterial infection, flu-like symptoms [1]. It creates a systemic problem for the host, which can include, and Experimental studies showed that treatment with antibiotics with 3-6 beta-glucan creates a synergistic effect on bacterial and viral infections due to Lyme-Multiple Systemic Infectious Disease Syndrome (MSIDS) [2]. In this mini-review, the therapeutical effect of beta glucan on Lyme disease is examined in detail.

Keywords: β-glucan, Beta Glucan, Lyme Disease.

INTRODUCTION

Lyme disease is a polyphasic systemic disorder formed due to the pathogenic infection caused by a bacteria named as Borrelia burgdorferi. Lyme disease, which has a full name as Lyme borreliosis, is caused by spirochete bacteria named as previously Borrelia burgdorferi. According to 30% of the patient reports, its main symptom is Lyme arthritis [1].

There are some treatments for healing Lyme disease but still they are not fully effective and cause some problems. At this point, glucan enables the reduction of bacterial load, suppression of arthritis, boosting the immune reactions, especially T helper cell 2 (Th2)-related cytokines.

Latest experiments showed that follistatin-like protein 1 has a significant role as a response to infection especially during the release of cytokine [2]. People with Lyme disease have interleukin 17 (IL-17). On the other hand, IL-17 builds a limited effect on animals with Lyme disease [3].

The complement receptor type 3 (CR3) receptors binding to glucan conducts the binding of opsonized Borrelia burgdorferi to mammalian cells and have a role in

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the phagocytosis of Borrelia burgdorferi [5, 6]. The daily intake of glucan on the effects of *B. burgdorferi* infection was investigated by Vetvicka *et al*. [7].

The induction of calcium transport, phagocytosis and oxidative burst can be achieved by CR3 receptors that is one of the main receptors for glucan, including Borrelia [8]. Also, toll-like receptors, that is mediated by TIR-domain-containing adaptor-inducing beta interferon (TRIF) action, carry important role in the development of Lyme disease and control the inflammatory and anti-inflammatory cytokine production [9].

Previous Studies

In Vetvicka *et al*.'s study, mice that are in the glucan group were fed 100 mg glucan. The results were recorded at 21st and 42nd days of supplementation. Then, ankle swelling due to acute inflammation was observed, as seen in Fig. (**1**) [7]. With the help of glucan supplementation, scores in joints and carditis were importantly decreased.

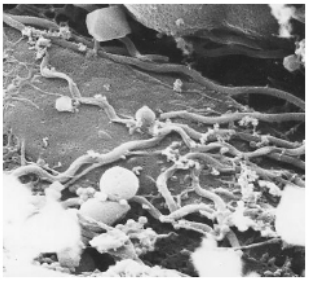

Fig. (1a). Electron micrograph image of spirochetes named Borrelia burgdorferi in the midgut of a deer tick with Lyme disease [4].

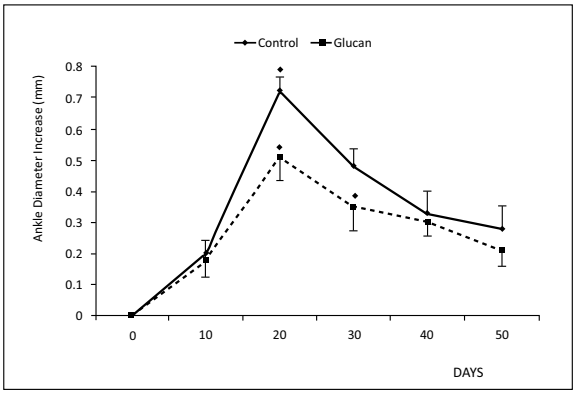

Fig. (1b). Effect of glucan supplementation on ankle swelling [4].

Also, Table **1** shows that glucan supplementation significantly lowered both scores in joints and severity score in carditis.

Table 1. Ankle and heart severity scores [4].

	Arthritic Score		**Carditis Score**	
Group	Severity	Type	Severity	Type
Control	3.0±0.0	3.0±0.0	4.0 ± 0.0	4.0 ± 0.0
Glucan	2.2±0.4*	2.1 ± 0.6*	2.7 ± 0.8*	3.5 ± 0.5

Also beta glucan triggers the cytokine production such as interleukin 2 (IL-2), interleukin 5 (IL-5), interleukin 9 (IL-9), interleukin 10 (IL-10), interleukin 12 (IL-12), and interleukin 13 (IL-13). Glucan supplementation lowers the titers of specific Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies. No differences were found on Day 21, but in the case of total inflammatory cells, neutrophils and T lymphocytes, significant improvements of infiltrating cells numbers were observed [7].

To examine the effects of adding glucan to a cellular infiltration diet, we used flow cytometry to analyze cellular infiltration into the joint tissue. Single-cell suspensions were made from joint tissue and gated on live cells. Next, inflammatory cells, macrophages, neutrophils, and T lymphocytes were counted on Day 21 and Day 42. No differences were found on Day 21, but in the case of total inflammatory cells, neutrophils and T lymphocytes, significant improvements in infiltrating cells numbers were observed (Figs. **2** - **4**).

