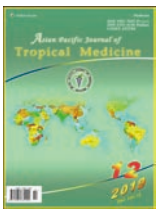

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Multi−targeting cytotoxic drug leads from mushrooms

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ABSTRACT

Due to genetic and epigenetic mechanisms, cancer have become a resistant disease and there is a need for new molecules having multiple targeting action that promotes apoptosis. Phytomolecules having multiple targeting anticancer activity are in high demand and there is less documentation or information available on these metabolites. It is evident that mushrooms are became the store houses of new anticancer molecules and mushrooms like *Agaricus blazei*, *Antrodia camphorate*, *Albatrellus confluens*, *Bolteus badius*, *Cordyceps militaris*, *Clitocybe maxima*, *Funalia trogii*, *Grifola frondosa*, and *Inocybe umbrinella*, are some of the medicinal mushrooms reported for their cytotoxic activity. Cytotoxic molecules like lentinan, grifolin, illudin-S, psilocybin, ganoderic acid, theanine, and hispolon, have been isolated from various mushroom species. However, studies have been limited only to *in vitro* cytotoxic mechanisms and very few trials have been conducted to prove the clinical efficacy of these drug leads. Hence, the current review focuses on new anticancer metabolites isolated from various mushrooms having multiple targeting mechanisms in cancer. However, an extensive research is needed to define the biosynthesis and clinical mechanism of these multiple acting metabolites. This review provides a platform for researchers new anticancer drugs and to bring out potent multiple acting anticancer newer drugs.

1. Introduction

Cancer is a resistant disease characterized by uncontrolled cell growth, which is the second leading cause of death. The cancer deaths may rise to 13 million by 2030. The most common types of cancer are lung cancer, breast cancer, and colorectal cancers[1].

There is an urgent need to treat this global burden known as cancer. Various multidirectional approach including behavioral and

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dietary change, chemotherapy, radiotherapy, surgery, and recently immunotherapy have intensified the cancer treatment. All these approaches have been linked with serious side-effects ranging from recurrence, loss of immunity, and reduced quality of patients life[2].

There is a high need to find better alternative therapies which can promote the host immune system to fight cancer. Complementary and alternative medicine is one among such therapy based on plant-derived, including algae and mushrooms. Mushrooms are the macro fungi, which can be either hypogenous or epigeous constituting 22 000 known species[3].

Enriched bio-sources of β-glucan, proteoglycan, lectin, phenolic compounds, flavonoids, polysaccharides, triterpenoids, dietary fibre, lentinan, schizophyllan, lovastatin, pleuran, steroids, glycopeptides, terpenes, saponins, xanthones, coumarins, alkaloid, kinon, fenil propanoic, kalvasin, porisin, AHCC, maitake D-fraction, ribonucleases and eryngeolysin helps in modulating immune system to fight tumors by a) augmenting the immune system through stimulating lymphocytes, NK cells, and macrophages, enhancing cytokine production; b) inhibiting proliferation of cancer cells; c) promoting apoptosis; and d) blocking angiogenesis[3-6].

Mushrooms have been used widely in traditional medicine for curing diseases such as microbial infections, cancer, inflammation, cardiovascular diseases, *etc*. The new lectin with highly potent antihepatoma and antisarcoma activities has been isolated from the oyster mushroom *Pleurotus ostreatus*[7]. The cancer is a multiple genes involved disease, current research on the discovery of novel phyto- molecules having multiple targeting action against cancer[8,9]. This discovery of new molecules is possible only from natural sources like plant, algae and mushroom sources. Hence this review focuses on the multitargeting novel anticancer molecules and their mechanism of action.

2. Anticancer primary metabolites

2.1. Anticancer polysaccharides from mushrooms

Mushrooms are the neglected phytochemical treasures have been reported for their anticancer primary metabolites, known as polysaccharides[10]. Mushroom polysaccharides are biological response modifiers supporting the major systems of the body, including nervous, hormonal and immune systems as well as regulatory functions. The polysaccharides from mushrooms do not attack cancer cells directly but produce their anti-tumor effects by activating a different immune response in the host[11].

