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Mini-review: Immunomodulating fungi for feed additives

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Abstract

Restriction of the feed antibiotics in the diet of farm animals formed a new economical and research challenge: a necessity for new feed additives which are able to provide immunomodulating effects. The review summarizes some international experience with the application of immunomodulating feed additives. There are numerous species/strains of fungi which could serve as immunomodulators. According to the known data, fungal activity has been established and well-known; however, till the present time, fungal preparations are not widespread because their production is complicated, time-consuming, and expensive. In this brief essay, we present information on some immunomodulating fungal feed additives as well as show the possibility of fungal cultivation directly on feed substrates to combine the immunomodulating additives and feed as a waste-free organic whole.

Keywords – Feed additive – Immunomodulating fungi – Residue-free cultivation

Introduction

The development of new feed additives is an important economic task. Recently, due to the limitation of the use of feed antibiotics, the importance of healing additives has significantly increased. The European Union (EU) banned the use of antibiotics in animal feedback in 2006, and the civil communities and lawyers have discussed new rules to provide safety and health since then (European Commission, 2021). The United States Food & Drug Administration (FDA) banned the use of antibiotics as additives in animal feed in 2017. The Indian government banned the use of the antibiotic, the "last resort", on farms in 2019 (Mordor Intelligence LLP, 2021).

Most of the feed additives currently occupying the market are focused on increasing the weight of animals by improving their metabolism or absorption of feed. These agents include additives created on the basis of fundamentally different groups of compounds: from cellulose fibres, e.g., Arbocel fibres, to peptides, e.g., vitapeptide, epidermal, ferropeptide, and lignohumate. On the one hand, the abundance and variety of feed additives on the market indicate high competition in this area. On the other hand, the problem with restricting the use of antibiotics revealed the absence of leading products with pronounced immunomodulatory properties. The latter is known as single products and never hit the market due to the complexity and high cost of their production.

Stimulating feed additives in the Russian Federation

The feeding practice of the Russian Federation is an example of special interest for the

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authors because the Russian feeding practice combines its own experience in animal husbandry with western and eastern traditional practices and official legislation. Thus, in the Russian Federation, following international and European agreements for productive animals, the official regulation "On the safety of feed and feed additives" subdivides all feed additives into the following groups: sensory, ensuring the biological value of feed, zootechnical, regulators of the intestinal microbiota composition. It is interesting that the immunomodulatory feed additives are not subject to any specific registration in Russia (Ministry of Agriculture, 2021). These stimulating preparations include, for example, (i) immunomodulatory feed additive based on bee swarm, bifidobacteria and kombucha culture fluid, (ii) purified multienzyme enzyme preparation, (iii) adaptogenic preparation of "Ribav", which is an alcoholic extract of the primary metabolism products of micromycetes living in symbiosis with medicinal plants, (iv) mussel hydrolyzate, and (v) preparation based on coniferous greenery "MIK-BAK" (Abashina et al. 2021). Thus, the rich feed additives for animals, for example, "Vita-Force", which contained royal jelly, bee bread, pollen, and bee venom, required a change for a new, cheaper version (Tukhfatullov et al. 2018).

The most known immunomodulating fungi

Along with the mentioned preparations, there are well-known at least several groups of fungi that exhibit immunomodulatory properties and whose preparations are approved for the medicinal treatment of people. The most famous medicinal mushrooms are chaga (*Inonotus obliquus*), reishi (*Ganoderma lucidum*), shiitake (*Lentinus edodes*), and oyster mushroom (*Pleurotus ostreatus*). Their preparations, including chaga *I. obliquus*, are patented in the USA as biostimulants (Bgatov et al. 2001, Glamočlija et al. 2015, Zhao et al. 2016), the last ones are under investigation as therapeutic anticancer drugs (Glamočlija et al. 2015, Zhao et al. 2016). On the basis of shiitake *L. edodes*, a therapeutic agent KS-2 has been developed, which induces the production of interferon by the body and stimulates macrophages of the immune system (Chang & Miles 2004, Laboratory Protocols in Applied Life Sciences 2014). Similar medicinal characteristics have been shown for preparations based on reishi *G. lucidum* (Boh et al. 2007). Other fungi are also known to exhibit an immunomodulatory effect, including for humans (Smiderle et al. 2013). For shiitake and oyster mushrooms, there is also antiviral activity (Santoyo et al. 2012).

