



Anticancer Mechanisms of Action of Macrofungus Extracts

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ABSTRACT: Mushrooms are delicious and nutritious food group and have been consumed by many societies in different parts of the world throughout history. Natural products derived from mushrooms have also been excellent source of medicine. They produce structurally various metabolites, many of which have served as excellent pharmaceutical sources. The most common types of cancer in the world are lung cancer, breast cancer, colon cancer, prostate cancer, skin cancer, thyroid cancer, stomach cancer, liver cancer, ovarian cancer, brain tumours and cervical cancer. Cancer cases are the forefront of death causes in the world along with cardiovascular diseases. It is a health problem that brings socioeconomically responsibility in the countries where it is seen. Cancer is a growing health problem worldwide. Epidemiological studies in societies confirm that fungi are the primary sources of drugs used in reducing cancer prevalence and preventing cancer-related deaths. As a result, they are potential candidates for natural anticancer drugs, thanks to more comprehensive future research on the anti-cancer activities of macrofungus extracts. In this study, information about the anticancer potential of macrofungi has been given.

Keywords: Anticancer, Macrofungi, Medicinal mushroom, Natural drugs

INTRODUCTION

There are 14 million cancer cases in the world every year and 8 million of these cases result in death. According to The World Cancer Report, new cancer cases are estimated to reach about 15 million in 2020. The treatment of cancer cases which has a high mortality rate and the use of medicinal products used in this treatment have gained great importance recently. In general, cancer treatment is carried out with chemotherapy and radiotherapy depending on the region where the cancer is in the body. However, these methods are not enough to fight cancer. While these methods destroy cancer cells, they also kill healthy cells. In order to strengthen the immune system of the patient, alternative therapies are also included in addition to the existing treatments (Wasser and Weis, 1999). Mushrooms have a very high potential for the production of alternative therapeutic drugs (Ndyetabura et al., 2010; Özaltun and Sevindik, 2020). Although macrofungi which has a medicinal properties have been used in far Eastern countries for a long time, the comprehensive examination of the properties of the fungi began in the 1940s (Salahuddin, 2008; Öztürk and Çopur, 2009; Sevindik et al., 2017). The nutritional values of macrofungi are quite high. It has a very important place in human health and nutrition. In addition, it has been used as a source of bioactive metabolites due to its bioactive components such as phenols, polysaccharides, terpenes, steroids, and tocopherols, and it has been accepted as nature's "superfood" (Cheung et al., 2003; Kalac, 2013; Bal et al., 2017; Sevindik et al., 2018; Sevindik, 2020). Components which has pharmacological properties have turned macrofungi into natural resources rich in antimicrobial, antiallergic, antidiabetic, antioxidant, anti-inflammatory, cholesterol-lowering and immune system stimulating properties. (Lindequist et al., 2005; Puttaraju et al., 2006; Kosanić et al., 2012; Acharya et al., 2016; Stojkovic et al., 2017; Sevindik, 2018a; Gürgen et al., 2020; Krupodorova and Sevindik, 2020). The β -glucan molecule within the macrofungi has recently become one of the most remarkable compounds. Located in the cell wall structure of macrofungi, β -glucan has many properties such as stimulating the immune system, antimicrobial, antioxidant, antiviral, antifungal, antitumor, cholesterol lowering and blood sugar regulator (Kidd, 2000; Ohno et al., 2001; Rahar et al., 2011). β -glucan molecules have a key-lock relationship with the surface receptors of important immune cells called macrophages. Macrophages swallow literally structures that our bodies describe as a harmful pathogen. This linking process with the-glucan molecule stimulates macrophage activity. β -glucan molecules lock onto the surface of macrophage cells and the pathogen is rendered inactive. (Dabal and Ezeronye, 2003; Lemieszek and Rzeski, 2012). Bioactive components isolated from the ascocarp, basidiocarp and mycelial structures of naturally grown from the past to the present, commercially sold and cultured fungi species have been proven to have medicinal and therapeutic effects. (Barros et al., 2008; Salahuddin, 2008; Wang and Marcone, 2011; Patel et al., 2012; Patel, 2012; Wasser, 2014; Chatterjee and Patel, 2016; Rathore et al., 2017; Souilem et al., 2017; Sevindik, 2018b). The search to use natural sources with medicinal properties as potential anticancer agents has shown that macrofungi overcome the side effects of chemotherapy and radiotherapy. Polysaccharides (such as β -glucan) have been shown to exhibit selective cytotoxicity and achieve success in cancer treatment without producing side effects like current treatment methods (Chen et al., 2013; Sevindik, 2019b). In this review focused on the anticancer action mechanisms of extracts from macrofungus species.