According to the primary scientific study by Ikekawa *et al*., 1 969 mushrooms belonging to the family Polyporaceae (Aphyllophoromycetideae) was active against Sarcoma 180 in animals[12-14]. Later β-glucans: krestin from cultured mycelial biomass of *Trametes versicolor*, lentinan from fruiting bodies of *Lentinus edode*s, and schizophyllan from the liquid cultured broth product of *Schizophyllum* commune was developed. Polysaccharides extracted from *Pleurotus ostreatus* mycelium, and an isolated compound POMP2 inhibited the proliferation of BGC 823 human gastric cancer cell line *in vitro*/*in vivo*[15]. Aqueous polysaccharide POPS-1 of fruiting bodies of *Pleurotus ostreatus* inhibited the growth of Hela tumor cell and human embryo kidney 293T cells *in vitro*[16].

The low molecular weight polysaccharides from the water extracts of *Agaricus blazei* Murill fruiting bodies suppressed tumor growth and angiogenesis in *in vivo*[17].

The common polysaccharide available in many mushrooms is beta-1,3-glucan and commercialised as an intravenous injection known as asgrifolan[18-20]. The beta glucans are present in the important medicinal mushrooms like *Hericium erinaceus*[21] *Pleurotusos treatus* (Vannucci *et al*., 2013), *Agaricus blazei*, *Grifola frondosa*, *Tremella fuciformis*.

The other multiple targeting anticancer polysaccharide is lentinan reported from *Lentinus edode*[22]. These mushroom glucans were gained global recognition for their potent anticancer activity[23] due to multiple targeting mechanisms like promotion of phagocytosis, proliferation of dendritic cells[24], promotion of caspase 9 & 3 expressions, inhibition of Bcl-2 expression[25], human topoisomerases[26], and increase in cytokines, interleukins and interferons *etc*.[27,28]. The mushroom glucans gained the pharmaceutical importance as an important commercial dietary supplement in boosting of immunity against cancer[29].

2.2. Anticancer proteins from mushrooms

Certain multiple targeting anticancer proteins like Lecitins, Hemolysin and Laccases have been reported from the mushrooms like *Trametes versicolor*, *Pholiota adiposa*, *Russula lepida*, *Tricholoma mongolicum* & *Hericium coralloides*[30].

The lecitins are proteins that bind to the carbohydrates easily and recently they became the compound of interest to many researchers due to its multiple mechanisms of action like ribosome inactivation in rRNA, carbohydrate receptors binding on human leukemic T cells[31], and DNA caspase 3 & 9 promotion activity[32].

Even these lecitins are also available from plants like soyabeans and sunflowers. They have been gained importance and became anticancer molecules of interest, however, in depth clinical research on these molecules is further needed.

The mushroom hemolysins were not explored in depth in comparison to fungal hemolysins. Eryngeolysin was isolated from the mushroom fruiting bodies of *Pleurotus eryngii*, aegerolysin isolated from the *Agrocybe cylindracea*, and ostreolysin from *Pleurotus ostreatus*.

However, in-depth research is still pending on the anticancer property of these lysin proteins in the sense of multitargeting anticancer activity[32,33]. Cibacron blue affinity- purified protein from *Pleurotus ostreatus* was active on Dalton lymphoma-bearing mice, Sarcoma-180, and B16F0 melanoma tumor-bearing mice[34].

3. Anticancer fatty acids from mushrooms

A number of fatty acids and their derivatives have been reported as a promising anticancer agents[35,36]. Even though many fatty acids and fats were reported from mushrooms, no extensive research was carried out on these moieties towards anticancer activity; hence the present review is representing various new fatty acids identified from mushrooms.

