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Fungi between Immunostimulatory and Immunosuppressive

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Abstract

Microbes in general and fungi especially are promising biotechnological tools that are used for green synthesis of numerous products. Fungi in particular are potent producers of many industrially important compounds. β-Glucans are a group of biologically-active fibres or polysaccharides from natural sources with proven medical significance. β-Glucans are known to have antitumor, anti-inflammatory, anti-obesity, anti-allergic, anti-osteoporotic, and immunomodulating activities. On the other hand, cyclosporin is a cyclic undecapeptide with a variety of biological activities including immunosuppressive, anti-inflammatory, antifungal, and antiparasitic properties. It is an extremely powerful immunosuppressant and is approved for the use in organ transplantation to prevent graft rejection in kidney, liver, heart, lung, and combined heart–lung transplants. Hence, this review aims to focus on β-glucan as immunostimulatory and Cyclosporine A as Immunosuppressants

Keywords: Fungi; Immunostimulatory; Iimmunosuppressive; Cyclosporine; β-glucan

Abbreviations: GRAS: Generally Recognized as Safe; FDA: Food and Drug Administration; EMA: European Medicines Agency.

Introduction

Fungi play important role in human life such as in agriculture, food industry, medicine, textiles, bioremediation, natural cycling, as bio-fertilizer and in many other ways. Fungi are ubiquitous on earth and represent essential components of many ecosystems where they are involved in many vital processes [1-5]. Fungal natural products have, historically, played an important role in drug discovery. Fungal natural products with diverse chemical structures and biological activities are rich resources of both drugs and toxins, thus causing Janus-like effects on human beings Fungi are rich sources of biologically active natural compounds, which are used in the manufacturing of wide range of clinically important drugs. Fungi produce important antibiotics such as the beta-lactam antibiotics members, penicillin and cephalosporin, which and whose derivatives are dominating the most important antibiotic market until now [6-10]. Fungi generally and endophytic ones specifically represent future factories and potent biotechnological tools for production of bioactive natural substances, which could extend healthy life of humanity [11-15]. There are unlimited uses of the numerous promising secondary metabolites originated and secreted by endophytic fungi. The application of fungal secondary metabolites in various fields of biotechnology has attracted the interests of many researchers. Bioactive compounds have various applications in pharmacology and agriculture [16,17].

β-Glucans are groups of dietary fibres or polysaccharides composed of D-glucose monomers, linked by 1,3; 1,4 or 1,6 β-glycosidic bonds, and are naturally found in the cell wall of bacteria, fungi, algae, and higher crops, such as cereals. Highly-pure β-glucans are enzymatically extracted from the cell wall of yeast, fungi, seaweed, or grain seeds [18]. The biological and physiochemical properties of β-glucans strongly differ, depending on the source of extraction [19]. The degrees of purification, as well as the extraction method, also influence the physiological activity of β-glucans [20]. β-glucans are allowed in several countries, including the United States of America, Canada, Finland, Sweden, China, Japan, and Korea, as potent immunological activators [21]. β-Glucans are used as a disease-preventing agent, as well as a part of anticancer or anti-inflammatory therapy. Among soluble fibres, β-glucans are the most commonly-consumed immunomodulators [22], with strong anticancer, insulin resistance, anti-hypertension, and anti-obesity effects. β-Glucans are believed to stimulate the immune system, modulating humoral and cellular immunity, and thereby have beneficial effects in fighting infectious diseases, such as bacterial, viral, fungal, and parasitic diseases [22]. Daou C, et al. [23] demonstrated the immune-stimulating activity of oat β-glucans by activating macrophages and increasing the amounts of immunoglobulin. Murphy E, et al. [24] reviewed the immune modulating effects of β-glucans and their subsequent benefits on infectious diseases and cancer. Ooi and Liu F [25] reviewed the immunomodulating and anticancer effects of β-glucans from mushrooms, as well as the relationship of their structures and antitumor activities. Cyclosporines A are a member of the group of cyclic peptides and are composed of 11 amino acids. Cyclosporin A is neutral and very soluble in all organic solvents. Molecular weight of cyclosporine A 1202.6 g/mol with UV absorption of 215 nm [26]. Cyclosporine A is the major component of the cyclosporines, which distinguishes from other cyclosporines by the type of amino acid at carbon number 2. It is the only member of this group used clinically [27]. It has anti-inflammatory, immunosuppressive by acts as T-lymphocytes suppresses and also inhibits interleukins, antifungal and antiparasitic properties [28]. Also, used in combination with other immunosuppressant and steroid medications and use to treat canine skin disease and rheumatoid arthritis [29]. The present study was, therefore, designed to explore β-glucan as immunostimuli and *cyclosporine* A as *Immunosuppressant.*