General characteristics of macrofungi

Macrofungi are organisms in the fungi kingdom, belonging to the Basidiomycetes and Ascomycetes classes, eukaryotic, heterotrophic, spore-producing, known as hyphae, having a filamentous somatic structure surrounded by a cell wall, containing complex carbohydrates in the cell wall and feeding on absorption. (Weier et al., 1970; Stern, 2008). Storage carbohydrates of fungi that do not contain chlorophyll are glycogen. They reproduce as sexually and asexually (Chang and Miles, 1987). It plays a major role in the continuation of the carbon-nitrogen cycle (Weier et al., 1970; Stern, 2008). They cannot move as they connect themselves to somewhere with their micelles. They are organisms that spread in forests and meadows, on plant and animal wastes, in habitats such as rotted branches and stumps, can develop as saprophytic, parasitic, symbiosis or mycorrhizal at appropriate humidity and temperatures and form fructifying organs in remarkable colors and shapes in the habitats where they develop. (Chang and Miles, 1987; Stern, 2008). Besides being consumed as food for many years, macrofungi have also been used as a medicine to treat many diseases such as cancer (Chan et al., 2009). Scientific research carried out in recent years shows that compounds produced by fungi have therapeutic properties. (Wasser and Weis, 1999; Zhang et al., 2006; Kim et al., 2008; Akgül et al., 2016; Akgül et al., 2017; Bal et al., 2019a; Sevindik et al., 2020).

Medicinal properties of macrofungi

Macrofungi have been in traditional Chinese medicine for centuries. Extracts obtained from macrofungi have an important share in the herbal-based pharmaceutical market in western societies (Money, 2016). The vast majority of macrofungi that contain medicinal properties are located in Basidiomycota division. Nowadays, alternative treatment methods are tried to produce all over the world, especially in the Far East countries and macrofungi are seen as biological resources in terms of their medicinal properties. (Wasser, 2008; Bal et al., 2019b; Sevindik, 2019a). Because of their many bioactive compounds, macrofungi can modulate immune responses, prevent some tumor growth, and show therapeutic effects in humans and animals. (Chan et al., 2009). These features attract the attention of many pharmaceutical companies that consider medicinal fungi as a rich resource (Wasser and Weis, 1999; Zhang et al. 2006; Kim et al. 2008; Sevindik et al., 2018a).

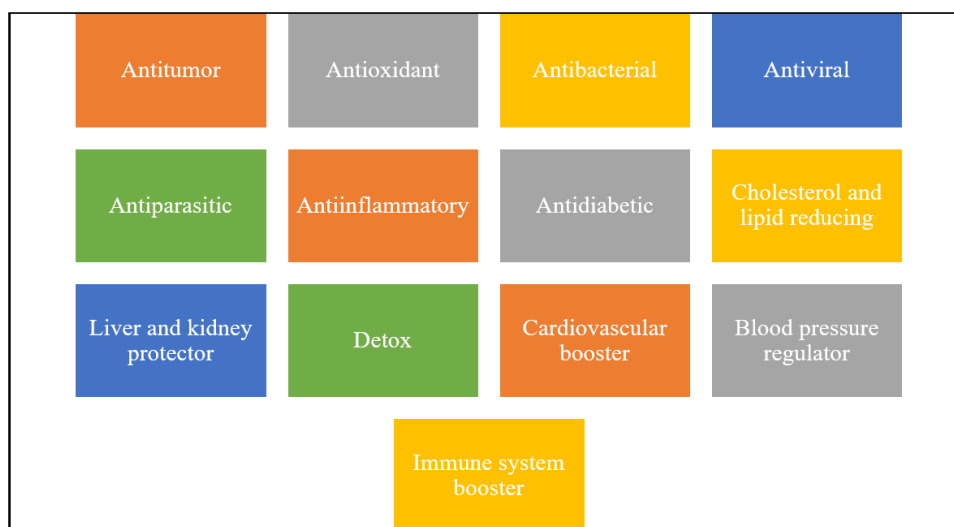


Figure 1. Biological properties of macrofungus components

Bioactive ingredients derived from macrofungi

A lot of research has been done on macrofungi so far and many bioactive compounds have been identified. Macrofungus components including polysaccharides, polysaccharide-protein complexes and various secondary metabolites have been proven to have many important functions such as immunomodulatory, anticancer and antioxidant activity (Figure 1) (Ren et al.2012; Sánchez, 2017; Sevindik et al., 2018b).

