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Review

Pharmacological and therapeutic inventory of fungi in cancertherapy—A comprehensive review

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Abstract: Cancer remains one of the foremost causes of death worldwide. Despite advancements in pharmaceutical therapies, patients continue to experience adverse effects. Consequently, there is a considerable interest in exploring mushrooms as a supplemental cancer treatment. In Asian countries, edible and medicinal mushrooms have long been consumed in both culinary practices and herbal remedies. Their health and nutritional benefits have also garnered rising attention in Europe. Food-grade mushrooms have a variety of pharmacological properties, including soothing and immunomodulating effects, and are associated with abundant therapeutic benefits. The primary mechanisms behind their anticancer activity comprise immune system improvement, cell cycle arrest, regulation of apoptosis, prevention of metastasis, and inhibition of cancer cell growth. Here, we thoroughly review the anticancer activities of several culinary and medicinal mushrooms, as well as some endophytic fungi, with a particular focus on potential bioactive compounds and their molecular mechanisms.

Keywords: anticancer compound; antitumor; endophytic fungi; cytotoxicity; immunomodulatory; mushroom; nutraceuticals; secondary metabolites

1. Introduction

1.1. Mushrooms as a dietary component and traditional medicine

Historically, conventional medical treatment and gastronomy have made use of mushrooms and their resultant extracts due to their small calorific content, wonderful flavor, and possible biological advantages. As a result, they are increasingly utilized in pharmacological and naturopathic goods [1]. Since they are a classic food and provide health advantages, mushrooms are ingested largely in India, China, and Japan, as well as the Asian subcontinent [2]. Some historic traditional medical systems, including conventional Chinese medicine, Korean Hanyak, customary Japanese medicine (Kampo) and Indian Ayurveda, have documented using them in folk medicine [3]. Numerous kinds of bioactive substances, including micronutrients, vitamins, minerals, polyphenols, complex sugars, alkaloids, and steroids, are found in the mushrooms [4,5]. A great deal of these substances is in charge of mushrooms' biological action, inevitably classified as designer foods or functional foods [1,6]. Because they are hypocaloric, mushrooms have a reduced lipid content (2–6% as a dry mass). The effectiveness of mushrooms and related secondary substances in medications and nutritional supplements has gained more attention in recent years, especially during the COVID-19 pandemic [7]. Many ingredients from mushrooms have the ability to treat various diseases and restore cellular balance. Furthermore, mushrooms are an excellent provider of vitamins, mineral content (notably phosphorus, magnesium, calcium and potassium), and important amino acids (involving leucine, tryptophan, valine and phenylalanine). Vitamins include tocopherols, thiamine, cobalamin etc. Since plant-based nutrients are frequently lacking in the diets of kids, grown-ups, and elderly individuals, this nutrient composition is valuable and appropriate for their needs [8–10].

Many diverse civilizations have historically employed a variety of mushrooms to maintain health as well as to avoid or alleviate a wide range of ailments. It is speculated that medicinal fungi and mushrooms produce 126 different medicinal functions, such as immunomodulating, antitumor, antioxidant, immunomodulating, radical scavenging, antioxidant, anti-hypercholesterolemia, cardiovascular, detoxification, hepatoprotective, antiviral, and antibacterial effects. Particular focus is placed on polysaccharides found in mushrooms [11].

According to recent research, several varieties of mushrooms offer strong anticancer qualities, which might make them an additional treatment option for cancer sufferers. Long linked to several health advantages, culinary mushrooms also seem to lower the likelihood of cancer [12]. Research on the ingestion of mushrooms and preparations derived from them have suggested a link between consumption of mushrooms and a decreased risk of developing malignancy and a greater likelihood of survival [12].

1.*2. Overview of cancer and its prevalence*

Despite its complexity and diversity, cancer is nevertheless one of the world's top causes of death. Cancer is distinguished by the unchecked proliferation of aberrant cells, which may influence almost any body organ and cause various manifestations and health issues. Millions of more cases of cancer are identified worldwide each year despite tremendous advancements when it comes to research and therapy. Cancer imbalances spanning HDI (Human Development Index), area, age, and sex have been demonstrated in 2022. They are expected to increase by 2050, according to this

cross-sectional analysis of data for 36 varieties of cancer covering 185 nations and regions. In 2050, it is anticipated that the number of malignancy instances and fatalities will rise by 77 per cent and 90 per cent, respectively, with low-HDI nations experiencing a threefold increase. Extremely high-HDI nations experiencing a small increase (142 per cent vs. 42 per cent for cancer cases and 146 per cent vs. 57 per cent for carcinoma deaths) [13]. According to the American Cancer Society's 2024 updates to Cancer statistical data, more than 2 million Americans will receive a cancer diagnosis this year. This is the first instance of the incidence surpassing two million [14]. Considering a prevalence of 2,308,897 incidents and a fatality rate of 665,684 participants, breast carcinoma is the most widespread type of cancer worldwide, according to GLOBOCAN's 2022 estimate [15]. With 33 per cent of instances occurring in the cerebellum, it is also the second most prevalent root of victims' brain metastases [16]. The proportion of people in extremely high HDI locations who experienced a diagnosis with cancer during the last five years in 2008 was much greater than that of people living in low HDI (a nearly seven times difference) and moderate HDI (a five-fold difference) regions [17].

The urgent need for new and efficient therapies for this serious health issue has led to a thorough investigation of natural remedies like mushrooms. Mushrooms, which are well-renowned for their wide variety of bioactive substances, have recently garnered great interest due to their possible anticancer qualities, which present exciting opportunities for prevention and treatment.

1.3. Importance of exploring natural sources for anticancer agents

The WHO projects that almost 80 per cent of African and Asian nations get their basic medical treatment from ancestral remedies. According to esoteric research, almost 60% of those diagnosed with cancer employ vitamins or herbal remedies as part of their treatment.

Most cancer treatments now in use are ineffective. Many adverse effects are associated with contemporary cancer therapies, such as radiation and chemotherapy, and tolerance to these treatments may eventually arise. Chemotherapeutic medications act on cancerous and healthy cells at the same time. Chemotherapy-treated cancer sufferers have hair loss and bone marrow destruction, which can result in aplastic anemia [18]. Radiation therapy patients have a variety of adverse effects, such as neutropenia, thrombocytopenia, and lymphopenia [19,20]. Damage from radiation to bone marrow stem cells might be teratogenic to the developing fetus [21]. Furthermore, radiation damages DNA and results in cell demise and apoptosis [21]. Finding novel cancer treatment strategies is therefore urgently needed.

Natural resources offer a viable source that is highly effective in treating and curing a number of illnesses, notably cancer. Bioactive ingredients and herbal remedies have emerged as a significant source of anticancer medications in the last several years when approached with a cooperative, integrative, and interdisciplinary strategy [22]. Over half of today's therapeutic medications come from natural sources and can cure cancerous cells [22]. Thus, the goal of conducting extensive research is to identify more potent therapies with the fewest possible side effects. Yet, because many chemotherapy medications do not selectively target cancer cells, their treatment range is limited. The creation of secure and efficient medications that can specifically destroy aggressive carcinoma cells or transform them into benign cancer cells, avoiding destroying healthy cells, is the principal goal of cancer therapy [23].

