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MEDICINAL SPECIES OF MACROMYCETES RECORDED IN THE REPUBLIC OF MACEDONIA

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INTRODUCTION

The territory of the Republic of Macedonia has been relatively poorly investigated from mycological aspect. Until now, few systematic analyses of fungi have been made what explains the fungia in some regions of the country (e.g. Pelister, Jakupica, Galicica, Kozuf, Sar Planina etc).

The first mycological paper in the Republic of Macedonia was published by Ranojevic [1] in 1909. Sydow determined fungi collected by Bornmüller in Macedonia in 1921 [2]. The published papers by Lindtner [3-5], are of great importance. He investigated micromycetes, but also he collected macromycetes and the results were partially published by Pilàt & Lindtner in 1938 [6] and 1939 [7]. Litschauer [8] in 1939 gave a great contribution to the investigation of corticoid fungi, especially from the genus *Tomentella* from Sar Planina and Korab. Minev [9] in 1953 explored mycosis on pine and fir trees in Pelister. About higher and lower fungi, parasites and saprophytes on forest trees, the following authors were writing: Tomasevic [10] (1955), Grujoska [11-13] (1970, 1973), Serafimovski & Grujoska [14] (1959), Koleva-Sekutkovska [15] (1959), Serafimovski and al. [16] (1968), Grujoska & Papazov [17, 18] (1974, 1975) and Papazov [19, 20] (1973, 1983). Higher fungi from the Macedonian pine forests on Pelister were investigated by Tortic in 1967 [21, 22] and 1987 [23], and also on Jakupica by Tortic and Cekova in 1975 [24] and by Sylejmani in 1980 [25].

Lignicolous fungi in the sub-Mediterranean region of Macedonia were explored by Tortic & Karadelev [26] in 1986, as well as on Kozuf, Nidze, Pelister and Galicica by Karadelev [27, 28]. Tortic included 585 species of macromycetes in the first Macedonian mycoflora [29].

Recently Karadelev has continued the investigations on fungi in various Macedonian areas [30-34].

Fungi represent a very heterogeneous group of organisms. However, studies to date have been concerned mainly with Ascomycota and Basidiomycota.

The other phyla have been studied insufficiently. Thus far, in the Republic of Macedonia approximately 1,250 species of fungi have been recorded [35]. The majority of them belong to the phyla Ascomycota (130) and Basidiomycota (1,050).

This plentiful gene fond of fungi might be a potential source for isolation of active principles with antioxidative, antitumor, immunomodulative, antiinfective and other actions [36-57].

MATERIAL AND METHODS

The Division of Mycology within the Faculty of Natural Sciences (Institute of Biology), possesses a large collection of macroscopic fungi called Fungi Macedonici.

The collection contains approximately 10,000 specimens as well as a fungi database named MACFUNGI.

Literature data for the antioxidative, antitumor, immunomodulative, antiinfective and other actions of fungi found on the territory of the Republic of Macedonia are included in the following databases: PubMed, Chemical Abstracts and Hinari.

RESULTS AND DISCUSSION

By synthesis of the secondary metabolites the enormous practicability of fungi as biosystems that humans can manipulate for their own benefit, could obviously be emphasized.

Although the majority of these metabolites were isolated from representatives of the subdivisions Zygomycotina and Ascomycotina, recently investigations have been transferred to the subdivision Basidiomycotina.

The advantage of the higher fungi is that in most of the cases cultivation in laboratory is not necessary.

Their macroscopic fruiting bodies could easily be identified in nature and collected if necessary. Especially interesting are the species that extensively grow on various substrates or forest phytocenoses.

According to the action of their metabolites fungi could be divided into: bazidiomycetes with antibacterial, antifungal, antiviral and anticancer (cytostatic) action 1.

1. Bazidiomycetes with antibacterial action Berdy (1974) [36] quoted 3222 antibiotics, out of which 140 were isolated from representatives of the