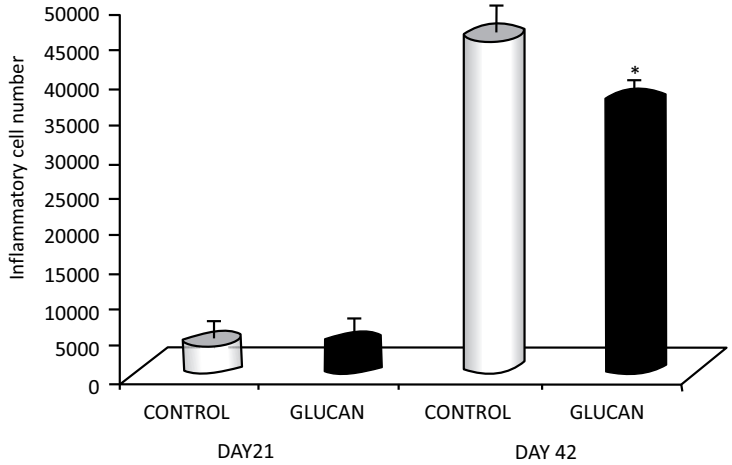

Fig. (2). Cellular infiltrates into infected joints - total inflammatory cells. Data are expressed as mean values ± SD of three independent experiments performed in triplicates.
*Represents significant differences between control (PBS) and glucan group at P ≤0.05 level [4].

CHAPTER 13

Beta Glucan for the Treatment Of Vulvovaginal Candidiasis (VVC) and Recurrent Vulvovaginal Candidiasis (RVVC)

Abstract: Vulvovaginal candidiasis (VVC) is one of the most common infections in women. It is one of the most common fungal infections with *Candida albicans* (*C. albicans*) as the major causative agent in humans. *C. albicans* is an opportunistic fungal pathogen and a normal colonizer of the intestinal mucosa, oral cavity, and vulvovaginal tract [1]. Overgrowth of the fungus followed by epithelial invasion and immune cell infiltration leads to inflammatory symptoms such as vaginal itching, burning, and pain. These clinical representations reduce the quality of life and cause high costs in the global health system [2]. It is known that the fungus-glucan is highly immunoreactive [3] and that β-glucan masking by mannan can inhibit the recognition and killing of fungi by macrophages [4-6]. The aim of this study was to evaluate the ability of β-glucan to protect against *C. albicans* vaginal infection.

Keywords: β-glucan, Beta Glucan, Vaginal Candidiasis, Vulvovaginal Candidiasis.

INTRODUCTION

Fungal diseases are a major infectious threat that requires increased medical attention. Several invasive mycosis (*e.g.* histoplasmosis and coccidiomycosis) are geographically limited, but worldwide infections caused by opportunistic fungal agents in immunocompromised hosts are of particular concern. In particular, candidiasis and aspergillosis are common in hospitalized patients and carry a high mortality rate even in the presence of effective treatment [7]. Early and accurate diagnosis of these systemic infections is often difficult due to the non-specific clinical symptoms and the lack of standardized diagnostic tools. Moreover, antifungal therapy can be prevented due to the emergence of toxicity and resistance [8]. VVC is characterized by genital itching, burning, frequent urination, dysuria, and dyspareunia and is often accompanied by thick white vaginal discharge [9]. This disease affects approximately 30-50% of all women at least once in their lifetime [10, 11]. The main exogenous factors for vaginitis are pregnancy-related reproductive hormone disorder, use of high estrogen contraceptives, hormone replacement therapy, uncontrolled diabetes and antibiotic use [9]. Recurrent vulvovaginal candidiasis, or RVVC, is defined as a woman who has had four or more episodes in a given year. It is estimated that about five

percent of women of reproductive age who have a primary VVC attack will develop RVVC [12]. Increased T helper cell 17 (Th17) mediated cytokine secretion (interleukin-22 (IL-22), interleukin-17A (IL-17A) and interleukin-17F (IL-17F)) and inflammation of the inflammation, hyperinflammatory immune cell infiltration during RVVC tissues followed by interleukin-1β (IL-1β) cleavage was observed.

Candida albicans (*C. albicans*) is a common etiological agent in acute vulvovaginal candidiasis (VVC) and a severe chronic condition known as recurrent VVC. *C. albicans* is a member of the normal microbial flora of the human body, usually found in the lower genitourinary tract. The most common pathogen, *C. albicans*, accounts for about 80% of cases [13]. β-glucans, chitin, and mannan are the three main polysaccharide components in the cell wall of *C. albicans* [14, 15]. A critical role of local innate immunity in the defense and pathogenesis of vaginal infection has been suggested by Candida. Mice immunized with *C. albicans* cells were treated with dithiothreitol and protease, *i.e*. exposed β-glucan on their surface, formed anti-βG antibodies but did not generate anti-mannoprotein antibodies were significantly protected against a lethal fungal challenge [15]. Dectin-1 is the cell surface receptor for β-glucan, an important component of the budding yeast cell wall [16]. The recognition of glucans by the innate immune receptor Dectin-1 is important during antifungal immunity. Previous studies have demonstrated that dectin-1 deficient mice have a greater susceptibility to *C. albicans* infections [17]. The β-1,3-glucans exposed to the *C. albicans* wall are synthesized by the enzyme β-1,3-glucan synthase with the putative catalytic subunit FKS1. Mutations in this area lead to lower or erroneous β-glucan production.

Experimental Method

Different studies follow various procedures and methodologies detailed in the literature. For example; In De Farias Sales and others' study; Fifty-four Balb / C mice under the influence of estrogen were inoculated intravaginally with 5x104 fixed-phase blastoconidia of *C. albicans* [18]. Mice were divided into three groups, treated with glucan vaginally (5 mg / mL) and intraperitoneally (1 mg / mL), and the control group receiving saline intraperitoneally.