Polysaccharides: One of the main bioactive components of fungi are polysaccharides, which are carbohydrate polymers. They contain different chemical components found in macrofungus, including complexes of β -glucans, hetero-hete-glucans, heteroglycans, and α -manno- β -glucans, all of which have immunomodulatory and antitumor properties. Polysaccharides are natural products that are beneficial for health and are considered to be very valuable. Their biological activity is considered to depend on both chemical structure and types of glycosidic bonds (Huang and Nie, 2015). All fungus polysaccharides contain a common β - bonded glucose backbone. (Figure 2). Fungus polysaccharides are classified as α -glucans (starch, cellulose, and

chitin) and β -glucans. However α -glucans are rarely responsible for bioactivity, β -glucans are generally responsible for a wide variety of bioactivity (Grienke et al., 2014).

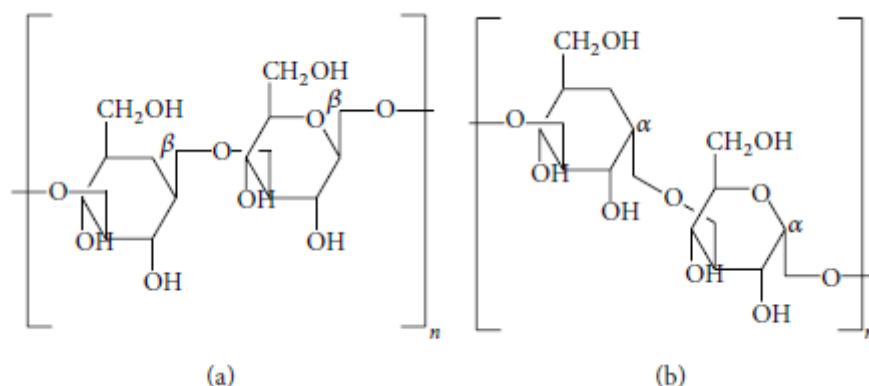


Figure 2. Structure of β -glucan(a) and α -glucan(b) bond (Elsayed et al., 2014)

Polysaccharides are large chains or branched biomacromolecules formed by the gather of many monosaccharide monomers. (Sharon and Lis, 1993). Many polysaccharides, which are classified as anticancer agents by NCI (US National Cancer Institute) and isolated from fungi belonging to Basidiomycota, promise us the feature of being a potential source due to their anticancer, antioxidant, immunomodulatory, antiviral activity and anti-inflammatory effects (Jong and Donovick, 1989; Wasser, 2002). There are some properties that polysaccharides must have in order to show their effects like anticancer (Figure 3). Because of these properties, bioactive components obtained from fungi play an important role as a natural resource in the prevention and treatment of diseases (Song et al., 2013).

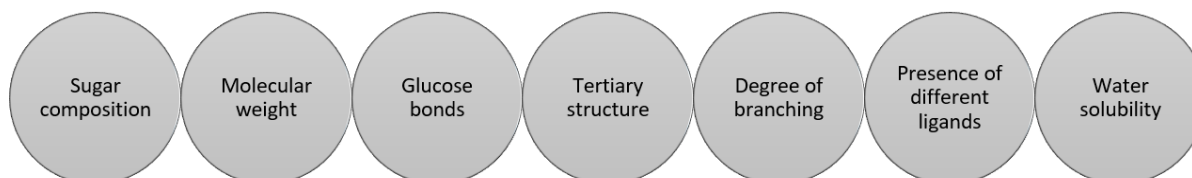


Figure 3. Some properties of polysaccharides

Polysaccharide-protein complexes (Glycoproteins): When polysaccharides bond with proteins, there is a maximum increase in complexity level. The α , β -glucanproteins and heteroglycan protein complexes that have bonded in this way and have increased complexity are glycoproteins with anticancer and immunomodulatory activity in macrofungi (Moradali et al., 2007).