subdivision Basidiomycotina.From the submerged culture of *Merulius tremelosus* the following antibiotics have been isolated: merulic acid A, B, C (also present in *Phlebia radiata*) and merulidial who acts bactericidally on Gram-positive (*Micrococcus roseus, Corynebacterium insidiosum, Bacillus brevis, B. subtilis, Streptomyces viridochromogenes, Sarcina lutea*), Gram-negative (*Proteus vulgaris*) and antifungal on micelial fungi and yeasts [37].From *Stereum hirsutum* hirsutic acid was isolated with effects on *Micrococcus pyogenes*, *Corynebacterium diphteriae* and *Neisseria meningitis*, from *S. rameale* - ramealin, active against some Gram-positive bacteria, and from the related *Xylobolus frustulatus* antibiotic frustulosinol, active against *Staphylococcus aureus, Bacillus mycoides, B. subtilis, Vibrio cholerae*, and in higher concentration on some fungi [38].From the poroid species of *Hirschioporus pargamenus* antibiotics biformin and biformic acid were reported with wide spectra of action on Gram-positive bacteria, *Mycobacterium phlei* and against fungi; on *Piptoporus betulinus* - poliporenic acid A and C, active against Gramnegative bacteria (*Escherichia coli*) and *Mycobacterium phlei*. Extract from this fungus is successfully used in therapy of brucellosis. From the species *Heterobasidion annosum* phytotoxins fomanosin and fomanocsin were isolated with antibacterial action, and from *Pycnoporus cinnabarinus* - cinabarin active against Gram-positive bacteria and *Mycrococcus pyogenes*. From *Gloeophyllum trabeum* termofilin was isolated, active against cocci, and from *G. sepiarium* antibiotic lenzitin was reported with vigorous bactericide and bacteriostatic action on many Gram-positive and Gram-negative bacteria. From the species *Laetiporus suphureus* and *Phellinus igniarius* sulfuridin was reported with bacteriostatic action on Gramnegative bacteria [39, 40, 41].From Agaricales the following antibiotic compounds were isolated: *Agrocybe aegerita* - egeritin, with wide spectra of action; *Marasmius alliaceus* - aliakolid, with antibacterial and antifungal action and crystal aliacol A and B; *Hypholoma fasciculare* - fasciculol D action on *Staphyllococcus aureus* and *Klebsiella pneumoniae*. From the species *Agaricus bisporus* agaritin was isolated [42]; from *A. campester*, kampestrin, which was used against typhoid and some other bacteria; from *A. xanthodermus*, psaliotin with bactericidal action on Gram + and Gram - bacteria. From the culture of *Colibia peronata* antibiotic compound was isolated active against *Staphyloccocus aureus;* the species *Coprinus picaceus* is used as a producer of a picace acid, active against micrococcus and typhoid. From the *Lactariusdeliciosus* antibiotic compound named as laktaroviolin was isolated, active against *Mycobacterium tuberculusis*, as well as laktarazulen and laktarofulven, till from the related species *Lactarius rufus* a compound active against micrococcus was isolated. From the species *Lepista nebularis* antibiotic nebularid was isolated with action on *Mycobacterium tuberculosis*, and from the related *Lepista nuda,* nudic acid A and B with action against Gram + and Gram - bacteria. From dried fruit bodies water extracts of *Lucopaxillus giganteus* and *Leucopaxillus candidus* antibiotics klitocibin A and B were isolated with bacteriostatic effect on penicillin-resistant bacteria. From the species *Marasmius scorodonius* skorodonin was isolated with inhibition action on yeast and bacteria [43]. From lignicolous Gasteromycetales, the folowing antibiotics were isolated: from *Cyathus striatus* - striatin A, B and C, active against Gram + aerobic and anaerobic bacteria, some Gram - bacteria and against Fungi imperfecti [44]. Musilek (1981)[45] investigated 338 culture races from 195 species of Bazidiomycetes on representatives of Gram + bacteria (*Bacillus subtilis*), Gram - bacteria (*Escherichia coli*) and fungi (*Candida pseudotropicalis*), and 101 of them or 51.7% showed antibiotic activity.

2. Antibiotics with antifungal action Among the above mentioned: merulidial, frustulozinol, biformin, egeritin and striatin, which besides antibacterial poses and antifungal action, from some species of macromycetes are isolated compounds with purely antifungal action. From *Gloeophyllum sepiarium* oosplakton was isolated, from *Omphalotus olearius* iludin M and S and lampterol, from *Oudemansiella mucida* mucidermin, active against *Candida* spp. (*C. albicans, C. tropicalis, C. pseudotropicalis, C. guilermondii, C. Krusei* etc), dermatophytes (*Trichophyton*, *Epidermophyton*, *Microsporum* etc) and against some keratomycosis. This species poses affirmed antifungal action on 30 dermatophytes. From the same species preparation oudemansin was isolated, and from *Oudemansiella radicata* oudenon was isolated which beside antifungal posed antihypertensive action, too [46, 47].
3. Bazidiomycetes with antiviral action From poroid species *Pyrofomes demidoffii* antiviral compound active against poliomyelitis entitled as fomecin A was isolated [48].
4. Bazidiomycetes with cytostatic action Based on the investigation of 7000 collections of cultures of micromycetes, their cytostatic action was verified on sarcoma 180, adeno carcinoma 755 and leukaemia L-1210, anticancer compounds were evidenced in 50 species from 20 various genuses. In these investigations the following species were

enclosed: *Tricholoma rickenii, Lepista luscina, Coprinus ephemerus, Lentinus lepideus, Schizophyllum commune, Clitopilus passeckerianus, Oudemansiella radicata, Gloeophyllum sepiariumn,* and the representatives from the genuses: *Irpex, Merulius, Polyporus, Boletus, Corticium, Stereum, Poria, Pholiota, Agaricus* and *Morchella* [49,50].