1.4. Introduction to the rising interest in mushrooms/fungi for their potential anticancer properties

Mushroom polysaccharides are referred to as "biological response modifiers". In addition to their many biological properties, their capacity to modulate the gut flora has sparked attention to their preventative capabilities [24]. The medicinally beneficial elements of mushrooms that have been investigated the most include triterpenes, lectins, fungal immune-modulating peptides, polysaccharides (especially beta-glucans), and polysaccharide-protein clusters. In addition, mushrooms provide organic biological barriers for use in agriculture, flavoring compounds for application in eateries, and ingredients with cosmetic qualities (cosmeceuticals). The biological processes that fungi employ to break down the lignin part of cultivation systems may additionally break down a variety of stubborn anthropogenic substances that contaminate our surroundings, such as insecticides, munitions, polychlorinated biphenyls, polybrominated diphenyl ethers, artificial colors, and polycyclic aromatic hydrocarbons [25]. The need for unconventional therapeutic tactics has been brought to light in recent years due to the negative consequences of traditional therapy and the inadequate outcomes of using standard medical procedures [26,27]. In addition to being potential sources of novel nutraceuticals, consumable and therapeutic mushrooms have shown promise as an additive to traditional chemo- or radiation treatment, either increasing the efficacy of the treatments or lowering their negative consequences and ultimately boosting the patient's overall quality of life [28].

2. Classification and pharmacological activity of anticancer compounds derived from mushroom/Fungi

Numerous valuable bioactive compounds exhibiting antimicrobial, plant growth regulatory, insecticidal, cytotoxic, and anticancer properties have been effectively identified from mushrooms or fungi over the last twenty years, which have been determined to be beneficial for humankind. The bioactive compounds of mushrooms/fungi having anticancer activities have been listed in Table S1. These compounds encompass quinones, lignans, lactones, alkaloids, terpenoids, steroids, and phenols [64,65].

2.1. Alkaloids

A: Camptothecin

Endophytic fungi produce camptothecin, a potent anticancer drug originally found in plants, making them medicinal sources akin to their hosts. Isolation of endophytic fungi has been conducted from *Camptotheca acuminata*, aium-sized deciduous tree inhabiting in Southern China [66], and their potential for tumor cell inhibition was evaluated [67]. The total number of numerous endophytic fungi has been identified from different *C. acuminata* plants were 94, and the resultant fungal members were classified into different genera using partial ITS sequencing. The most active members belonged to several genera like *Fusarium* sp., *Alternaria* sp., *Pestalotiopsis* sp., and *Cephalosporium* sp. Moreover, cytotoxic activity against Vero cells and/or PC3 cells was exhibited by 16 of 94 members [67].

B: Vincristine and Vinblastine

These are popularly recognized anticancer drugs derived from periwinkle plants, i.e., *Catharanthus roseus* G. Don [68]. Vinblastine, a dimeric indole alkaloid, is created through the pairing of catharanthine and vindoline, a reaction catalyzed by the enzyme horseradish peroxidase [69]. This compound is further transformed into vincristine via the oxidation of its methyl group. Many crucial enzymes that are engaged in indole alkaloids' biosynthesis have been identified from seedlings and/or cultures of *Catharanthus roseus* cells in suspension [70]. By attaching to microtubules, these alkaloids obstruct the formation of the spindle apparatus during the metaphase stage, thereby impeding the cell cycle progression [71]. Elicitors, whether biological or chemical, are increasingly being utilized to enhance the production of secondary metabolites, as they induce defensive responses, physiological alterations, and phytoalexin accumulation. Examples include proteins, glycoproteins, polysaccharides, and fragments of cell walls derived from microbes (chitin and glucan), plants (cellulose and pectin), and fungi [72].

C: Ergot alkaloids

Ergot alkaloids originate from the fungus *Claviceps purpurea* of the phylum Ascomycota, having psychoactive and vasoconstriction properties, historically associated with poisons from the Middle Ages, like ergotism (known as St. Anthony’s Fire) is additionally recognized to prevent the formation of tumors both *in vitro* and *in vivo* [73]. They are generated by a number of fungi belonging to two distinct orders. Fungi in the Clavicipitaceae (order Hypocreales), including various *Claviceps* species [74], as well as some *Epichloe* and *Neotyphodium* species living as endophytic symbionts in grasses, produce ergot alkaloids. Additionally, *Aspergillus fumigatus* and various *Penicillium* species, having close relatives of Eurotiales, have been reported to produce ergot alkaloids [75]. The mechanism of cytotoxic behavior of ergot alkaloids does not adhere to the traditional drug resistance mechanisms, thereby offering the ability to go around opposition and treat tumors that are otherwise resistant to conventional drugs and refractory. Studies show that one of the reasons a membrane efflux transporter protein is at the root of multidrug resistance called P-glycoprotein/MDR1, which expels a range of chemically and functionally diversified drugs from the cancer cells. However, Mrusek et al. (2015) have found that IC50 values of ergot alkaloids did not show any correlation with Transcription of the MDR1 gene or P-glycoprotein action, which suggests ergot alkaloids may avoid multidrug resistance in cancer cells by not being affected by the P-glycoprotein efflux pump. Additionally, they can surge intracellular levels of standard anticancer agents and improve cancer cell-killing rates by inhibiting P-glycoprotein's efflux function [73].

D: Indole alkaloids

Indole alkaloids include a broad class of secondary metabolites and are abundant in the natural world, exhibiting diverse biological properties and structural diversity. They are also used as adjuvants [44,76]. Indole diketopiperazine alkaloids are frequently isolated from fungi, particularly species of *Penicillium*, *Aspergillus*, *Chromocleista* and *Pestalotiopsis*. They are especially abundant in the genera *Aspergillus* and *Penicillium*. In a study conducted by Peng et. al. (2019), two new indole alkaloids, namely chetoseminudin F and chetoseminudin G, were isolated, along with eleven

identified substances derived from *Chaetomium globosum*. Among those Chetoseminudin G showed stronger cytotoxicity (IC50 = 26.49 μmol L−1) than paclitaxel (considered as a common chemotherapeutic drug) against MDA-MB-231 cells. Additionally, four other compounds also exhibited strong cytotoxicity (IC50 = 2.75–8.68 μmol per L) in opposition to MDA-MB-231 and A549 cell lines [77].

E: Stephacidin A

Two naturally occurring substances categorized as prenylated indole alkaloids are stephacidin and notoamide that features a core bicyclo[2.2.2]diazaoctane ring system and were obtained from an *Aspergillus* species derived from marine environments. The compounds have earned growing attention due to their several biological actions, including antitumor, insecticidal, calmodulin inhibitory, anthelmintic, and antibacterial properties and unique structural features [78]. Another alkaloid called Stephacidin B, isolated from *Aspergillus ochraceus* WC76466, has been shown to exhibit strong and focused antitumor action, especially targeting LNCaP cells that are reliant on testosterone, with an IC50 value of 60 nM.

F: Verticillin A

Chemically, verticillin belongs to epipolythiodioxopiperazine alkaloids, primarily found as dimers that contain both diketopiperazine elements and disulfide linkages. These secondary metabolites are commonly obtained from terrene and oceanic fungi with filaments, including *Verticillium* sp., *Gliocladium* sp. and *Penicillium* sp., which are the members of Sordariomycetes and Eurotiomycetes classes [79]. Verticillin A was the first analogue invented in 1970, and since then, 27 verticillin cognate compounds have been described in the literature. Verticillin A has been shown to sensitize the phenomenon of apoptosis Inside human intestinal cells brought on by factor-associated suicide (FAS) or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) at nanomolar concentrations *in vitro* [45]. Liu et al. identified Verticillin A as a compound that induces apoptosis in hepatoma and suppresses the development of tumor xenografts *in vivo* and *in vitro*, which shows its potential effectiveness to be utilized as an adjuvant in order to defeat the pharmacological resistance in cancer chemotherapy.

2.2. Peptides

A: Leucinostatin A

An oligopeptide, named Leucinostatin A, possessing phytotoxic, anticancer, and antifungal attributes, has been taken from the culture of *Acremonium* sp., a fungal endophyte residing within *Taxus baccata*. This is a mycotoxin which induces necrotic symptoms in numerous non-host plants, likely due to their inability to convert it into the considerably less harmful leucinostatin α,β-di-*o*-glucoside, whereas the host plant *T. baccata* is capable of that [80].