Polysaccharide-peptide complexes: They are complexes which have smaller amino acid chains than glycoproteins that thought to have been developed as immunomodulatory and anticancer agents (Moradali et al., 2007).

Proteoglycans: This group consists of a core protein with one or more linked glycosaminoglycan chains. These are repetitive, non-branching polysaccharides and show like immunomodulatory properties (Moradali et al., 2007).

Secondary metabolites: These secondary metabolites isolated from fungi have a wide variety of pharmacological effects such as antioxidant, anticancer, anti-inflammatory and immunomodulatory activity (Chang et al., 2001).

Phenolic compounds: Phenolic compounds containing one or more aromatic rings or OH groups are classified as flavonoids, tannins, stilbens and curcuminoids (Fresco et al., 2006). These compounds have many effects on biosystems, especially on antioxidant defense mechanisms (Ferreira et al., 2009).

Terpenes: Terpenes isolated from fungi and primarily responsible for anti-inflammatory activity are volatile unsaturated hydrocarbons. Besides anti-inflammatory activity, terpenes are responsible for many pharmacological activities such as anticancer anticholinesterase, antiviral, antibacterial and anti-inflammatory (Brown, 2017).

Mechanisms of action of compounds

Polysaccharides: Polysaccharides generally have two main mechanisms: indirect (immunostimulation) and direct (tumor cell growth inhibition and apoptosis induction). The indirect effect due to the activation of T and B lymphocytes and macrophage and natural killer (NK) cells is based on the stimulation of the host's immune system (Lemieszek and Rzeski, 2012). In addition, the production of interferon, interleukin and other cytokines also occurs through β -glucans (Lemieszek and Rzeski, 2012). The direct effect is the modulation of NF- κ B activity. If we list the mechanisms of action that occur in various polysaccharides, these are cell cycle arrest, depolarization of the mitochondrial membrane, nitric oxide pathway, immunomodulation, activation of MAPK and PI3K and NF- κ B inactivation. For compounds using more than one route, the mechanism of action is not well defined (Brown, 2017).

Cell cycle arrest: Manipulating the cell cycle can prevent or stimulate an apoptotic response. This occurs when tumor suppressor genes such as the tumor protein gene (p53) and retinoblastoma protein gene (RB), the dominant oncogene, c-Myc, and various cyclin-dependent kinases (Cdks) are suppressed (Khan et al., 2019). Proteins in proliferative pathways can act mainly by sensitizing cells to apoptosis through the caspas cascade (Pucci et al., 2000). Some polysaccharides have been reported to stop the cell cycle in the G2 / M phase, S phase, or G0 / G1 phase and act as such.

Depolarization of the mitochondrial membrane: It has been determined that mitochondrial dysfunction is at the center of the apoptotic pathway. Some polysaccharides have been shown to cause a decrease in mitochondrial membrane potential. Mitochondrial membrane depolarization resulted in the release of cytochrome c, which is generally located in the mitochondrial membrane space, into the cytoplasm, and the release of cytochrome c led to the release of caspases, a group of cysteine proteases that promote apoptosis (Figure 4) (Tian et al., 2016). Polysaccharides obtained from fungi show anticancer effects through this pathway (Thangam et al., 2014).