Torosantucci *et al*. Wister rats were inoculated at weekly intervals with 50 µg Lam-CRM conjugate (polysaccharide) / rat using 3 µg / rat cholera toxin (CT, supplied by Swiss Serum and Vaccine Institute) intravaginally or intranasally. adjuvant [19]. Control rats received unconjugated laminarin plus CT, unconjugated CRM plus CT, or CT only. All rats, s.c. estradiol benzoate application (Benzatrone; Samil). For experimental infection, rats were inoculated

intravaginally with *C. albicans* (107 cells / 0.1 ml saline / rat) as described elsewhere [20]. Prior to infection, samples of vaginal fluid (PBS vaginal wash) were taken from vaccinated and control animals and pooled and assayed for vaginal anti-β-glucan antibodies.

In the study of Kitamura *et al*.; Drugs were given orally three times a day for 1 day, starting 1 hour after vaccination at a dose of 3.3 or 10 mg/kg body weight for D21-6076 titled β-1,6-glucan [21]. In all experiments, each group contained 10 mice, and the control group received 0.2 ml of 5% glucose solution with 1% (v / v) lactic acid. Mortality of mice was recorded 14 or 30 days after infection.

Previous Studies

Previous second-order evidence suggests that intact *C. albicans* and *Saccharomyces cerevisiae* cells treated to expose glycan rather than mannoprotein on the cell surface provide significant anti-Candida protection [22]. Torosantucci *et al*. The selected laminarin (Lam), a highly characterized β-(1,3) glucan preparation from brown alga Laminaria digitata [23], and β-glucan laminarin conjugated to the diphtheria toxoid CRM197 showed that immunization protected mice from *C. albicans* and *Aspergillus fumigatus* infection. Protection was associated with the presence of β-glucan-specific antibodies (anti-β-glucan Immunoglobulin G (IgG)). When transferred to naive animals, these antibodies significantly reduced the fungal burden in the kidneys of the subsequently threatened recipients by *C. albicans* [24]. β-Glucan-specific antibodies have been shown to bind the hyphae and germ tubes of *C. albicans* and hypha strands of A. fumigatus and inhibit fungal growth by providing a potential mechanism by which these antibodies can protect against fungal infection. In the rat model of experimental vaginal candidiasis, a single intravaginal administration of mAb 2G8 resulted in a significant acceleration in fungal clearance with the resolution of infection on day 21 compared to control animals treated with unrelated anti-CRM mAb (Fig. **1**).

Sun *et al*. found that mice receiving salecan (0.5 mg per mouse) after infection had 85% less CFU than infected mice given saline. Compared to *C. albicans* group, salecan reduced the migration of polymorphonuclear neutrophils (PMNs) in the vagina, mRNA levels of cytokines IL23, IL22, IL17a and IL17f, anti-candidal genes S100a8 and S100a9 and *C. albicans* pattern recognition receptor Dectin1. Analysis of the vaginal microbial community composition at different taxa levels revealed that the bacterial flora composition in the vagina of mice treated with salecan was similar to that of uninfected mice and differentiated from infected mice [25].

CHAPTER 14

Beta Glucan for the Treatment of Human Papilloma Virus (HPV) and Cervical Cancer

Abstract: Cervical cancer is the fourth most frequently diagnosed cancer. For the treatment of this relentless disease, chemotherapy is the most widely applied cure now. However, this treatment carries some important side effects, such as neutropenia which having an abnormally low concentration of neutrophils in the blood. Also, chemotherapeutic drugs cause harm to blood formation. Therefore, chemotherapy affects the patients' immune system badly by making them open to infections. Another treatment method is radiotherapy for the healing of cervical cancer. This technique also carries some side effects being hematopoietic and harm to the immune system. Beta-glucans modulates the immune system by affecting a wide range of cells like antigen-presenting cells (APCs), including macrophages, dendritic cells, T cells, monocytes. It regulates both adaptive and innate immune systems. It has different kinds such as sizofiran (SPG), zymosan, curdlan, and PBG to prevent and protect from cervical cancer. Beta-glucan provides a novel therapeutic method for the healing of human papillomavirus (HPV) and cervical cancer.

Keywords: β-glucan, Beta Glucan, Human Papilloma Virus.

INTRODUCTION

Human papilloma virus (HPV) is a necessary cause of cervical cancer; this means that the other risk factors can increase the risk of cervical cancer, but they are not able to develop this kind of cancer in the absence of HPV [1]. It has been indicated that a variety of therapies could be used in the treatment of different cancers, such as cervical cancer. In this word, many therapeutic approaches, i.e., surgery, chemo, and radiotherapy, utilization of immune checkpoint inhibitors, therapeutic vaccines, and antibody-drug conjugates, gene- and cell-based therapy, and nanotechnology-based therapies could be employed as primary lines of therapy in cancer therapy [2 - 8]. Cervical cancer is the fourth leading cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020 [9]. The distribution of cases for cancers in 2020 for women is summarized in Fig. (**1**). According to this chart, cervical cancer covers 7% of all the other cancer types.

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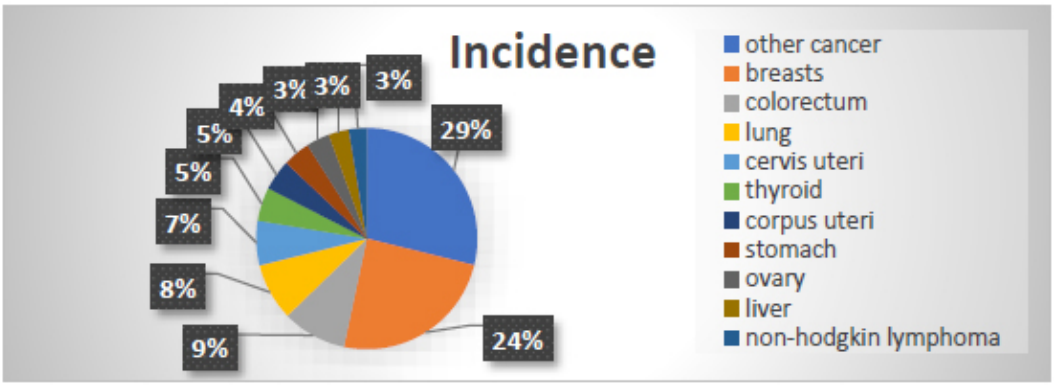

Fig. (1). Distribution of Cases for the Cervical Cancers in 2020 for women [9].