3-hydroxy-2,4-dimethylheptacosyl acetate was isolated first time from the *Rhizopogon luteolus*. However, studies were restricted only to anticholinesterase activity and no attempt were made towards anticancer activity[37]. Linolenic acid and linolenic acid present in the *Agaricus bisporus* extract inhibits aromatase activity by modifying or mutating active cell sites.

Three oxylipids *viz*., 2R-hydroxy -9Z,12Z- octadecadienoic acid, 8R-hydroxy-9Z,12Z-octadecadienoicacid and 8R,11S-dihydroxy-9Z,12Z-octadecadienoic acid were first time produced by *Agaricus bisporus*.

However, pharmacological properties of these compounds were still pending and there is a wide scope for the researchers to work on these mushrooms to trace out more novel fatty acids as an anticancer novel leads. Linolenic acid is a widely distributed fatty acid in various varieties of mushroom- like *Agaricus bisporus*, *Agaricus campestris*, *Boletus edulis*, *Coprinus comatus*, *Pleurotus ostreatus*, *Oudemansiella radicata* and *Armillaria mellea*[37].

The linolenic acids have been reported for their antiproliferative action using multiple mechanisms like increase in Prostaglandin E1, also reduces proinflammatory IL-1 and tumor necrosis factor-α useful in the inhibition of cancer cell growth[38]. Some of our in-silico research showed that the methyl gamma linoleate showed human topoisomerase Ⅰ & Ⅱ inhibition activity. However, in-depth studies are required to prove its topo-inhibition activity.

4. Anticancer secondary metabolites

4.1. Anticancer alkaloids from mushrooms

Alkaloids are the secondary metabolites gained importance due to their potent anticancer properties, and the discovery of newer anticancer alkaloids became an important area of research. Even though current research is showing that mushrooms are an excellent bio generators of alkaloids, the studies were limited and few indole alkaloids like bisnoryangonin, hispidin, baeocystin, norbaeocystin, bufotenin, aeruginascin psilocin and psilocybin were identified in magical mushrooms genus like *Agrocybe*, *Amanita*, *Conocybe*, *Galerina*, *Gymnopilus*, *Hypholoma*, *Inocybe*, *Panaeolus*, *Psilocybe*, *Pholiotina*, *Pluteus*, and *Weraroa*[39,40]. Psilocybin have been proved to reduce anxiety, improve the mood, and reduce anxiety in cancer patients[41]. However, no attempts have been made on the anticancer activity of these alkaloids to study in depth. There is a wide area to carry out research on multiple targeting anticancer action of these moieties, as the entire globe is looking for novel multi -targeting anticancer compounds.

4.2. Anticancer triterpenes from mushrooms

Terpenes are a large group of secondary metabolites widely distributed in the plant and animal kingdom. There are novel anticancer terpenoids reported from certain mushrooms like *Inonotus obliquus*. Terpenoid anticancer metabolites like 3b-hydroxy-8,24-dien-21-al, ergosterol, trametenolic acid and inotodiol were identified[42].

Some triterpenoid fractions were from *Ganoderma lucidum*, which are a class of highly oxidised lanostanes, and ganoteric acids were isolated from these species claimed to have broad- spectrum anticancer activity[43,44].

5. Anticancer glycosides from mushrooms

Even though, the phytochemical reports claim that certain species of *Agaricus* have glycosides in the form of terpenoid, flavonoid and alkaloids. However, till date, there are no documentary evidence on the mushroom glycosides as anticancer agents or no single glycoside has been isolated from these mushrooms. Hence there is a wide scope for natural product researchers to focus on this area[45].

6. Anticancer saponins from mushrooms

Even though saponins are gaining their importance in anti cancer research, fewer attempts were made to discover new saponin leads from these mushrooms. The species like *Pleurotus florida* documented for their saponins presence in qualitative analysis. However, there is a wide scope to focus on these mushroom saponins for their anticancer activity and also to discover new saponin leads[46]. Not even single multitargeting anticancer saponin has been reported till date.