B: L-Asparaginase

The enzyme L-Asparaginase plays a crucial role in cancer treatment by depleting L-asparagine in the serum, thereby keeping out large amounts of asparagine needed for the growth of the tumor cells, effectively controlling tumor growth. The purified L-asparaginase exhibited anticancer activity against HCT-116, Hep-G2, and MCF-7 cell lines, with IC50 values ranging from 3.79 to 12.6 μg/mL [81,82].

C: Aureobasidin A

It is an antifungal antibiotic which has been found to constrain in yeast and mammalian cells. ATP-binding cassette (ABC) transporters are present and particularly affect a transmembrane phospholipid flippase, the 170-kDa membrane protein MDR1 P-glycoprotein (Pgp), which is in charge of mediating multidrug resistance (MDR) in cancer cells [50].

2.3. Terpenoids

A: Paclitaxel

A widely recognized and very functionalized tetracyclic diterpenoid bioactive compound called Paclitaxel (also known as taxol) was first discovered in 1971 from the bark of *Taxus brevifolia* [65]. Its distinct method of action has been shown to be particularly effective against lung, breast, ovarian, and prostate malignancies. Paclitaxel binds directly to β-tubulin, preventing it from depolymerizing during the processes involved in cell division [83]. Obtaining 1 kg of paclitaxel requires about 10,000 kg of *Taxus* bark, leading to the felling of numerous trees. To address the scarcity and ecological concerns, scientists sought alternative sources. Stierle et al. identified an endophytic fungus, *Taxomyces andreanae*, within *Taxus brevifolia*, which can produce paclitaxel.

B: Cordycepin

Nakamura et al., in their *in vitro* studies, found that Cordycepin pronouncedly inhibited the growth of B16-BL6 cells and LLC cells with an IC50 value of 39 μM and 48 μM, respectively. Cordycepin is observed to achieve this by directly inducing cytotoxicity in Mice with lung cancer and cells with melanoma through the excitation of adenosine A3 receptors, which further highlights cordycepin's role as a potent active ingredient in water extracts of *Cordyceps sinensis* (utilized as a highly esteemed traditional Chinese medicine). Cordycepin not only triggers cell death by exhibiting proapoptotic and anti-proliferative effects but also hampers the outspread of the cancer cells [84]. It significantly inhibits the functionality of matrix metalloproteinase MMP-9 and MMP-2 while simultaneously increasing the activity of inhibitors (TIMP-1 and TIMP-2), thereby resulting in the obstruction of platelet clumping and intrusiveness of melanoma cancer cells *in vitro* [85]. Cordycepin can also achieve similar inhibitory effects by reducing MMP-9 activity in human lung [86] and breast cancer cells. Additionally, TNBC MDA-MB-231 and MCF7 human breast cancer cells have demonstrated cytotoxic behavior in response to *C. sinensis* isolates. The creation of ROS, impairment of mitochondrial activity, and cellular discharge of lactate dehydrogenase were the major causes of this impact. The cordycepin tumor-suppressive action was additionally facilitated by DNA

damage, autophagy and targeting cancerous embryonic stem cells [87].

C: Ganoderic acids

Ganoderic acid, a triterpene found in polypore fungi, aims to promote apoptosis through both intracellular and extracellular pathways by modulating adaptor molecules and proteins involved in cancer signaling. Jiang et al. highlighted the effectiveness of varied isoforms of Ganoderic acid, such as GA-A and GA-H, in the treatment of breast cancer as these isoforms repress cell multiplication, metastasis, and adhesionby the downregulation of Cdk4 and the urokinase-type plasminogen activator resulting in less AP-1 and NF-κB nuclear transcription factor activation. GA-A isoform has been found to target STAT3, leading to the inhibition of cell proliferation, viability, and ROS levels according to the dosage in PC-3 cells. It also targets Wnt protein, influencing cell proliferation, viability, and ROS levels in pancreatic cancer cells in adose-dependent way. Whereas another isoform, GA-X, targets apoptosis through the mitochondrial pathway, involving topoisomerases, JNK, ERK, and mitogen-activated protein kinases (MAPKs), as well as bcl-xL leading to the release of cytochrome c. Several other isoforms have also been investigated to have prominent potential in the promotion of apoptosis [88,89,90].

D: Pleuromutilin

Pleuromutilin, a diterpene antibiotic, targets ribosomes and is derived from basidiomycete fungi like *Clitopilus pseudo-pinsitus* and various other fungi [91].

2.4. Phenolics

A: Podophyllotoxin

A compound categorized as lignan, produced by some fungal members like *Fusarium oxysporum* of Nectriaceae, *Trametes hirsuta* of Polyporaceae, *Fusarium solani* of Nectriaceae, *Aspergillus fumigatus* of Trichocomaceae, *Sinopodophyllum hexandrum*, and *Dysosmaveitchii* has proved to have anticancer activity. The precursors of podophyllotoxin have shown to have promising effects in targeting early metastatic cells and are widely utilized in the treatment of various cancers, including leukemia, testicular, prostate, lung, and ovarian cancer [92,93].

B: Resveratrol

Another phenolic compound, having the potential to slow down or prevent the incidence of many diseases has found to be produced from several endophytes of *Vitis vinifera* L., *Vitis quinquangularis* Rehd and *Polygonum cuspidatum* Siebold & Zucc. Isolates capable of producing resveratrol have been identified across seven genera, including *Alternaria, Penicillium, Mucor, Cephalosporium, Botryosphaeria, Aspergillus*, and *Geotrichum* [94]. *Alternaria* sp. MG1, screened from Merlot cob in GA1 medium, exhibited consistent and elevated resveratrol production in subculturings.

2.5. Polyketides

A: Fumagillin

Fumagillin, derived from the fungus *Aspergillus fumigatus*, is a meroterpenoid formed by the condensation between fumagillol's hydroxy group and (all-E)-deca-2,4,6,8-tetraenedioic acid's carboxylic acid group and is used to treat *Nosema* infection in honey bees. In brief, it needs two components to be synthesized: A sesquiterpene with high oxygen content and a polyketide-derived tetraenoic diacid. Interestingly, Fumagillin and its analogues are utilized in cancer treatment to inhibit angiogenesis, thus restricting the blood supply. The concept of treating cancer tumors by impeding angiogenesis was initially introduced in 1985. The explicit mechanism of fumagillin binding to the MetAP-2 (methionine aminopeptidase type 2) enzyme was elucidated through the crystallization of MetAP-2 with fumagillin [95,96].

B: Lovastatin

Lovastatin, an active secondary metabolite naturally found in fungi, primarily aggregates in fungal hyphae and was first isolated from *Monascus* in 1979, subsequently isolated from *Aspergillus terreus*. Because studies demonstrate that lovastatin can suppress multiplication and trigger apoptosis in a variety of cancer types, it has great promise for treating cancer cell types, including breast, colon, liver and cervical cancers. Furthermore, combining lovastatin with other chemotherapeutic agents can help reduce drug resistance in cancer cells, enhancing overall treatment efficacy [97,98].

C: Radicicol

Radicicol, a macrocyclic antifungal antibiotic, is the lead compound for a class of Hsp90 inhibitors and was initially described as an inhibitor of tyrosine kinase. These compounds inhibit or degrade Hsp90-associated proteins like v-src and Raf-1 kinases, which obstruct the downstream signal transduction pathway. One derivative, O-(Piperidinocarbonyl) methyloxime, showed potent antiproliferative and v-src kinase inhibitory activity, along with reducing Raf-1 protein levels in KNRK5.2 cells. The same compound also exhibits significant anticancer activity against MX-1 and A431 xenografts in nude mice. While radicicol has limited or no activity in animals due to its instability, its oxime derivatives have demonstrated potent anticancer activities in tumor xenograft models in humans [99,100].