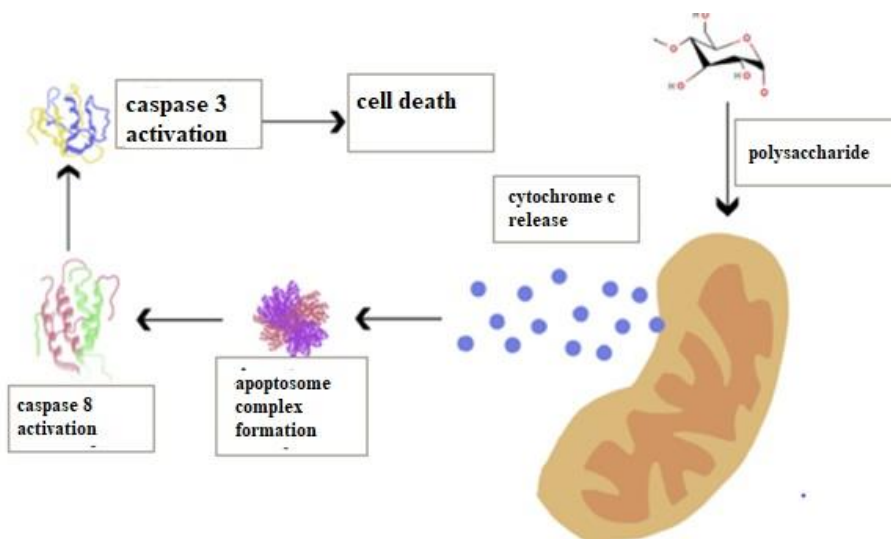


Figure 4. Depolarization of the mitochondrial membrane

Nitric oxide pathway: Several polysaccharides are reported to stimulate macrophages to produce NO through regulation of inducible NO synthase (iNOS) activity. NO has been recognized as an important messenger in various pathophysiological functions, including immune modulation, neuronal conduction, vascular relaxation, and cytotoxicity against tumor cells (Jiang et al., 2014). Thus, increased NO production causes the death of tumor cells via the caspas path (Figure 5).

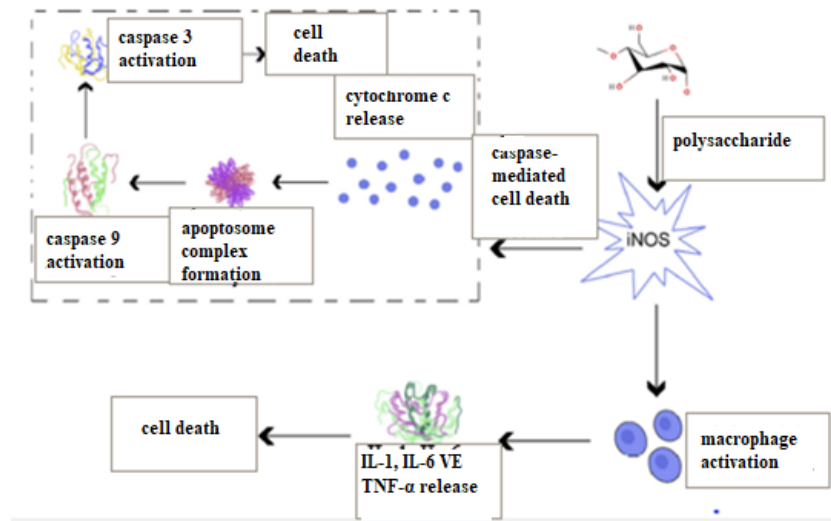


Figure 5. Nitric oxide pathway

Immunomodulation: Anticancer agents are known to have immunosuppressive effects. It is known that 5-fluorouracil, which is used in cancer treatment, significantly reduces the production of cytokines and the formation of immune responses. Suppression of the immune system is one of the mechanisms known to cause immunogenic tumors to escape from the host immune system and metastasize (Bao et al., 2013).

Therefore, increasing the host immune system responses in the host cell can restore the lost balance between the tumor-immune responses and as a result, it may show anticancer activity (Singh et al., 2018). Some polysaccharides are known to stimulate the immune system. They cause the production of cytokines including tumor necrosis factor (TNF- α) and interleukins (IL-2, IL-4, IL-6, IL-12), increase the expression of lymphocytes and in this way provide anticancer activity (Figure 6).

β -glucans are also immunomodulators that are highly effective on the immune system. Dectin-1, the type II transmembrane protein receptor that links-1,3-1,6 glucan chains together, can initiate and regulate the innate immune response. With this binding, phagocytosis is induced and immune reactions occur. Thus, agents that cause infection are eliminated (Rahar et al., 2011). Some of the signaling pathways of dectin-1 involved in macrophage, neutrophil and dendritic are NF- κ B and nuclear factor of activated T cells (NFAT). These lead to the release of cytokines including interleukin (IL). Other possible receptors and signalling pathways induced by-glucans are currently unclear. However, it was determined that lentinan, a form of β -glucan, binds to a receptor on the surface of myeloid cells and this binding triggers a protein induced by PI3K, Akt kinase (Rahar et al., 2011).