7. Anticancer steroids from mushrooms

Ergosterol peroxide is the steroid, which has been identified in mushroom genus like *Plerurotus*, *Lentinula*, *Agaricus* and *Flammulina*[47]. This ergosterol peroxide is a multitargeting anticancer drug lead inhibits ovarian cancer by following multiple mechanisms like promoting β-catenin and STAT3 signaling pathways and inhibiting or reducing Cyclin D1 and c-Myc expression levels[48]. Water extracts of *Agaricus blazei* Murill that contain ergosterol is capable of inducing apoptosis in leukemia cells and inhibit tumor-induced angiogenesis[49].

Table 1. Anticancer drug leads from mushrooms.

No.	Anticancer drug leads	Sources	Mechanism of action	References
1.	Beta-1,3-glucan and lentinan	*Hericium erinaceus*, *Pleurotus ostreatus*, *Agaricus blazei*, *Grifola frondosa*, *Tremella fuciformis* Lentinusedode	Promotion of phagocytosis, proliferation of dendritic cells, promotion of caspase 9 & 3 expressions, inhibition of Bcl-2 expression, human topoisomerases, increase in cytokines, interleukins and interferons	[28,29]
2.	Lecitins, Laccases	*Trametes versicolor*, *Pholiota adiposa*, *Russula lepida*, *Tricholoma mongolicum* & *Hericium coralloides*	Ribosome inactivation in rRNA, carbohydrate receptors binding on human leukemic T cells	[27,28]
3.	Eryngeolysin, Ostreolysin	*Pleurotus eryngii*, aegerolysin isolated from the *Agrocybe cylindracea*, *Pleurotus ostreatus*	Unknown	[32]
4.	3-hydroxy-2,4-dimethylheptacosyl acetate	*Rhizopogon luteolus*	Unknown	[37]
5.	8R-hydroxy-9Z,12Z-octadecadienoic acid and 8R,11S-dihydroxy-9Z,12Z-octadecadienoic acid	*Agaricus bisporus*	Unknown	[37]
6.	Linolenic acid	*Agaricus bisporus*, *Agaricus campestris*, *Boletus edulis*, *Coprinus comatus*, *Pleurotus ostreatus*, *Oudemansiella radicata* and *Armillaria mellea*	Antiproliferative action using multiple mechanisms like increase in Prostaglandin E1, also reduces proinflammatory interleukin-1 and tumor necrosis factor-alpha production useful in the inhibition of cancer cell growth	[39]
7.	Alkaloids (bisnoryangonin, hispidin, baeocystin, norbaeocystin, bufotenin, aeruginascin psilocin and psilocybin)	*Agrocybe*, *Amanita*, *Conocybe*, *Galerina*, *Gymnopilus*, *Hypholoma*, *Inocybe*, *Panaeolus*, *Psilocybe*, *Pholiotina*, *Pluteus*, and *Weraroa*	Unknown	[40]
8.	Terpenoids (3b-hydroxy-8,24-dien-21-al, ergosterol, trametenolic acid , inotodiol , lanostanes and ganoteric acids	*Inonotus obliquus*, *Ganoderma lucidum*	Unknown	[42]
9.	Ergosterol peroxide	*Plerurotus*, *Lentinula*, *Agaricus* and *Flammulina*	β-catenin and STAT3 signaling pathways and inhibiting or reducing Cyclin D1 and c-Myc expression levels	[53]
10.	Hispidin	*Gymnopilus marginatus* and *Ionotus hispidus*	inhibition of PKβ receptors	[51,52]

8. Anticancer phenolics from mushrooms

Mushrooms also consist of phenolic compounds, but only a few catechols have been isolated from these mushrooms; still there is a wide scope to do research on discovery multiple targeting anticancer phenol drug leads[50]. Hispidin is a common catechol present or identified in wild mushrooms like *Gymnopilus marginatus* and *Ionotus hispidus* which inhibits cancer by inhibition of PKβ receptors[51,52].