Also, the distribution of deaths due to the different cancer kinds is summarized in Fig. (**2**). According to this chart, 8% of all cancer deaths are due to cervical cancer.

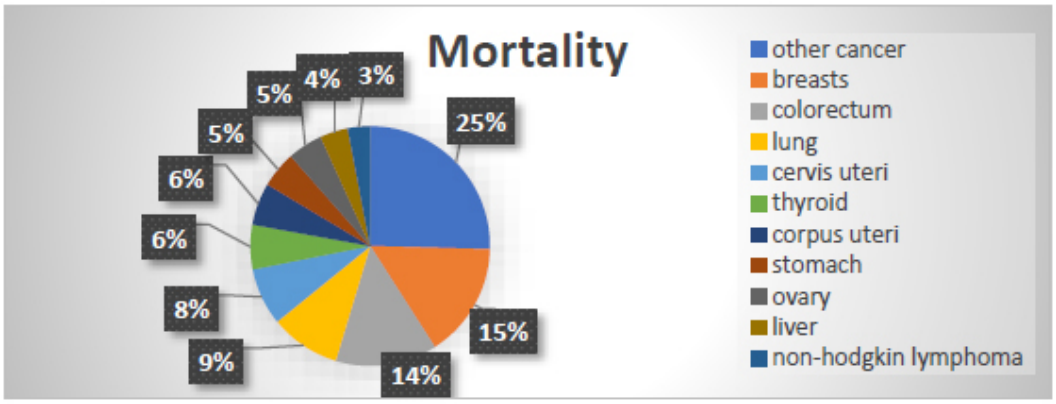

Fig. (2). Distribution of Deaths for the Cervical Cancers in 2020 for women [9].

The most widely applied treatment of cervical cancer is chemotherapy. However, one of the most important side effects of chemotherapy is neutropenia [10]. Also, chemotherapeutic drugs disrupt blood formation [11]. Therefore, chemotherapy adversely affects the defense system of cancer patients and makes them open to infections [12]. On the other hand, another cure for cervical cancer is radiotherapy. Radiotherapy also creates some side effects by causing hematopoietic and immune damage to the body [13]. Among the damages of radiotherapy are anemia, lymphocytopenia, thrombocytopenia and granulocytopenia [14].

Beta glucan can cure hematopoiesis due to injured bone marrow [15]. It can be

concluded that beta-glucans not only have anti-cancer effects but can also be used as a supplement for cancer patients in order to reduce the side effects that are caused from traditional treatments. Consequently, beta-glucan presents a new and promising therapeutic pathway for cervical cancer.

Beta-glucans are a group of glucose polymers that are derived from the cell wall of fungi, bacteria, and *etc* [16]. It has been shown that beta-glucans have some anti-cancer properties due to their impacts on adaptive and innate immunity [17, 18]. Beta-glucans can be found in different plants such as oat, barley, and seaweed. In addition, they are also involved in fungal and pathogenic bacterial cell walls [17]. Cellulose, curdlan, laminarin, chrysolaminarin, lentinan, lichenin, pleuran, zymosan, and schizophyllan are some examples of beta-glucans (Fig. **3**, Table **1**) [19]. These glucose polymers could be linked together by β (1 → 3) linkages and provide the linear β-glycosidic chain core [18]. The glycosidic core could provide different kinds of branches. Two important groups of them are 1 → 4 or 1 → 6 glycosidic chains [20].

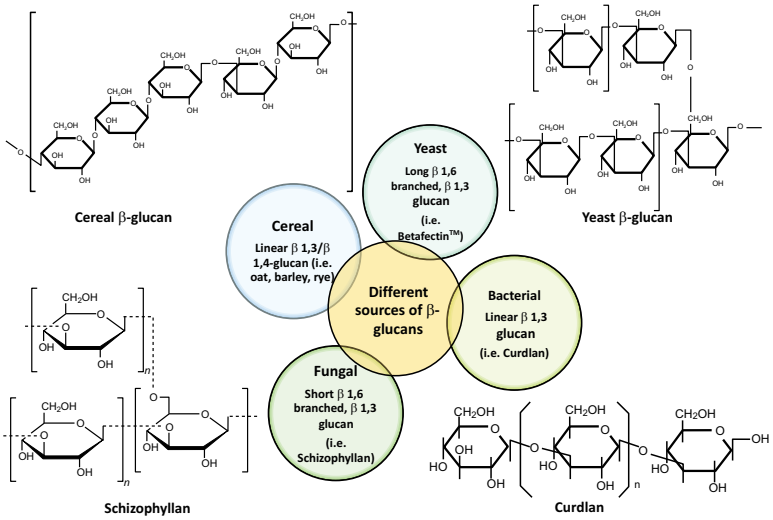

Fig. (3). The molecular structures of beta glucans from different sources [21].

Table 1. Various beta-glucans, their properties, resources, and potential applications [16].