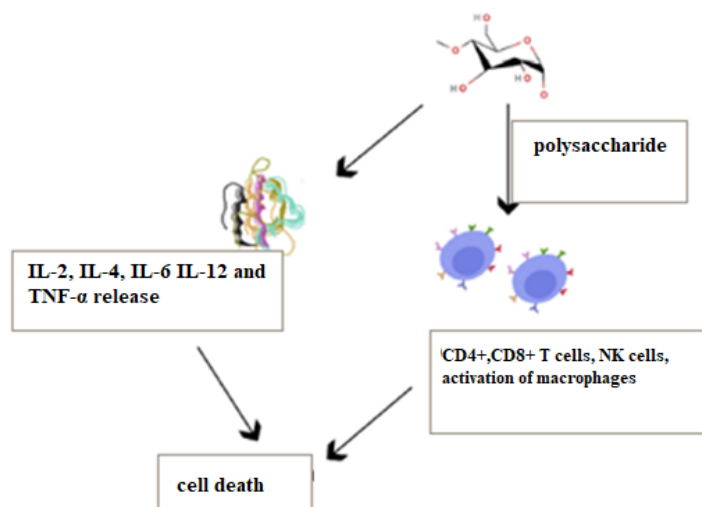


Figure 6. Anticancer activity of polysaccharides by immunomodulation

NF- κ B activity: By stimulating the expression of various target genes involved in cell cycle progression, cell survival, cell adhesion, angiogenesis, and immune-inflammatory responses, NF- κ B activates the cell cycle and the release of cyclins through

c-myc synthesis. NF- κ B, which induces caspas 3, 7, 9 and mitochondrial activation by enhancing the activation of BAX or BAK is of great importance in the regulation of apoptosis. NF- κ B mediates apoptosis activation and cell survival by CD40-CD40L or CD28-B7 interactions, protecting T and B lymphocytes from CD95 / Fas- or Apo2L / TRAIL-induced apoptosis. Thus, NF- κ B plays an important role in activation of immune response (Ravi and Bedi, 2004).

Secondary metabolites: Oxidative stress (OS) expressed by excessive production of reactive oxygen species (ROT) and reactive nitrogen species (RNT) as a result of the reduction of antioxidants that cause changes in cellular redox balance can damage lipids, proteins or DNA. OS is known to induce protein kinase pathways (these alter gene transcription) (Ma, 2010). ROT-mediated protein kinase/activating protein-1 (MAPK/AP-1) has a great effect on cell proliferation and apoptosis (Napolitano et al., 2010). Phenolic compounds show anticancer activity by reducing ROS formation during metabolism. It is known that the anticancer activities of monoterpenes such as D-limonene are realized by the inhibition of post-translational isoprenylation of oncoprotein p21ras (an oncoprotein that regulates cell growth and cellular signal transduction). This inhibition can occur through changes in gene expression level, the formation of apoptosis, the occurrence of cellular differentiation, and regression of cancer.

Epigenetic changes: Cancer initiation and progression are the result of genetic-epigenetic changes. Acetylation-mediated histone / nonhistone protein modification plays an important role in the epigenetic regulation of gene expression (Singh et al., 2018). Histone modification is controlled by the balance between histone acetyl transferase and (HAT) and histone deacetylase (HDAC) enzymes. The imbalance between the activities of these two enzymes is associated with various forms of cancer. Histone deacetylase inhibitors (HDACi) regulate the activity of HDACs and are used in cancer treatment alone or in combination with other chemotherapeutic drugs / radiotherapy. Secondary metabolites and other fungal compounds have been reported to show potential histone deacetylase (HDAC) inhibitory activity (Singh et al 2018). Histone deacetylase inhibitors (HDACi) may exert their antitumor effect by cell cycle arrest activation, apoptosis and autophagy induction, angiogenesis inhibition, increased reactive oxygen species formation causing oxidative stress, and mitotic cell death in cancer cells. The acetylation / deacetylation state of histone proteins and transcription factors modulate gene expression. The acetylation process also affects the stability of the proteins. Acetylation also blocks the activity of retinoblastoma protein (pRB) by blocking cyclin E-cdk2-dependent phosphorylation and causes cell cycle arrest. HDACi induces cell cycle arrest, differentiation, apoptosis, and inhibits angiogenesis (Singh et al 2018).