Fungi as Immunostimulatory

β-glucan has promising bioactive properties. Therefore, the use of β-glucan as a food additive is favoured with the dual-purpose potential of increasing the fiber content of food products and enhancing their health properties. This review aim to evaluate the important of Beta glucan (β-glucan) as immunostimulatory and represent the other biological activities (antimicrobial, antitoxic, immunostimulatory, and anticancer). β-glucan extracted from *Saccharomyces cerevisiae* and from many other natural sources [30]. β-glucan is a natural polymer of D-glucose which is produced by many different types of organisms. It is found in the cell walls of fungi, bacteria, algae and some higher plants such as barley and oat. The glucose monomers are linked together by β-glycosidic bonds [31]. Different source of β-glucans and fine structure are shown in the Table 1 [32].

Type of β –glucan	Organisms and sources
(1,3)-β-glucans	Bacterium *Alcaligenes faecal - curdulan*
(Linear homogeneous)	Algae *Euglena gracilis - paramylon*
	Poria cocos Pachyman
	Vitis vinifira – callose
(1,3),(1,6)-β-glucans	Algae *Laminaria* Sp.- Laminarin
(linear with (1,6)-linkage β-glucosyl side branch)	*Claviceps purpurae* - wall glucan
	Sclerotinia sclerotiorum - wall glucan
	Brown algae *Eisenia byciclis* - Laminarin
	Mushroom *Lentinula edodes* - wall glucan
(1,3),(1,6)-β-glucans	Yeast *Saccharomyces ceréveciea* - cell wall glucan
(branch structure)	Mushroom *Schizophyllum commune* - wall glucan
(1,3),(1,4)-β-glucans (linear)	Cereal β-glucans
	Iceland moss *Cetraria islandica*

Table 1: Examples of β-glucans with different structures, isolated from different natural sources.

β-glucans are naturally occurring homopoly saccharides in fungi such as mushrooms and *Saccharomyces cerevisiae* [33]. The yeast cell wall consists of 30-60% polysaccharides (β-glucan and mannan oligosaccharides), 15-30% proteins, 5-20% lipids and a small amount of chitin. The yeast cell wall, especially of baker's and brewer's yeast (*Saccharomyces cerevisiae*), is an important source of β-D-glucans. Yeast β-glucans have been proven as beneficial for many human and animal diseases and disorders. β-1,3-D-glucans and 1,6-D-glucans are called biological response modifiers (BRMs) due to their ability to enhance and stimulate the human immune system [34,35]. Among yeasts; *Saccharomyces cereveciea* is the major source of β-glucan, other sources include *Zygosaccharomyces bailii*, *Kloeckera apiculata, Kluyveromyces marxianus, Debaryomyces hansenii*, *Schizo- Saccharomyces pombe* and other fungal group. Among them are the edible fungi that are grown in the form of eaten mushrooms. The most famous mushroom sources include *Agaricus brasiliensis*, *Pleurotus tuberregium*, *Grifola frondosa*, *Pleurotus eryngii* and *Pleurotus ostreatoroseus* [36]. The β-glucan component in the *Saccharomyces cerevisiae* cell wall with the function of maintaining the rigidity and shape of the cell is often named simply glucan or yeast glucan [35]. Major factors that affect yeast cell wall composition include yeast strain, growth conditions (growth medium, temperature, osmotic pressure, toxic metabolites) [37]. Fuel alcohol fermentation is a high stress process and the cell walls of the yeast collected as a by-product contain a high amount of β-glucans. In general, yeast strains of *Saccharomyces cerevisiae* that are used in baking (baker's yeast) have a higher β-glucan-to-α-mannan ratio than those that are used for alcohol fermentation (brewer's yeast), therefore it is advantageous to use pure baker's yeast for producing high quality (1,3), (1,6)-β-D-glucan for medicinal applications [37].