The progression of resistant cancer is due to unsolved genetic and epigenetic mechanisms. In an alternative to dangerous chemotherapy, there is an urgent need for new drug leads with multiple targeting action that can cause apoptosis (programmed cell death) and are in high demand due to the cancer resistance and high mortality rate during chemotherapy.

All these agents failed to treat cancer due to lack of multitarget action. As cancer is multiple genes involved disease, the pharmaceutical industries are in hunger towards novel single molecule that having multiple targeting action against cancer. The current trend is the discovery of single molecule that targets dual or multi- targeting agents and this may be highly possible from phytochemically unexplored or less explored wild mushrooms.

There is a high demand for new anticancer molecules having multitarget anticancer action and the pharma dragons are showing high interest towards new anticancer molecules that having multiple targeting action and to be safe on normal cell lines. However, getting new drug leads with multiple targeting action is highly challenging and possible only from unexplored wild natural resources. Hence this review is laying a platform towards the discovery of new anticancer drug leads from the phytochemically less explored mushroom genus. The important drug leads discovered from these mushrooms were represented in Table 1.

Mushrooms are widely distributed in and around the different parts of India that grows wildly in damp areas; the recent research revealed that there are many mushrooms having medicinal values yet are very less explored phytochemically. Only a few literatures is available that these mushroom extracts have chemopreventive properties and there is no evidence to prove the multitargeting action of drug leads isolated from these mushrooms.

Multitargeting is the current area of interest in cancer treatment; hence the current research is focused on the anticancer drug discovery of multiple targeting drug leads from the selected mushrooms. From time immemorial, mushrooms have been valued by humankind as a culinary wonder and folk medicine in oriental practice.

The last decade has witnessed the overwhelming interest of western research fraternity in the pharmaceutical potential of mushrooms. The chief medicinal uses of mushrooms discovered so far are as anti-oxidant, anti-diabetic, hypocholesterolemic, anti-tumor, anti-cancer, immunomodulatory, anti-allergic, nephroprotective, and anti-microbial agents. The mushrooms credited with success against cancer belong to the genus *Phellinus*, *Pleurotus*, *Agaricus*,

Ganoderma, *Clitocybe*, *Antrodia*, *Trametes*, *Cordyceps*, *Xerocomus*, *Calvatia*, *Schizophyllum*, *Flammulina*, *Suillus*, *Inonotus*, *Inocybe*, *Funlia*, *Lactarius*, *Albatrellus*, *Russula* and *Fomes*.

Topoisomerase inhibitors elicit their effect *via* enzyme-mediated DNA damage, and eventually result in cancer cell death. Dual topo drugging is an important phenomenon in cancer treatment and many synthetic drugs have been developed and used in clinical trials as topopoisons.

However, there are many associated challenges such as resistance which have reduced their success rate. Hence, there is a current demand for the discovery of new human topopoisons, particularly, dual topopoisons Ⅰ & Ⅱ as a means of achieving the simultaneous blockage of both targets. Caspases are also crucial mediators of programmed cell death (apoptosis).

Among them, caspase-3 is a frequently activated death protease, catalysing the specific cleavage of many key cellular proteins. Thus caspase activators also required for causing apoptosis in most cancers. Currently, multiple targeting has gained grounds in cancer therapy.

5. Conclusions

This review explains the urgency in discovery of new multitargeting drug molecules against cancer. The importance of wild mushrooms in this area is highly significant, and hence this article focuses on the anticancer research that has been carried out on these mushrooms as sources for discovery of new multitargeting leads.

Even though the research was started on these mushrooms, there is a wide scope for the researchers to explore new multitargeting drug leads from these wild and marine mushrooms. This research team is working hard towards the drug discovery of multitargeting cancer agents using high throughput techniques and applying towards various funding agencies and also looking for collaborators to lead.

Conflict of interest statement

We declare that we have no conflict of interest.

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Authors' contributions

MVNLC designed the concept, AJ drafted the graphical abstract, PR drafted the conclusion, SCM proof read the manuscript and PN edited and checked the plagiarism.

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