Studies on anticancer effects of macrofungus compounds

Altinsoy et al. (2017), investigated the effectiveness of ethanol and methanol extracts obtained from *Clitocybe geotropa* (Bull.) Quél. on MDA-MB-231 breast cancer cells. Cytotoxic activity of the extracts was determined by trypan blue method. For *C. geotropa*, no cytotoxic effect of methanol extracts at a concentration of 50–400 μ g/mL on MDA-MB-231 cells was observed, while the 400 μ g / mL ethanol extract was 51.5%; 200 μ g /mL ethanol extract 17.9%; and 100 μ g / mL ethanol extract reduced cell viability by 6.6%.

Methanol extracts were prepared from 22 fungi including fungi belonging to the genus *Lepista* from Tricholomatales order. Their cytotoxic activity on mouse cancer cell lines (L1210 and 3LL) was determined by the MTT method (Bézivin et al., 2002). The cytotoxic effect of *Lepista inversa* on K562 and Du145 cells was found to be most effective when compared to *Taxus baccata* shell extract used as a positive control.

Desert et al. (2017), used ethanol extracts of *Schizophyllum commune* obtained from dry fungus and micelle. Cytotoxic activity of these extracts was determined by MTT method. Three cell lines, one healthy (Beas2B) and two cancer cell lines (PC-3 and HeLa), were used in the antitumor activity studies. It has been observed that *S. commune* has cytotoxic properties against HeLa and PC-3 cells. It was emphasized in this study that it has a selective cytotoxic effect against PC-3 and HeLa cancer cell lines, especially at concentrations of 0.25 mg/mL and below compared to Beas-2B.

Liu et al. (2019), Aspernolid A, a secondary metabolite of butyrolactone, was purified from *Cladosporium cladosporioides*, an endophytic fungus derived from *Camptotheca acuminata* Decne roots. The antitumor activity of Aspernolid A in HepG-2 and TU212 cells was measured by MTT test (Liu et al., 2019). Expressions of Bax, Kaspas-9, Kaspas-3 and PARP (poly ADP-ribose polymerase), revealed by Western blotting method, increased with increasing dosage, and Bcl-2 decreased. This has shown that the apoptotic mechanism may be related to the mitochondrial apoptotic pathway. In addition, the expression of the phosphorylation of STAT3 suggested that the apoptotic mechanism may be involved in the STAT3 signalling pathway.

Gao et al. (2019), investigated the effects of various extracts of dicerandrol B, a natural antitumor agent that can be isolated from endophytic fungus, on human cervical cancer HeLa cells. MTT testing and flow cytometry showed that Dicerandrol B significantly inhibited HeLa cell viability and induced G2 / M cell cycle arrest. Western blot analysis showed that dicerandrol B increased levels of GRP78, ubiquitin, fragmented PARP and Bax protein, decreased Bcl-2 protein level, and induced apoptosis by showing that it caused an increase in the Bax / Bcl-2 ratio in HeLa cells. Dicerandrol B increased the production of reactive oxygen derivatives (ROS) in HeLa cells weakened by the antioxidant N-acetyl-cysteine. These findings suggest that dicerandrol B induces apoptosis in human HeLa cells, possibly through endoplasmic reticulum stress and mitochondrial apoptotic pathways.

The antitumor effect of carboxymethyl β -glucan (CMPTR) isolated from *Pleurotus tuber-regium* sclerotia on MCF-7 breast cancer cells was studied (Zhang et al., 2006). CMPTR inhibited the proliferation of MCF-7 cells by stopping the G1 phase of the cell cycle after 48 hours of incubation. In addition, the fact that CMPTR decreases the expression of Bax / Bcl-2 ratio is an indication that it induces apoptosis.

In the study, Mizuno (1995), determined that Lentinan polysaccharide, which is contained in methanol and ethanol extract of *Lentinus edodes*, is used with increasing doses to help the immune system of cancer patients during radiotherapy and chemotherapy treatment in Japan and this practice prolongs the survival of some cancer patients.