β-glucans are reported to have several beneficial properties and because of that they have found a wide variety of uses in human and in veterinary medicine, immunopotentiation, pharmaceutical, cosmetic and chemical industries as well as food and feed production [38]. β-glucan, derived from yeast, could have numerous applications in curing of patients by improving their immune system. Among the most attractive properties of β-glucans are activities against many types of cancer and infectious diseases. They can also prevent negative effects of radiation exposure, septic shock, allergic rhinitis, elevated blood cholesterol and fatty acids and help in wound healing, arthritis and others. Natural preparations of β-glucans like oat milk, barley or yeast β-glucans preparations added to juicy drinks could be used instead of expensive drugs with dangerous side-effects [39,40]. One of the most important biological activities of β-glucan is prevention of bacterial infection. It can elevate the general level of resistance to pathogens and reduce the risk of infections. Numerous studies and clinical trials have proved that soluble β-glucan improve resistance to bacterial infection [41-43]. β-(1,3), (1,6)-glucan increases resistance to many diseases enhancing leukocyte anti-infective activity in human whole blood. Numerous studies and clinical trials have proved that soluble β-glucan improve resistance to bacterial infection [23]. β-(1,3), (1,6)-glucan increases resistance to many diseases enhancing leukocyte anti-infective activity in human whole blood, without increasing the inflammatory cytokine production [23]. *Saccharomyces cerevisiae* β-glucan extract was shown to have antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* resistant to antibiotics [42,43].

Other β-glucans Medical Applications

Many other therapeutic applications of β-glucans have been published. One of those is their use as: Radio protective agent, in fact preparations of soluble β-glucans are able to protect blood macrophages from free radical attack during and after the radiation allowing the cells to continue their function in the irradiated body [44]. β-glucan could also be used to prevent some digestion problems, like constipation and stomach troubles. β-glucan as prebiotics can improve the growth of lactic acid bacteria from genus *Lactobacillus* and *Bifido bacterium*, microorganisms living in intestinal tract that have healthy effect in humans [43-45].

Other β-glucans Applications

β-Glucans obtained from yeasts cell wall can also be used in food industry as dietary fibres, fat replacers and emulsifiers due to their ability for holding water, oil and fat [46]. Their incorporation in food helps in lowering blood sugar. Yeast β-glucan extract is considered as safe for oral applications and recognized as generally recognized as safe (GRAS) by the US Food and Drug Administration [47].

Fungi as Immunosuppressive

Immunosuppressants, such as cyclosporine A, Tacrolimus, Rapamycin, and Mycophenolate mofetil, have gained considerable importance in the world market [48]. Tacrolimus (FK-506) is an immunosuppressant agent that acts by a variety of different mechanisms which include inhibition of calcineurin. It is used as a therapeutic alternative to cyclosporine, and therefore represents a cornerstone of immunosuppressive therapy in organ transplant recipients [49]. Rapamycin (Sirolimus), is an immunosuppressive drug that was approved by the United States Food and Drug Administration (FDA) in 1999 and by the European Medicines Agency (EMA) in 2000 as an immunosuppressive agent for renal transplantation patients once its T-cell suppression characteristics were recognized [50]. Mycophenolate mofetil is one of the most frequently used immunosuppressive drugs in solid organ transplant recipients. Mycophenolate mofetil is an inhibitor of inosine-5′-monophosphate, and is able to preferentially inhibit B-cell and T-cell function. The immunosuppressive abilities of Mycophenolate mofetil have made it one of the most successful anti-rejection drugs in transplant patients [51]. In this review we will focused on cyclosporine as the most common immunosuppressive compound.

Cyclosporine has received meticulous attention owing to its immunosuppressive and biological activities. Cyclosporine is a cyclic 11 membered fungal peptide metabolite which is widely used as a powerful immuno-suppressant to prevent graft rejection in transplantation surgery [28]. Cyclosporins were initially discovered by Dreyfuss M, et al. [26], as antifungal antibiotics produced as a secondary metabolite by a fungus namely *Trichoderma polysporum.* The striking specific immunosuppressive activities of Cyclosporins observed in early experiments [52] started an extensive investigation of these fungal secondary metabolites, which led to its use in organ transplant surgery. Twenty five natural occurring Cyclosporins have been described to date [28]. The subsequent dramatic increase in the success of using cyclosporine A in organ transplant surgery made, cyclosporine A is one of the very important therapeutic agents of the last decade. Cyclosporine has been approved by food and drug administration (FDA) as immunosuppressive drug for clinical use for the prevention of graft rejection in transplantation. It is applicable in treatment of autoimmune diseases (rheumatoid arthritis, psoriasis, and systemic lupus erythematosus) [53]. Cyclosporine A is a major secondary metabolite usually produced by an aerobic filamentous fungus, *Tolypocladium niveum* [54]. Although cyclosporine A was initially developed as an antifungal antibiotic, it is currently prescribed as one of the most important immunosuppressive drugs for the treatment of organ transplants, as well as patients with autoimmune diseases, including AIDS, owing to its superior T-cell specificity and low levels of myelotoxicity [28,54,55]. The drug was first isolated from *Tolypocladium inflatum* and after that very few studies were planned to explore other sources for its production. Until now most of the research work related to cyclosporine A deals with *Tolypocladium inflatum* and *Aspergillus terreus* [28].