3. Anticancer properties and biosynthesis of some bioactive substances in mushrooms/fungi

3.1. Exploration of key biologically active substances found in fungi with prospective anticancer activity

Natural products harvested from endobiotic Fungi are symbolic of a precious and abundant source of anticancer agents, offering enormous potential for the development of anticancer medications in modern medicine [101]. The identification of powerful medications with less or no negative implications from these sources presents an alternative to conventional techniques for

illness prevention and treatment [102,103]. According to studies, organic substances and their byproducts make up a sizable percentage of the compounds entering clinical research for cancer treatment[104]. These biologically active substances hold promise for designing novel anticancer medications [105].

Most researchers assess the use of large-scale screening and antiproliferative tests in cancer cell lines to assess the cytotoxicity of endophytic fungal substances and evaluate multiple compounds simultaneously for potential anticancer activity [106,107]. Isolating and screening natural bioactive compounds offer a pathway for discovering drug candidates [108]. It has been determined that certain endophytic fungal strains generate unique chemicals that work well in anticancer tests [109]. Some plant-based anticancer medications, such as Taxol, vincristine, and etoposide, are in clinical use for treating various cancers [110].

3.2. Mechanism of anticancer action and biosynthetic pathway of selected bioactive substances

Camptothecin: In 1996, the Food and Drug Administration authorized irinotecan (CPT-11), a camptothecin derivative alongside one of the most well-researched topoisomerase I blockers with notable anti-cancer properties, for the management of progressive cancer of the colon [111]. A number of biochemical pathways, including the cell cycle checkpoint route, featuring numerous check point kinases, especially ATM, ATR, and their switches, CHK1 and CHK2, are believed to respond to camptothecin analogues. The stimulation of these pathways results in stalled cell cycle advancement [112]. A Western blot examination was employed to look into the possible consequences of PCC0208037, a recently manufactured novel topoisomerase blocker, on the cell cycle checkpoint process. According to the findings, the process significantly increased the amounts of a number of significant molecules, such as ATM, p-ATM, γ-H2AX, ATR, p-ATR, DDR, p-Chk1, p-Chk1, p-Chk2, and Chk1. The ATR/ATM-Chk1/Chk2 route may be the mechanism by which PCC0208037-induced cell cycle cessation is mediated, according to the findings. The process of apoptosis causes cells to die and can be triggered by unrepaired breaks in DNA strands. Derivatives of camptothecin have been shown to trigger apoptosis in a p53-dependent way. As a result of p53's ability to elevate genes like PUMA and BAX and restrict genes like Bcl-2 to induce cell death by means of apoptosis in the reaction to DNA damage, PCC0208037 implementation was found to be significantly upregulating the expression levels of DDR-related proteins like BAX, PUMA, p53 and downregulating the degree of Bcl-2 expression [113]. The pathway for biosynthesis of camptothecin is given in Figure 1.

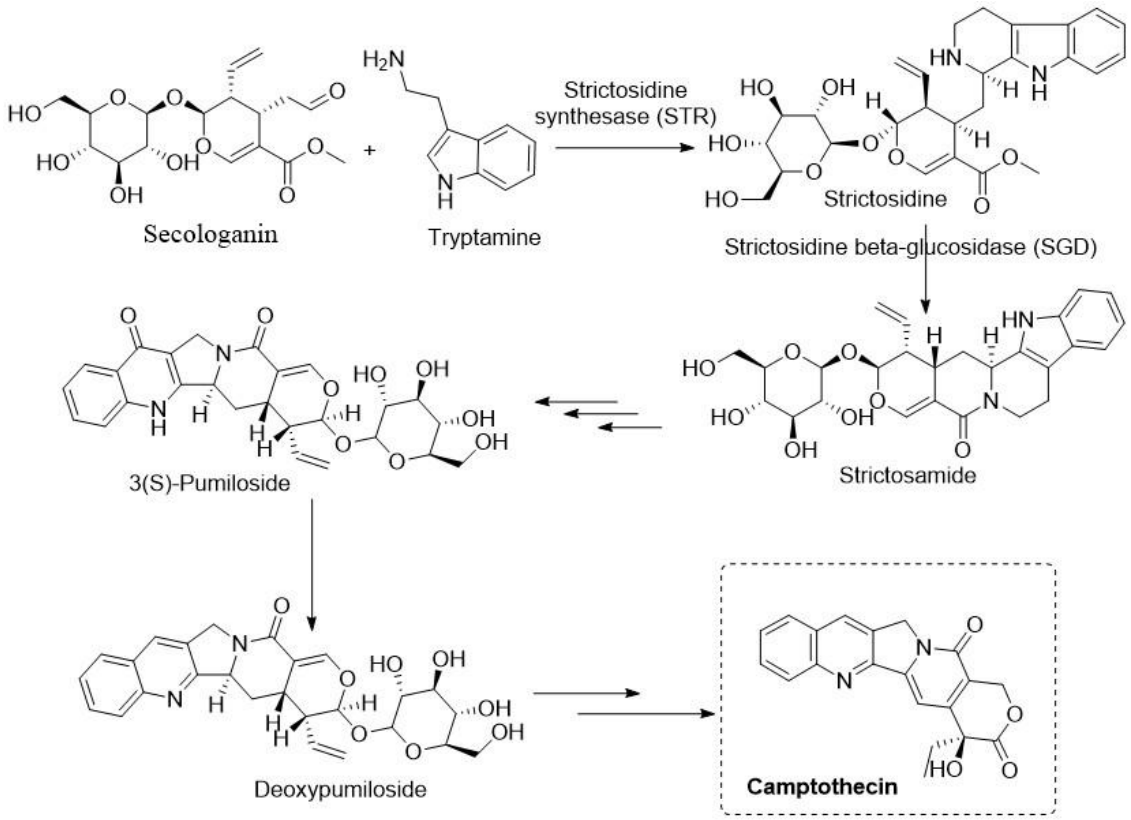

Figure 1. Biosynthesis of Camptothecin [114].

Strictosidine synthase is the key enzyme that catalyzes tryptamine with secologanin condensing to create camptothecin. Pre-strictosidine, strictosidine, and post-strictosidine are the three steps that makeup camptothecin biosynthesis. Tryptophan is first produced from chorismate through the shikimate route in the pre-strictosidine pathway. The tryptophan decarboxylase enzyme subsequently decarboxylates the tryptophan to turn it into tryptamine. Moreover, isopentenyl pyrophosphate and dimethylallyl pyrophosphate are employed in synthesizing secologanin, which is then further processed to create geranyl pyrophosphate and is then transformed into loganin. An enzyme called secologanin synthase converts loganin into secologanin.

The second step, the reaction that converts tryptamine and secologanin to strictosidine, is catalyzed by strictosidine synthases. A multi-step reaction produces camptothecin in the post-strictosidine pathway. Intramolecular cyclization of strictosidine results in strictosamide, which is further transformed into pulmioside and deoxypulmioside. To create camptothecin, these intermediates are oxidized, rings B and C are recycled, ring D is further oxidized, the C-21 glucose component is eliminated, and ring E is finally oxidized [115].