In the same year, Wang et al. (1995), by examining the immunomodulatory and antitumor activities of methanol and ethanol extracts of *Tricholoma* sp. For this reason, most species of the *Tricholoma* genus are directly used in some cancer treatments.

In a study conducted by Tuğrul and Oktay (2014), strong evidence was obtained for the antioxidant, anti-inflammatory, antiproliferative and proapoptotic effects of hydroxytyrosol, a phenolic compound, with in vitro in vivo experiments with various cancer cell lines. It was aimed to develop new strategies for the treatment of cancer, cardiovascular and inflammation-related diseases by demonstrating on which molecular mechanisms and cellular pathways hydroxytyrosol shows its anticancer activity.

In the study by Chan and Chan (2009), it is found in both bacterial and fungal cell walls and acts on various immune receptors, mainly Dectin-1, complement receptor (CR3) and TLR-2/6, and macrophages, neutrophils, monocytes, β -glucans, which trigger a group of immune cells, including natural killer cells and dendritic cells, and play a major role in immunity have been studied. As a result, it has been shown that β -glucans can be modulated and increase phagocytosis. In vivo studies, it has been determined that the linear 1-3 β -glucosidic chain of β -glucans, which is the specific backbone, cannot be digested and is captured by macrophages and transported to the endothelial reticular system. Small bits of β -glucans are released by macrophages and captured by immune cells. As a result of the study, it was determined that β -glucans with different sizes and branching shapes have varying immune power.

Chen et al. (2013), investigated the properties and antitumor activities of *Sarcodon aspratus* polysaccharides in terms of their applicability in health and medicine. Two polysaccharide fractions (PSAN and PSAA) were isolated from *S. aspratus* mycelium. It has been determined that PSAN and PSAA, which are different in terms of both molecular weight and branching chain, show high antitumor activity against Hela cells in vitro. PSAN and PSAA exhibited significantly lower cytotoxicity against human normal liver cell line L-02 than Hela tumor cells compared to 5-Fu. It has been demonstrated that polysaccharides extracted from *S. aspratus*, an edible fungus, could be a potential candidate to develop a new low toxicity antitumor agent.

Jiang et al. (2014), a water-soluble polysaccharide fraction (LP1) was prepared from *Dimocarpus longan* Lour and determined the lymphocyte proliferation of this fraction, the pinocytic activity of macrophages and nitric oxide (NO), interleukin 6 (IL-6), IL-1 β and tumor necrosis factor-alpha (TNF) production was determined to increase. These results revealed that LP1-S could be useful in the development of safe antitumoral drugs.

Tian et al. (2016), LGPS-1 was isolated from *Lentinus giganteus* and its anticancer activity was evaluated using HepG2 hepatocellular carcinoma cells. The results showed that LGPS-1 inhibited the proliferation of HepG2 cells, inducing the activation of caspase-3 and the cleavage of PARP-1. Western blot analysis revealed that LGSP-1 caused significant loss of mitochondrial membrane potential, increased the Bax / Bcl-2 ratio, promoted the release of cytochrome c into the cytoplasm, and inhibited the phosphorylation of Akt in HepG2 cells. This suggests that LGPS-1 induces apoptosis in HepG2 cells via intrinsic mitochondrial apoptosis and PI3K / Akt signaling pathways.

CONCLUSION

Today, as the incidence of cancer disease and the risk of cancer increase, the need and demand for natural products increase. In accordance with the analysis of the literature data, the anticancer activity of the extracts obtained from the macrofungus exhibited the increasing interest of the researchers and it was determined that the macrofungus components have anti-cancer activity. Mycologists all around the world think that the discovery of unique macrofungus species which have undiscovered medicinal properties in nature yet and using more knowledge about macrofungi can cure many types of cancer at various stages. The fact that macrofungi are rich in active metabolites has provided them to be used in cancer treatment. The unique and diverse metabolite groups that macrofungi contain within itself are responsible for their therapeutic effects. Pharmacological studies have shown that different macrofungi have anticancer, antioxidant and antimicrobial activity. However, in the studies done so far, although a number of compounds have been identified and the underlying mechanisms elucidated, researches are needed to elucidate the different roles of multiple active compounds as well as their respective pathways. As a result, with new information to be obtained about the possible therapeutic uses of macrofungi, macrofungi may be promising in the formation, progression and treatment of many cancer types.

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