β-glucan name	Type	Resource	Properties	Potential uses	Ref.
Cellulose	Beta-1,3-glucan	Plant and bacterium (Acetobacter species)	Insoluble in water, straight-chain, high mechanical strength	Wound-dressing	[22-26]

CHAPTER 15

Beta Glucan And Chronic Kidney Disease (CKD)

Abstract: Chronic kidney disease (CKD) is a global health problem that is associated with a high risk for cardiovascular morbidity and death. It is a clinical syndrome characterized by the progressive and irreversible loss of renal function. Dietary supplementation with grains containing high β-glucan fiber has been shown to attenuate the progression of CKD and vascular calcification in animal models. In this mini-review, the therapeutic effect of beta glucan on CKD was investigated. For this reason, many studies were examined and promising results were obtained for the use of beta glucan in the treating of CKD.

Keywords: β-glucan, Beta Glucan, Chronic Kidney Disease, CKD.

INTRODUCTION

10% of the population worldwide is affected by chronic kidney disease (CKD), and millions die each year because they do not have access to affordable treatment [1]. An acute and chronic proinflammatory state exists in patients with CKD [2]. Renal cell injury results in a cascade of events that culminate in enhanced inflammation and vascular endothelial cell injury. The end result is renal parenchymal and endothelial injury as summarized in Fig. (**1**) [2].

Traditional mediators of chronic inflammation in adult CKD patients include hypoalbuminemia/malnutrition, atherosclerosis, beta-glucans, L-fucose, exotoxins, acetate, silicone, and lipopolysaccharides [2].

Angiotensins and statins may also play a vital role in controlling inflammation in CKD. In 66 the treatment of adults with stages 2–4 CKD and hyperlipidemia with atorvastatin also resulted in a reduction of both serum lipid levels and inflammation, the latter measured by C reactive protein (CRP), tumor necrosis factor α (TNF-α), and interleukin 1 β (IL-1β); in comparison, no changes were observed in the untreated patients [3]. Also, in a rat remnant kidney model of CKD, the administration of melatonin raised serum levels and reduced markers of oxidative stress and renal inflammation. It significantly slowed the decline in glomerular filtration rate (GFR) [4]. Clopidogrel also reduced rates of proteinuria, lower serum creatinine, and better renal histology compared with control rats [5].

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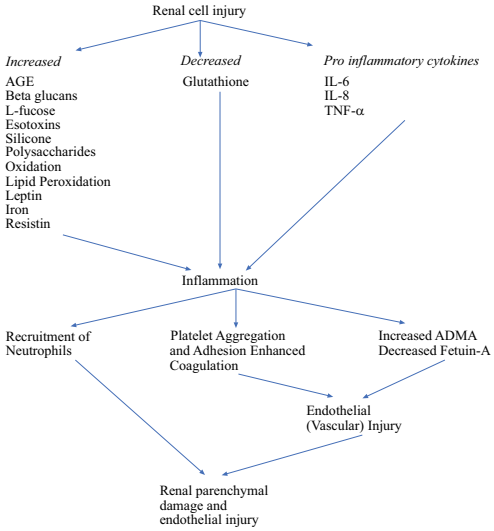

Fig. (1). Pathogenesis of immune mediated renal-injury, Advanced glycation end (AGE) products, IL interleukin, TNF-α tumor necrosis factor-alpha, ADMA asymmetric dimethyl arginine) [2].

Apart from aforementioned conventional drugs, β-glucan presents a regulation in gut microbiota by decreasing the release of uremic toxins and improving the renal functions [6]. β-glucan is a soluble fiber consisting of chains of glucose molecules linked by β-1,3 and β-1,4 glycosidic bonds [7]. β-glucan is associated with a change from proteolytic metabolism to saccharolytic metabolism in gut microbiota found in healthy individuals [8]. As a consequence, it limits the production of colon-derived uremic toxins. High levels of (1,3)-β-D-glucan also falsely elevate endotoxin measurements [9]. Cosola *et al.* gave 100 g pasta, including 3 g beta glucan to 26 healthy individuals [10]. As a result, a reduction in low-density lipoprotein (LDL) and total cholesterol was observed, and also proteolytic uremic toxins p-cresyl sulfate (pCS) level decreased.

Some studies have shown that high dietary fiber intake lowers blood urea nitrogen and creatinine levels in patients with CKD [11 - 15]. Epidemiologic studies have linked elevated levels of trimethylamine N-oxide (TMAO), a gut microbiota-derived metabolite, with increased cardiovascular events [16]. TMAO is related to the intake of animal-based proteins, including red meat, and is associated with worse kidney and cardiovascular outcomes [17]. A diet supplemented with β-glucan is safe and potentially efficacious in lowering serum concentrations of TMAO in patients with CKD.

In haemodialysis (HD) patients, high blood levels of beta glucan can activate blood endotoxin detection assays such as the Limulus Amoebocyte Lysate (LAL) assay leading to apparently increased blood endotoxin levels [18]. False positive

signals for endotoxemia occurred in 50% of HD patients which were extinguished on remeasurement incorporating a BG-blocking agent with the LAL assay [19].

Studies on the Effect of Beta-Glucan on the Course of CKD

Oat (Avena sativa L.), a type of cereal grain and a source of dietary fiber including 3-5% of beta glucan, builds beneficial effects on serum albumin and serum potassium in patients with CKD [20].

Paramylon, which is a novel β-glucan that is stored by Euglena gracilis Z, may suppress the progression of CKD *via* the elimination of uremic toxins or modulation of gut microbiota, leading to the alleviation of inflammation. Nagayama *et al.* studied eight-week-old male Wistar rats with a 5/6 nephrectomy, and they were given a normal diet or a diet containing 5% paramylon for 8 weeks [21]. As a result, paramylon mainly inhibited the absorption of non-microbiotaderived uremic solutes including tricarboxylic acid (TCA), leading to protection of renal injury *via* anti-inflammatory and anti-fibrotic effects.