Taxol: Once the mold *Taxomyces andreanae* was competent to produce Paclitaxel (PTX), researchers started looking for commercially viable and ecologically appropriate bioreactors to replace the partially synthetic method. Unlike vinca alkaloids, paclitaxel alters microtubule mechanics in a distinct way as an antimitotic drug. It accelerates tubulin dimer building, which results in the creation and stability of microtubules. However, it then prevents them from depolymerizing, which throws off the mechanics of the production of mitotic spindles and, eventually, the interphase of the cell cycle. In the stage of G2/M of the cell cycle, subjected cells are

inhibited and finally experience apoptosis [116]. It has been demonstrated that PTX reduces the quantity of migrating regulatory T-cells, or Tregs, at proportionately greater amounts than in other lymphocyte communities via promoting the activity of CD95 (the cell-death sensor Fas) [117]. Taxol regulates mitosis, but it also affects cell survival by controlling the Bcl-2 group of apoptosis-controlling proteins along with additional signaling networks, including the NFκB and JNK/SAPK circuits. Taxol has the ability to destroy the endoplasmic reticulum's calcium retention and discharge the calcium, which upsets its equilibrium and makes the longevity of cells more difficult. Because of its LPS-mimetic properties, taxol can trigger signaling networks that are dependent on Toll-like receptor 4 (TLR4) for the purpose of causing apoptosis [118]. The pathway for biosynthesis of taxol is given in Figure 2.

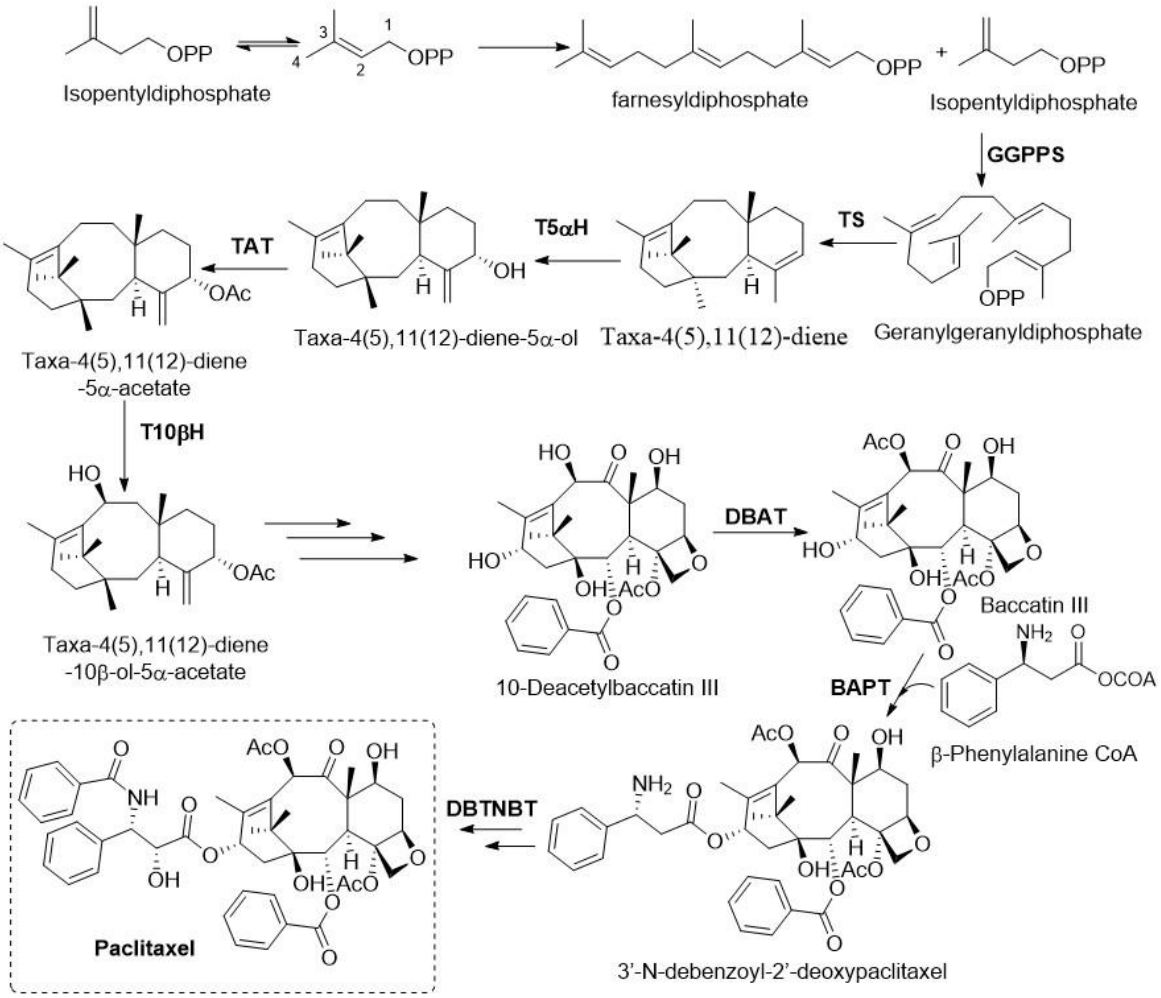

Figure 2. Biosynthesis of Taxol [Acceptable biosynthetic route for Paclitaxel.] [Key enzymes involved: GGPPS: geranyl-geranyldiphosphate synthase; TAT: taxa-4(5),11(12)-diene-5a-ol-O-acetyltranseferase; TS: taxa-4(5),11(12)-diene synthase; T10βH: taxane-10β-hydroxylase;BAPT: baccatin III 13-O-(3-amino-3-phenylpropanoyl) transferase; DBAT: 10-deacetylbaccatin III-O-acetyltransferase; DBTNBT: 30 -N-debenzoyl-20 -deoxytaxol-N-benzoyltransferase] [119].

Taxol synthesis is fundamentally based on the route of methyl-erythritol phosphate. The diterpene synthase, taxadiene synthase, transforms geranylgeranyl pyrophosphate into the taxadiene isomers. The important intermediate baccatin III and, eventually, taxolare produced by further functional decorating of the taxane framework using members of the superfamilies ofdioxygenase, cytochrome P450, transferase, and ligase [120].

Cordycepin: A large quantity of cordycepin may disable a signaling cascade known as mTOR (mammalian target of rapamycin) [121]. According to the investigation, cordycepin has the ability to turn on AMPK, which inhibits the mTORC1/mTORC2 complex's functionality. Because the disabled complex is unable to properly stimulate AKT 1 kinase, translation is inhibited, and cell division and differentiation are further suppressed by blocking mTOR signal transmission [122]. Human renal carcinoma cells were made to undergo cell death by cordycepin via inducing the MKK7-JNK regulatory channel, which in turn activated the Bax/caspase-3/PARP-mediated cascade by suppressing the production of an anti-apoptotic protein called cellular caspase 8 (FLICE)-like interfering protein (c-FLIP) [123]. Moreover, cordycepin triggers caspase-independent cell death in cancerous cells. Cordycepin was found to reduce both EGFR signaling and dividing of cells in a murine model of oral carcinoma mice. Accordingly, the therapy clearly lowered EGFR and ki-67 regulatory component levels to cause cancer cells to undergo apoptosis [124]. Cordycepin markedly reduced the dimension of the tumor in nude mice with lung adenocarcinoma in humans by inducing tumor cell death via caveolin-1-upregulated JNK/Foxo3a signaling cascade [125]. The pathway for biosynthesis of cordycepin is given in Figure 3.