Use of preparations based on filamentous fungi *Trichoderma* is of particular interest (Pavlovskaya et al. 2016). Fungi of this genus are widely used in the processing of agricultural soils; however, formally, some species of this genus are classified as possible causative agents of diseases (Kuhn & Ghannoum 2003, Hatvani et al. 2013), which means that each strain must be tested for its avirulence prior to use (Harman et al. 2004). The same warning is also relevant for immunomodulating fungi *Acremonium*, which are recommended to increase the immunity and productivity of calves and cows (Li et al. 2016, 2017). Among representatives of this genus, there are strains that cause infectious diseases (Kalinina et al. 2012).

Immunomodulating compounds and feed additives

An industrial problem in pharmaceutical/veterinary immunomodulatory drug production is the high cost of isolating pure biochemical compounds from fungi. For this reason, it is much more promising not to prepare drugs for the treatment of animals but to include the biomass of fungi in feed as biologically active additives. In recent years, the immunomodulatory activity of fungi-based feed additives was confirmed by a number of scientific studies. These examples are feed additives based on shiitake and reishi, which were effective for broilers (Willis et al. 2012). An even wider range of "medicinal" fungi is recommended for laying hens (Mahfuz & Piao 2019). Similar research studies have shown the effectiveness of polysaccharides in the cell wall of fungi/beta-glucans for both broilers and rabbits (Crespo et al. 2017, Kovitvadhi et al. 2019). Beta-glucans are long molecular chain polysaccharides, units of which are represented by glucose. These compounds belong to biologically active substances and represent a family of polysaccharides, where D-glucose monomers are connected by beta-glycosidic bonds and differ in molecular weight, density and three-dimensional structure. The biological activity of glucans is multi-vector and depends on

many factors. Accordingly, the mechanisms of their action are diverse, although it has already been shown, in particular, that they all stimulate phagocytosis (Brown & Gordon 2003, 2005). The immune response of animals to fungal beta-glucans (in particular, isolated from the reishi strains) has been considered in a number of scientific publications over the past two decades (Brown & Gordon 2003, 2005, Lukyanchuk et al. 2011, Wang et al. 2017, van Steenwijk et al. 2021).

Unfortunately, in the majority of works on the study of microbiological additives, such as immunomodulating probiotics for chickens, pigs, cows, goats and sheep, fish, rabbits, horses, dogs and cats, the fungal research is limited, for example, in the review on 921 publications only 27 referred to fungi (Brufau et al. 2015). However, in many situations, numerous investigators agree with the strategy of using immunomodulators rather than antibiotics (Sarkar et al. 2016).

In addition to polysaccharides, mycelium has many active ingredients, e.g., terpenes and proteins, including those with selective anticancer or antiviral activity (Lull et al. 2005, El Enshasy & Hatti-Kaul 2013, Liu et al. 2020). However, for a long time, biotechnologies using immunomodulating mycelial feed additives were not widespread since there were technical problems in their preparation. The mycelial biomass was grown either on media that were not used in feed, therefore, requiring the separation of mycelium from cheap insoluble substrates, or on liquid media oriented to the preparation of extracts. Thus, the task was to create a method for growing mycelial biomass in which the substrate can be used not only as a starting material but also for the after-enrichment with mycelium and its active biological products, together with mycelium as a total feed product.

Currently, this problem has been solved by using the mycelium grown on plant raw materials to use together with plant residues (Jeon & Kim 2001). In modern practice, such mixed plant-fungal feed raw materials are most widely used in poultry farming (Wang et al. 2015, Bederska-Łojewska et al. 2017). Based on these data, it can be assumed that granulation of immunomodulatory additives together with feed allows them to maintain their target properties, despite the increased temperature. In our studies (our unpublished data), mycelium retained its composition and fundamental properties at 70 °C.

Conclusions

The current prescribed limitations of antibiotics in animal husbandry led to the search for alternative arsenals. The accumulated information has shown that immunomodulatory fungi could serve as an effective substitute for antibiotics. Using immunomodulatory fungi just as veterinary drugs seems to be expensive. This review also shows that immunomodulatory fungi and their mycelium can serve as protective/healing food additives. Cultivation of mycelial biomass is possible directly on inexpensive forage substrates, including low-grade cereals or potato waste; such cultivations provide low-cost fungal immunomodulators.

Conflicts of interests

The authors declare no conflict of interest. All authors have significantly contributed to the presented mini-review.

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