Hill *et al.* used oat beta glucan supplement in order to investigate its effects on certain uremic toxins and markers of mineral metabolism in patients with CKD [22]. As a result, serum levels of TMAO decreased by a median of −17% (interquartile range: −46%, 7%) at the end of the intervention. A nonstatistically significant change was observed for asymmetric dimethylarginine (median −0.6% [−12%, 20%]) and serum Klotho (median −3% [−8%, 7%]). There were no changes in serum levels of calcium and phosphorus. One month after discontinuation of β-glucan therapy, TMAO levels increased by a median of 16% (−12%, 36%) but remained slightly below the pretreatment levels. The effect of oat beta-glucan supplementation on clinical and laboratory parameters is summarized in Table **1**.

Table 1. Effect of Oat β-Glucan Supplementation on Clinical and Laboratory Parameters [22].

Characteristic	Pre-beta glucan n=18	Post-beta glucan n=18	P value
Clinical data			
Body mass index (kg/m2)	33.2 ± 6.8	33.1 ± 6.9	0.59
Systolic blood pressure (mmHg)	130.7 ±11.7	129.2 ± 16.4	0.70
Diastolic blood pressure (mmHg)	74.1 ±7.2	74.6 ± 8.7	0.82
Laboratory data			
Creatinine (mg/dL)	2.0 ± 0.8	2.2 ± 0.9	0.16
Blood urea nitrogen (mg/dL)	39.2 ± 20.4	43.8 ± 21.1	0.05
eGFR (mL/min/1.73 m2)	35.3 ± 14.0	35.1 ± 16.3	0.88

CHAPTER 16

Beta Glucan and Rheumatoid Arthritis (RA)

Abstract: Rheumatoid arthritis is encountered in 3 out of 10000 people every year worldwide. It is usually seen between the ages of 35 and 50. If precautions are not taken, it may lead to synovial inflammation, destruction of bone and cartilage. Finally disability occurs in the later stages of the disease. It can shorten the patient's life span by 10 years. The previous studies show that β-glucan alone decreased both the hind paw swelling and the arthrogram on days 21 and 28 of supplementation in rats. *In vivo* studies lead to the potential application of (1→3)-β-d-glucan derivatives in treating human rheumatoid arthritis.

Keywords: β-glucan, Beta Glucan, Collagen-induced Arthritis, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid Arthritis (RA) is one of the most common systemic autoimmune diseases formed in the articular joint, which causes pain, swelling, and loss of function in joints [1]. It is a chronic systemic inflammatory disease that primarily affects the synovial membranes of multiple joints [2]. It is characterized by chronic joint inflammation, the formation of a rheumatoid pannus, and eventually, tissue degradation and joint destruction, as seen in Fig. (**1**). It occurs in approximately 0.5-1% of the adult population [3]. 70% of those with rheumatoid arthritis are women. 10% of patients experience improvement in their condition once a year [4].

Both genetic and environmental factors are involved in pathogenesis [2, 6, 7]. The pathogenesis of RA is associated predominantly with the formation of free radicals and proinflammatory cytokines at the site of inflammation. Macrophages cause cartilage and bone destruction by stimulating inflammation and regulating osteoclast activity [8]. Macrophage-like synoviocytes, which normally phagocytize debris in the joint fluid, are intrinsically capable of secreting proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Fibroblast-like synoviocytes, which physiologically produce hyaluronic acid, synthesize matrix metalloproteinases and prostaglandin E2 when stimulated by TNF-α and IL-1 [2, 9, 10]. Major histo-

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compatibility complex (MHC) and non-MHC genes play significant roles in determining the genetic susceptibility to RA [2, 7, 11]. Various infectious agents, including viruses and bacteria, have also been suspected to be causative agents of RA [5, 12, 13]. $CD4^+$ T cells play crucial roles, at least in the initial phase of RA.

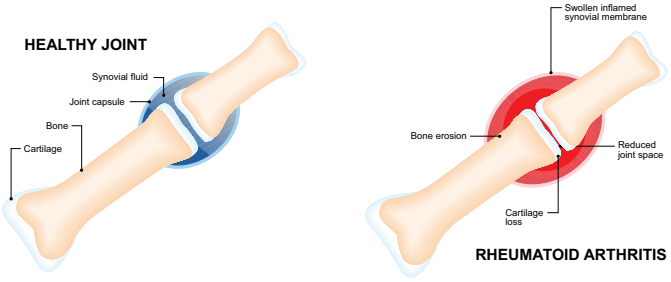

Fig. (1). Differences between healthy joint and joint with RA [5].

Beta-glucans are naturally occurring polysaccharides, which are integral constituents of the cell wall of bacteria, plants, and yeasts. Glucans differ not only in the molecule length and branching, but also in their tertiary structure based on their source [14]. They modify the biological response, have anticarcinogenic activity and enhance non-specifically the host immune system by activating the complement system, enhancing the function of macrophages, leukocytes and natural killer cells. Their antioxidant, analgesic and anti-inflammatory effects provide a therapeutic effect on RA. In patients with rheumatoid arthritis, this immunomodulator may prevent secondary infections and restore impaired immunological homeostasis [15].

The Therapeutic Effect of Beta-Glucan on RA

Systemic administration of β-glucan to rats and mice has been demonstrated to protect against various infections by activation of macrophages and attenuation of proinflammatory cytokine release. β-(1,3/1,6)-D-glucan, an effective activator of the immune system, may also be beneficial in humans in preventing or eliminating bacterial infections, which are known to induce reactive arthritis.