From the representatives of ordo Aphyllophoralles the following anticancer compounds were isolated: from *Merulius tremellosus* - merulidial, active against carcinoma Ehrlich; from the extracts of *Fomes fomentarius* and *Piptoporus betulinus*, preparations for treatment of carcinoma of mammary gland, and carcinoma Sticker are prepared and from *Inonotus obliquus* - inotodiol with proved cytostatic action and oblikvol with cytostastic effect on sarcoma in mice. From dried and minced imperfect fruit bodies of *I. obliquus* preparation noted as "Befungin" is prepared in Russia.

It is used for healing various types of carcinomas, and also has tonic action and normalises the disorganized enzymes functions [51, 52].

From the genus Agaricales the following anticancer compounds are detected: from *Omphalotus olearius* - iludin M and S; *Pleurotus ostreatus*; *Flammulina velutypes* - flamulin; *Marasmius alliaceus* - aliakol A and B; *Armillaria mellea* s.l.- peptidoglucan fraction B; *Agaricus campestris* - agaridoksin, *Amanita phalloides* - amanulin.

From the water extract of dried fruit bodies of *Boletus edulis* compounds active against some types of sarcoma are isolated. From *Phalus impudicus* antitumour compound is described which has manifested good results in healing of skin cancer. Antibiotic nebularin isolated from *Lepista nebularis* has showed antitumour action. From the fruit body of *Tylopilus felleus* compound with antimicotic activity was tested on cancer cells [43, 53, 54, 55, 56].

From lignicolous Gasteromycetales anticancer compounds were verified in *Lycoperdon pyriforme* [57].

Almost all of the above mentioned species are registered in the Republic of Macedonia. They are with different distribution and frequency. In adequate conditions extensively grow of some species occur. In beech forests, generally in autumn, large quantities of the following species appear: *Marasmius alliaceus, Oudemansiella mucida, O. radicata.* They grow only on Fagus, but the parasite *Armillaria mellea* s.l. in addition to its beech extensive grow it is found on oak and Molika-pine forests (Pelister), too.

It is of special interest the extensive presence of *Fomes fomentarius* which in some parts of Europe became rare, but in Macedonia grows as a parasite and saprophyte on 10 hosts, most often on *Fagus sylvatica*. *Fomes fomentarius* is particularly frequently found on the beech forests on mountain Kozuf. From the other species the following are frequently found on Fagus: *Hypholoma fasciculare, Merulius tremellosus, Pycnoporus cinnabarinus* and *Pleurotus ostreatus,* although they could be found on other substrates, too.

The following non - specific and wide-spread species could be distinguished: *Stereum hirsutum*, in Macedonia grows as a saprophyte on 28 various kinds of trees and bushes, *Trametes versicolor* on 21 species, *Schizophyllum commune* on 11, *Flammulina velutipes* on 11 (especially frequent on cultivated trees and bushes) and *Laetiporus sulphureus* (prefers Salix spp.) on 6 different substrates. From the coniferous species, the following could be found *Heterobasidion annosum*, as a parasite on the roots of Abies, Picea and Pinus (rare Fagus) and *Gloeophyllum sepiarium*, as a saprophyte on Picea and *Pinus peuce*.

From the substrate specific species are: *Agrocybe aegerita* that's grows frequently as a saprophyte on the trunks of Populus spp., *Phellinus igniarius* as a parasite on *Salix* spp, *Pyrofomes demidoffii* on *Juniperus excelsa*, *Piptoporus betulinus* and *Inonotus obliquus* on Betula spp. *Inonotus obliquus* species is still not registered in Macedonia, probably because of poor investigation on its host. Rare species in Macedonia or those insufficiently investigated are the following: *Cyathus striatus* (frequently on beams and prepared wood), *Gloeophyllum trabeum (Populus), Trichaptum biforme (Betula, Fagus), Lentinus lepideus (Pinus peuce), Lycoperdon pyriforme (Fagus), Omphalotus ollearius (Quercus)* and *Xylobolus frustulatus (Quercus).*

ABSTRACT

Fungi have a long history of usage in traditional medicine. The content of medicinal species (about 200 species) has not been researched enough in Macedonia. Therefore, in the present study an attempt has been made to present the medicinal species of macromycetes recorded in the Republic of Macedonia together with the literature data for their effects in human therapy. Their large number facilitates selection of those characterized by a significant medicinal quality.

CONCLUSIONS

In this paper selection has been made of compounds with antibacterial, antifungal, antiviral and cytostatic effects, isolated from the medicinal species of macromycetes recorded in the Republic of Macedonia. Some of the registered medicinal species: *Armillaria mellea* s.l., *Fomes fomentarius, Marasmius alliaceus, Stereum hirsutum, Trametes versicolor* etc, very frequently could be found on beech and oak

forests in mass quantities on the territory of the Republic of Macedonia. Their large number will facilitate selection of those characterised by a significant medicinal quality for our further investigations.

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