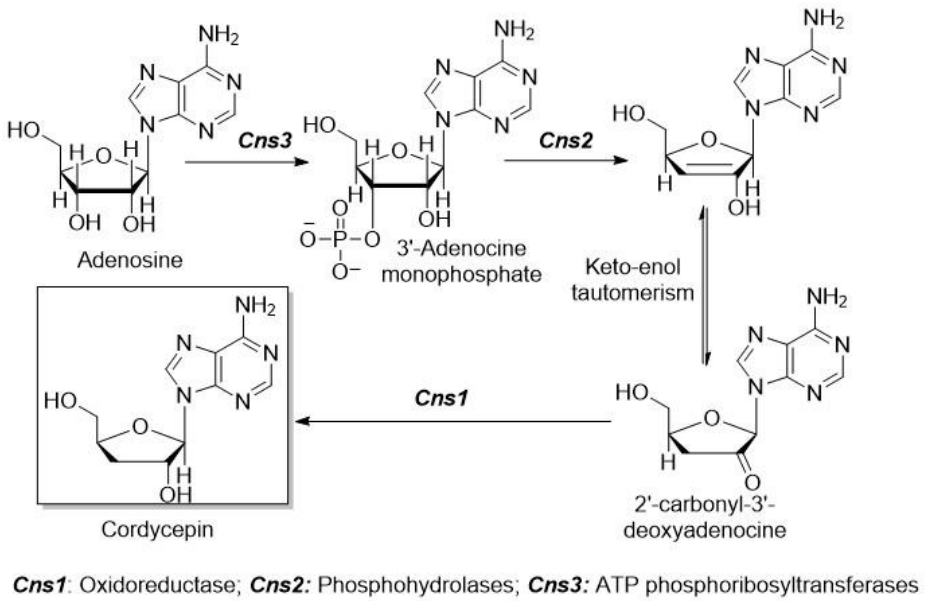

Figure 3. Biosynthesis of Cordycepin [126,127].

Following the phosphoribosyl pyrophosphate route, adenylosuccinate synthase transforms inosine monophosphate and L-aspartate to produce N6-(1, 2-dicarboxyethyl)-AMP. Adenylosuccinate synthase and 5′-nucleotidase then catalyze the sequential formation of adenosine monophosphate and adenosine. Phosphohydrolase NK domain activity transforms the precursor adenosine into adenosine-3′-monophosphate (3′-AMP). After being catalyzed by phosphohydrolase

to form 2′-carbonyl-3′-deoxyadenosine, oxidoreductase transforms it into cordycepin [126,127].

Fumagillin: Among the two MetAPs found in the cytoplasm, methionine aminopeptidase 2 (MetAP2), is the particular biochemical focus of fumagillin. N-terminal methionine excision (NME), a crucial process for cotranslational protein development, is catalyzed by MetAPs[128]. MetAP-2 suppression by TNP-470 (drug candidate analogue of fumagillin) inhibits noncanonical signaling of Wnt, which is vital for cell development, differentiation and carcinogenesis. Furthermore, Wnt signaling is regulated by TNP-470 over conventional Wnt signaling [130]. Signaling via Wnt can be regulated by TNP-470, though not conventional Wnt signaling. MetAP-2 functioning is required for Wnt to connect to its receptor, Frizzled, downstream, but ahead of the non-canonical Wnt regulatory proteins, JNK, CamKII and Rho, according to epistasis tests. Therefore, research is being conducted to determine the significance of noncanonical signals mediated by Wnt in angiogenesis. Fumagillin and TNP-470 have strong antiangiogenic action and specifically block noncanonical Wnt signaling [130]. The pathway for biosynthesis of fumagillin is given in Figure 4.

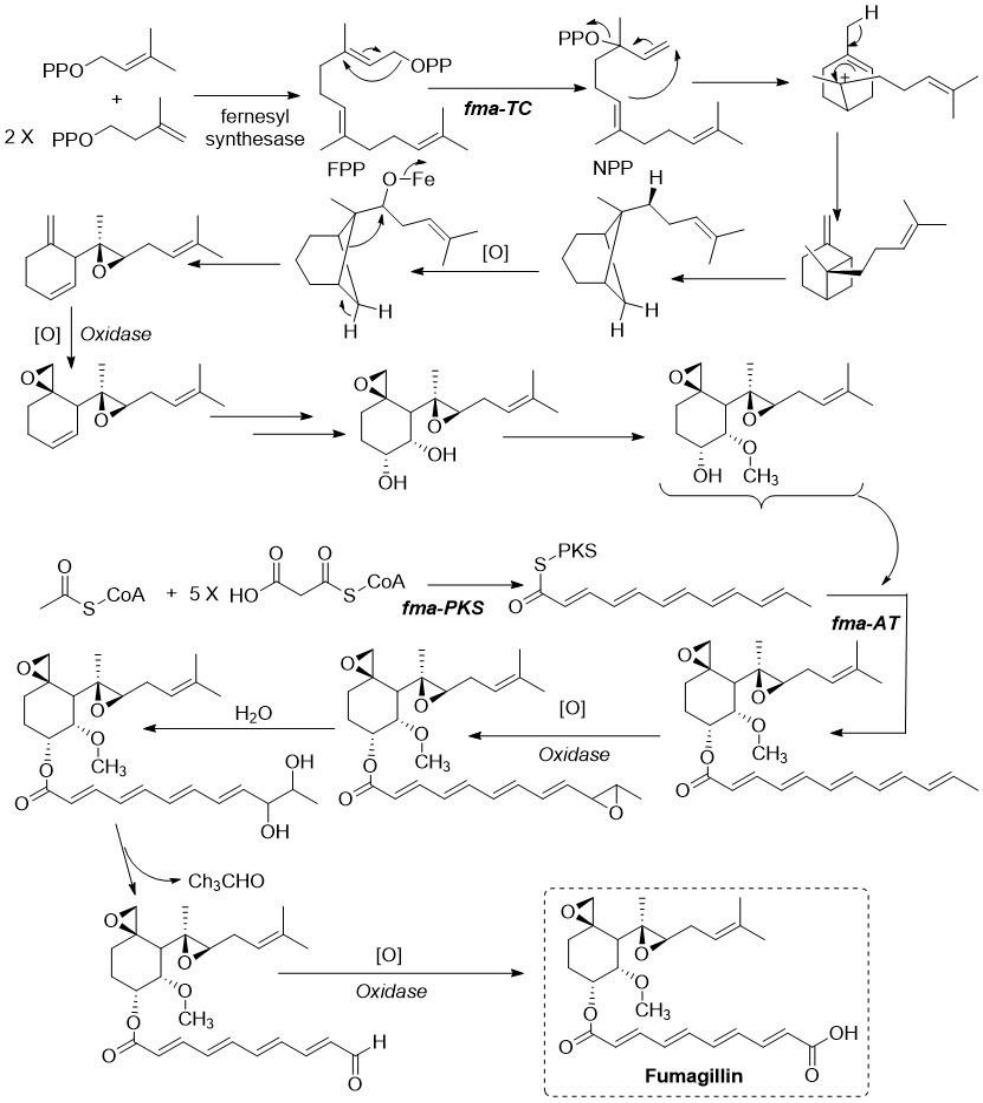

Figure 4. Biosynthesis of Fumagillin [129].

Lovastatin: Research has demonstrated that lovastatin has anti-proliferative and anti-apoptotic properties in breast cancer, both *in vitro* and *in vivo* [32]. The cellular levels of TNF agonist 1-associated death domain protein (TRADD), DR3 and caspase-7 were all elevated by lovastatin. Cells from breast carcinoma were inhibited by lovastatin due to the downregulation of histone H1, transglutaminase II (TGM2), and hypoxia-inducible factor 1α (HIF-1α). This resulted in the modulation of the epithelial-to-mesenchymal transition (EMT) protein [131]. When levofloxacin was added to certain breast carcinoma cell lines, it stopped the cells in the G_0/G_1 phase and increased p21 transcription [32]. On the other hand, lung cancer cell lines exposed to lovastatin showed increased discharge of cytochrome c together with decreased pro-caspase-3 and enhanced functional caspase-3. By altering the cell cycle, lowering glutathione, triggering p53, Bax protein, and caspases, and raising cytochrome c in apoptosis routes, lovastatin causes death and necrosis in pulmonary cancer cell lineages [132]. The pathway for biosynthesis of lovastatin is given in Figure 5.