Cyclosporine A is the first microbial metabolite to be used clinically to regulate the growth and function of a normal mammalian cell. It spurred studies providing unique insights into cell biology, and is proved to be invaluable tool of basic immunological research. A better insight into the mechanism of cyclosporine A action on the molecular level might help to design novel highly potent immunosuppressants with no or negligible side effects [55]. The twenty five naturally occurring cyclosporine and their structures they are modified in nine of eleven amino acid positions. Various cyclosporins differ in amino acid composition often by only one residue [56]. Cyclosporine A is widely produced by submerged fermentation of aerobic fungi identified as *Trichoderma polysporum* but currently identified as *Tolypocladium inflatum*. Since its discovery, very few studies have been carried out to search for other microbial sources for its production. Most of the research work on cyclosporine A is based on fungi *Tolypocladium inflatum* and *Aspergillus terreus* [57]. Besides being produced by *Tolypocladium inflatum* so far, this drug has been reported to be produced from *Aspergillus terreus*, *Fusarium solani* and *Fusarium oxysporum* [58]. Anjum T, et al. [57] reported that *Penicillium fellutanum* is a new fungal source of cyclosporine A production. On the basis of the broad therapeutic uses of cyclosporine A, fermentation processes have been made using submerged and solid-state cultures of several fungal species, particularly *Tolypocladium inflatum* [59]. Cyclosporine A was also produced by *Fusarium solani* [60], *Fusarium roseum* [61], *Fusarium oxysporum* [62], *Neocosmospora vasinfecta* [63], and *Aspergillus terreus* [58]. Cyclosporine A production was also reported by submerged fermentation using different fungal species such as *Aspergillus terreus, Cladosporium columbinum*, *Penicillium fellutanum, Cylindrocarpon lucidum*, and many *Trichoderma species* [57]. *Trichoderma polysporum* was reported as a producer of both cyclosporine A and cyclosporine C in submerged culture and were extracted therefrom using organic solvents. Similarly, *Trichoderma harzianum*, has produced cyclosporine A, and the amount of drug calculated was 44.06 μg/mL on a medium composed of glucose, 5%; peptone, 1%; KH2PO4, 0.5%; KCL, 0.25% (w/v), and using butyl acetate for the extraction process, and high-performance liquid chromatography for detection [52].

Endophytic Microbes the New World of Immunosuppressive Drugs

Endophytic microbes represent a relatively untouched reservoir of biologically active compounds that have potential uses in medicine and agriculture [64]. Some of these organisms make such notable compounds as the anticancer drug taxol, and a plethora of antibiotics, antioxidants and immunosuppressants [65]. Immunosuppressants are required for an array of medical purposes, such as organ transplantations and the treatment of autoimmune-associated diseases [66]. However, most of the currently available immunosuppressive drugs have been shown to inevitably possess severe adverse effects, such as hepatotoxicity, nephrotoxicity, and hypertension induction [67]. Therefore, there is an urgent need for new therapeutic agents for modulating the autoimmune response. Dalesconols A and B are potent polyketides with a unique carbon skeleton. These immunosuppressive agents are produced by a mantis-associated fungus [68].

Colletotrichum dematium is an endophytic fungus recovered from a *Pteromischum* sp. growing in a tropical forest in Costa Rica. This fungus makes a novel peptide antimycotic, colutellin A. Both cyclosporine A and collutellin A possess immunosuppressant effects. Most of the immunosuppressant compounds isolated from nature are lipopeptides, cyclic peptides or cyclic lipopeptides, but few have low cytotoxicity accompanied with high immunosuppressive activity. This fact makes the prospects for collutellin A, as a potential drug, seem promising since it has little or no toxicity and reasonable immunosuppressive potential [69]. Immunosuppressive activity guided chemical investigation, four alkaloids (1–4) and eight polyketides (5–12) were isolated from mangrove-derived *Aspergillus fumigatus* HQD24. Amongst, immunosuppressive agent fumigaclavine C (2) used to be isolated as a major component from *Aspergillus fumigatus* CY018 by Ramana Murthy MV, et al. [70-80].

Conclusion

β-Glucans are believed to be strong immune-modulatory, modulating humoral and cellular immunity, and thereby have beneficial effects in fighting infectious diseases, such as bacterial, viral, fungal, and parasitic diseases. Also, cyclosporin A is one of the mostly used antifungal that are easily produced from a biological organism fungus. This compound is used to treat patients with organ transplantation, canine skin disease and rheumatoid arthritis.

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