β-(1,3/1,6)-D-glucan isolated from *Pleurotus ostreatus* is applied to rats with adjuvant arthritis (AA). It is understood that β-(1,3/1,6)-D-glucan decreased activities of pro-inflammatory cytokine TNF-α, IL-1 and IL-6 in the serum of arthritic rats, decreased oxidative stress and suppressed inflammatory and arthritic signs in rats [10, 16].

The findings show that β-glucan isolated from mushroom *Pleurotus ostreatus*, applied both preventively and therapeutically, has a beneficial effect on the

clinical symptoms of arthritis, even at a high dose of 15 mg/kg, may be interesting also in the prevention and treatment of various infections in humans with rheumatoid arthritis [17].

Kim *et al*. gave beta glucan known as Polycan^{TM,} to the subjects with RA in three different dosages; 21.25, 42.5, and 85 mg/kg once a day for four weeks. While 21.25 mg couldn't inhibit the effects of RA, 42.5 mg and 85 mg inhibited the histopathological changes caused by collagen-induced RA [18].

Carboxymethyl (1/3)-β-D glucan (CMG) isolated from S. cerevisiae was given to rats adjuvant arthritis (experimental model of rheumatoid arthritis). CMG resulted in an evident decrease of plasma carbonyl content—an oxidative parameter associated with the progress of arthritic condition by the antioxidant activity [19].

Zymosan contains an endotoxin-like substance that activates innate immunity. It acts as an adjuvant for collagen-induced arthritis. β-glucan derived from zymosan by treatment with NaClO is a good adjuvant for a collagen-induced arthritis model with anti-type II collagen (anti-CII) autoantibody production [20].

Arthrogram score similarly as hind paw swelling was importantly decreased by β-glucan obtained from *Pleurotus ostreatus* (β-glucan-PO) and Methotrexate (MTX) applied preventively. MTX is an antifolate that is commonly applied in the treatment of rheumatic disorders and malignant tumors. The combined treatment with MTX + β-glucan-PO is more effective than MTX alone Table **1** [17].

Table 1. The effect of MTX, β-glucan-PO and their combination on the arthrogram score in AA rats [17].

Group of Rats	Day 14	Day 21	Day 28	Day 35
AA controls	13.44 ±1.81	16.22 ±1.99	14.89 ±2.26	12.84 ±2.14
AA rats treated from day 0 with:	-	-	-	-
β-glucan-PO	11.30 ±1.46	14.25 ±0.53*	12.14 ±2.10*	-
MTX	8.50 ±1.52**	13.33 ±3.44**	11.00 ±2.53*	-
MTX + β-glucan-PO	8.25 ±2.25***	10.88 ±2.85***†	9.88 ±2.10***†	-
AA rats treated from day 13 with:	-	-	-	-
MTX	14.10 ±1.54	15.40 ±1.98	13.92 ±2.18	11.38 ±2.83
β-glucan-PO	13.80 ±2.10	12.13 ±1.73**	11.63 ±2.39*	10.50 ±2.27*
MTX + β-glucan-PO	13.64 ±3.22	14.38 ±4.72	13.38 ±3.96	12.13 ±3.64

Data represent mean value and standard deviation (mean value ± SD) for groups of 8 rats. Significantly different from arthritic control rats: *$p < 0.05$, **$p < 0.01$, *** $p < 0.001$. Significantly different from arthritic rats treated with MTX: †$p < 0.05$ AA – adjuvant arthritis, MTX – methotrexate.

CHAPTER 17

The Use Of Beta Glucan In The Treatment Of Fibromyalgia (FMS)

Abstract: Fibromyalgia syndrome (FMS), is a long-term condition that causes pain all over the body. FMS symptoms may also include increased sensitivity to pain, extreme tiredness, muscle stiffness, irritable bowel syndrome (IBS) and problems with memory and concentration. Beta 1,3/1,6 glucan in the micro glucan (MG) form is a potent antioxidant to aid in nutritionally minimizing oxidative (free radical) stress while nutritionally potentiating and normalizing the immune response and promoting phagocytosis or removal of toxins and cellular debris from the body. Beta glucan enhances white cell mobility, white cell production and pathogen destruction. Also, it enables immune system modulation by balancing on an underactive or overactive immune response.

Keywords: β-glucan, Beta Glucan, Chronic Fatigue Disease, Fibromyalgia.

INTRODUCTION

Fibromyalgia (FMS) is a condition of muscle pain on the larger muscles of the back, neck, and limbs, debilitating fatigue and weakness, as well as joint pain not related to arthritis. The person with FMS has difficulty moving due to pain and fatigue, let alone attempting any increase in activity. FMS involves chronic fatigue and chronic pain throughout the body, due to oxidation and inflammation in the neuro-muscular connections of the skeletal muscles, along with mitochondrial dysfunction. The first major criterion include damage to the mitochondria of cells of FMS patients. Cell mitochondria convert organic materials into cellular energy in the form of Adenosine Triphosphate (ATP) and are essential in cell proliferation and apoptosis, or cell death critical in cancer treatment, plus nerve (neural) damage repairs. A second major criterion include generalized pain to be experienced in at least three anatomic sites for 3 months and 11 or more body tender points.

Other ailments such as Osteomalacia (softening of the bones due to mineral depletion), Diabetes, Depression, and Hypothyroidism with similar symptoms must be excluded, in addition to negative drug side effects causing pain and fatigue.