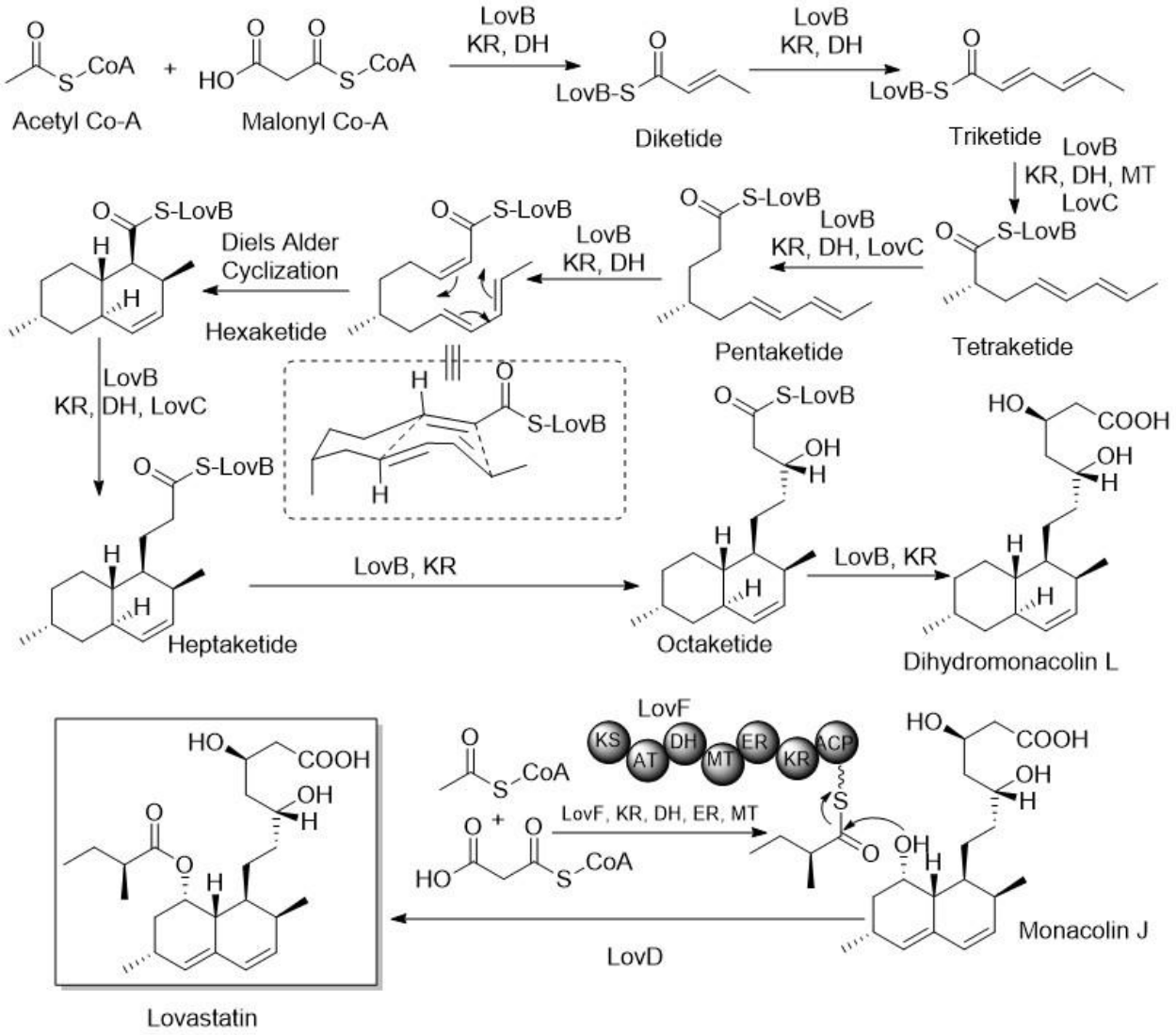

Figure 5. Biosynthesis of Lovastatin [133].

The manufacture of lovastatin involves highly reactive polyketide synthases. Love B-encoded lovastatin nonaketide synthase and Love C-encoded enoyl reductase co-catalyze the universal production of lovastatin. One molecule of malonyl-CoA and nine molecules acetyl-CoA combine to form dihydromonacolin L, a nine-ketone chemical. It is subsequently joined with methylbutyryl-CoA via oxidation and catalysis by lov G,36, which is carried out by lov F-inscribed lovastatin diketide synthase to create lovastatin [134].

Resveratrol: One of the key variables in the onset and progression of cancer is proliferation. According to one experiment, resveratrol deactivated the phosphorylation event of STAT3 at Tyr705 without any impact on Ser727 and, therefore, successfully suppressed the growth of ovarian cancer cells (SiHa and HeLa cell lines) at dosages varying from 5 to 40 μM [135]. Utilizing β1-integrin sensors, resveratrol made colorectal carcinoma cells more sensitive to 5-fluorouracil by modifying the tumor milieu and focusing on the β1-integrin/HIF-1α signaling cascade [136]. Resveratrol affects several molecular targets and signaling cascades. Resveratrol is believed to inhibit the AKT, NF-κB, and PI3-kinase signaling networks. Resveratrol affects several molecular targets and signaling cascades. Resveratrol is believed to inhibit the NF-κB, PI3-kinase and AKT signaling networks [137]. Resveratrol reduces NF-κB, COX-2, and cytokines, exhibiting anti-inflammatory characteristics. Additionally, resveratrol blocks the actions of channels of signaling linked to cancer, including protein kinase C (PKC), Protein kinase stimulated by AMP (AMPK), and mitogen-activated protein kinase (MAPK) [138]. The pathway for biosynthesis of resveratrol is given in Figure 6.