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Often FMS is associated with insomnia, depression, anxiety, difficulty in thinking or concentrating, and irritable bowel syndrome (IBS). Minor criteria for an FMS diagnosis include IBS experienced by 70% of FMS patients, which is characterized by alternating diarrhea and constipation, intestinal cramps, flatulence, and nausea.

Due to the association with depression, some may confuse pain and fatigue as secondary to a mental disorder, in fact, FMS is very much an inflammatory condition of the muscles. Fatigue and overwhelming tiredness without immediate cause, similar to Chronic Fatigue Syndrome (CFS), are suffered by 85%. Some have described the fatigue as "brain fatigue or fog" with concentration difficulty and arms and legs so tired they are difficult to move and lift. Symptoms overlap with CFS, with the symptom of fatigue, but FMS creates pain in the soft fibrous tissues – the muscles, ligaments and tendons. However, patients with FMS, fortunately, do not develop deformities, nor do they suffer damage to internal body organs based on current research. FMS patients have:

- Decreased blood flow to some areas of the brain on a brain single-photon emission computed tomography (SPECT) scan.
- Decreased glucose uptake by certain areas of the brain.
- Small lesions in various areas of the brain on a magnetic resonance imaging (MRI) Scan.
- Abnormalities in pain processing areas of the brain documented by MRI scans.

The Therapeutic Effect of Beta Glucan for FMS

Beta 1,3/1,6 glucan aids in minimizing negative liver side effects due to taking pain relievers to reduce muscle pain caused by FMS. Beta glucans have been used as cancer fighters and immune modulators in Chinese medicine for years. Immune cells are activated by beta glucans without over-reaction that is experienced with autoimmune diseases. Beta glucan, also Baker's Yeast extract, are polysaccharides obtained from the Reishi and Shiitake mushroom. Beta glucan is formed from polysaccharide fiber micronutrients gathered from the Reishi and Shiitake mushrooms, besides Baker's Yeast extract.

Reishi mushroom (Fig. **1**) has a high antioxidant content and assists with immunity, hormone balance, and sleep. Reishi mushrooms contain over 200 unique and active ingredients. This powerhouse antioxidant has an antimicrobial action, which means it not only takes on bacteria and viruses, but it stimulates the immune system, and also calms the autonomic nervous system.

Fig. (1). Reishi mushroom.

Reishi mushrooms are also highly effective in treating IBS (Irritable Bowel Syndrome) – a condition that most people with FMS struggle with. They treat IBS by reducing spasms in the muscles and helping the liver to detoxify waste.

Kaufmann *et al*. advised to use of beta glucans derived from Reishi and Shiitake mushrooms and Baker's Yeast extract to those with fibromyalgia and chronic fatigue syndrome [1]. Reishi and Shiitake mushrooms are rich in Vitamin D, and it has been documented that people with FMS are Vitamin D deficient. Vitamin D is known to lower inflammation in patients with FMS and other inflammatory diseases. They do this by reducing cytokine production, which is a protein that causes inflammation.

The working mechanism of beta glucan is summarized in Fig. (**2**). White blood cells such as macrophages and natural killer cells have beta glucan receptors. When induced by beta glucans, shown as small blue balls in Fig. (**2**), cells are activated to actively and precisely attack and inhibite foreign microbes (bacteria, yeast, fungi, and viruses) and cancer cells.

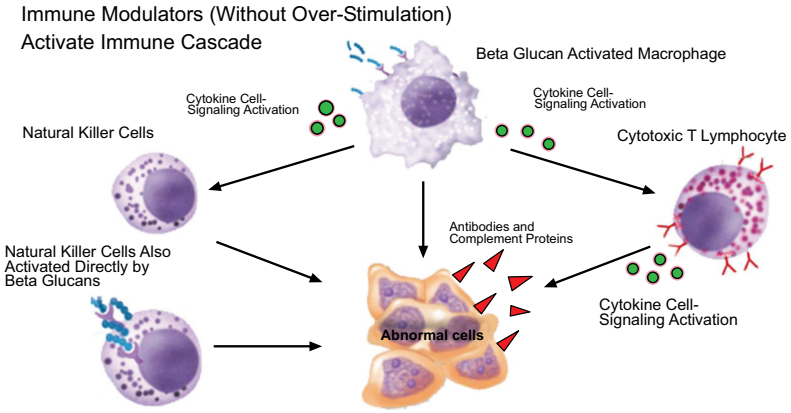

Fig. (2). Beta Glucan Modulating of Immune System.

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Dr. Betül Gürünlü, (PhD-Chemical engineering). She studied Trimethyl Borate Synthesis from Borax Decahydrate and got her B.Sc. degree from the chemical engineering department of Yildiz Technical University in 2009. She studied the development of iron-based zeolite supported Fischer Tropsch catalysts and got her M.Sc. degree from the chemical engineering department of Istanbul Technical University in 2012. She also published a book named "New Applications and Approaches in Fischer-Tropsch Catalyst Synthesis" by Lambert Academic Publishing in 2017. She studied at the mechanical engineering department of Sheffield Hallam University for a year (2015 – 2016). Then, she studied the development of an efficient synthesis method for graphene during her Ph.D. and got her doctorate degree (Ph.D.) from the chemical engineering department of Gebze Technical University in 2019. She is reviewing papers in various fields, basically in chemistry, medicine, biology, electronics. She was awarded "The Reviewer of the Year for 2020" by IOP Publishing. Dr. Betül Gürünlü focused on developing sensor technologies for health monitoring and diagnosis during her post-doctoral study. Currently, she is working as Assistant Professor at the Bioengineering Department of Üsküdar University, Istanbul, Turkey.