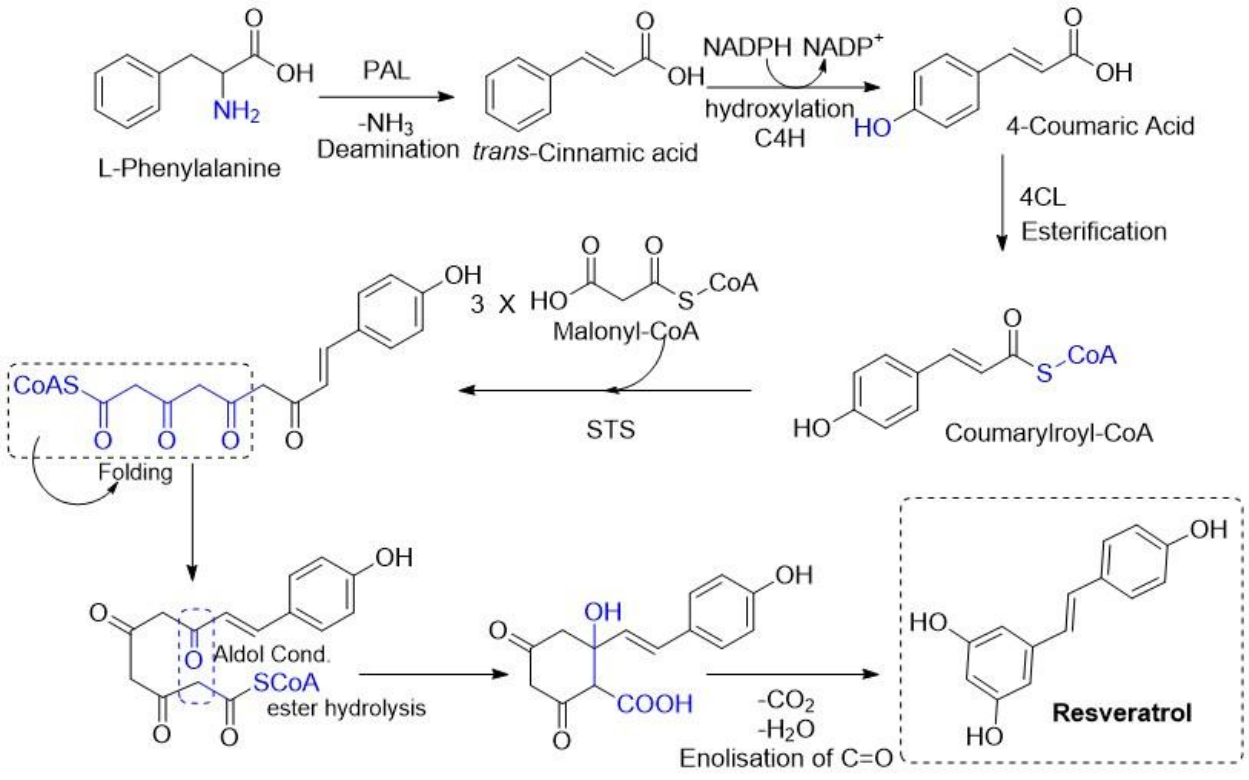

Figure 6. Proposed pathways of Resveratrol biosynthesis [139,140].

Only in plants has the phenylpropanoid route been identified as the resveratrol biosynthesis process. Nonetheless, the endophytic fungus *Alternaria* sp. and certain yeast strains have been found to possess their essential enzymes. L-Phenylalanine is the initial compound that gets deaminated to form trans-cinnamic acid, which further undergoes hydroxylation and esterification to be converted into Coumarylroyl-CoA. This combines with malonyl-CoA, and through successive stages of intramolecular rearrangements and aldol condensation, it finally transforms into Resveratrol. The enzymes participating in the said events are phenylalanine ammonia lyase (PAL), trans-cinnamate 4-hydroxylase (C4H), 4 coumarate-CoA ligase (4CL), stilbene synthase (STS), and resveratrol synthase respectively [139].

Vincristine and Vinblastine: The passing of vincristine treated HeLa cell line within 48 hours underwent apoptosis-like lysosomal membrane permeation, cytochrome c discharge, Bax and caspase activation, chromatin condensation and G2-M cell cycle halt [141]. Vinblastine destabilizes microtubules, suppresses the production of proteins and nucleic acids, increases levels of oxidized glutathione and cyclic adenosine monophosphate (cAMP), prevents the calcium-calmodulin-regulated phosphodiesterase of cAMP, and modifies the lipid makeup of membranes [142]. The pathways for biosynthesis of vinblastine and vincristine are given in Figures 7 and 8.

Geraniol synthase converts geranyl pyrophosphate, a middle product in the terpenoid path, to geraniol, which is then converted to nepetalactol by hydroxylation (catalyzed by geraniol 8-hydroxylase), oxidation (catalyzed by 8-hydroxygeraniol oxidoreductase), and cyclization (catalyzed by iridoid synthase). Nepetalactol subsequently proceeds through further hydroxylation, oxidation, glycosylation, and methylation to yield loganin, which is thereafter targeted to a distinctive ring-opening step that is catalyzed by secologanin synthase and P450. Through a Pictet–Spengler-type reaction facilitated by strictosidine synthase, the resulting secologanin interacts with l-tryptamine, the decarboxylation product of l-tryptophan (catalyzed by tryptophan decarboxylase) to generate strictosidine. After a series of steps, catharanthine synthase or tabersonine synthase, respectively, converts strictosidine into these two compounds. To produce vindoline, tabersonine again goes through a number of changes, including hydroxylation, methylation, reduction, and acetylation. Last, a peroxidase-mediated operation condenses vindoline and catharanthine to yield vinblastine [145].

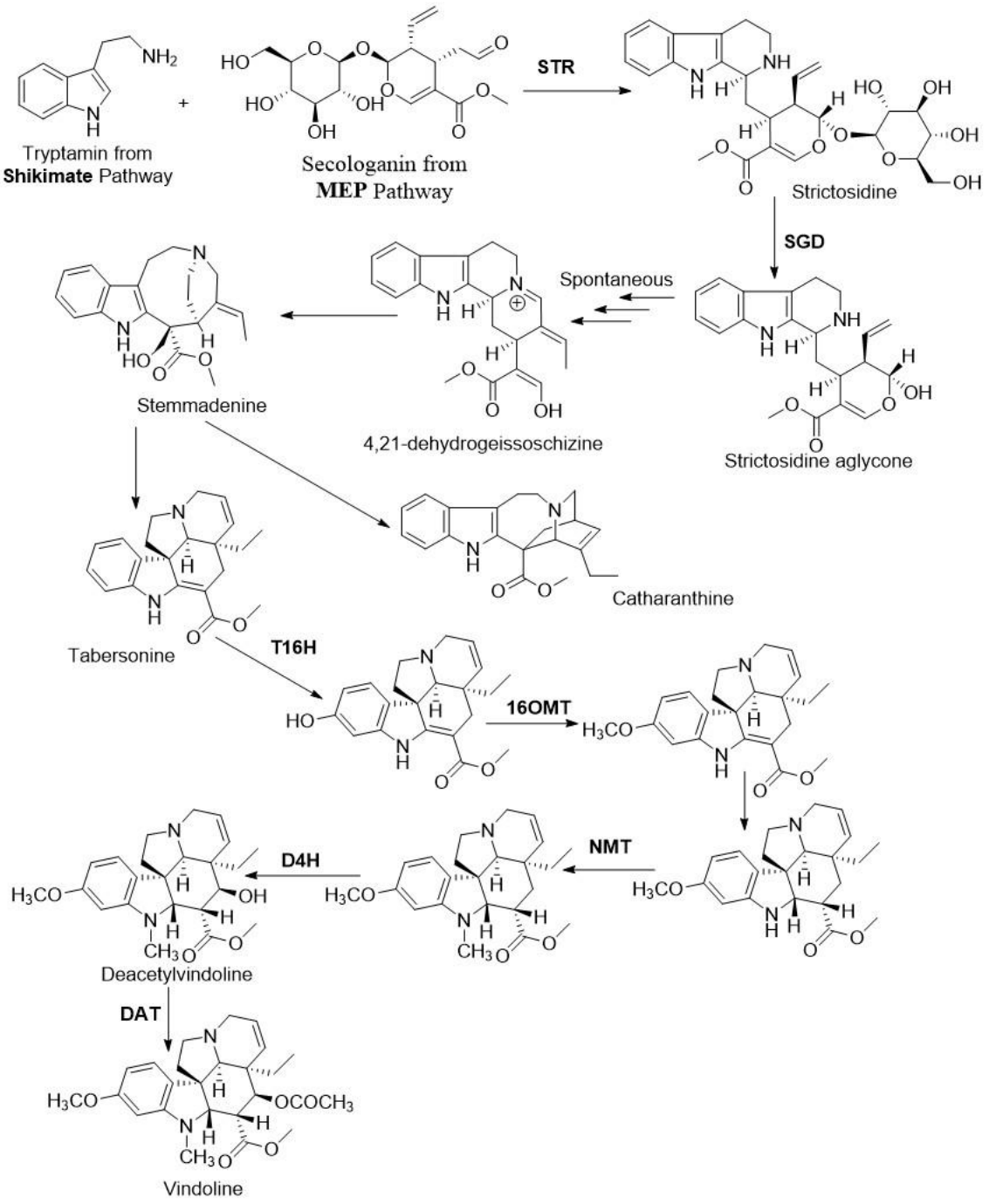

Figure 7. Proposed biosynthesis of terpenoid indole alkaloids (TIAs): vindoline and catharanthine. [Key enzymes involved, SGD:Strictosidineβ-D-glucosidase; STR:Strictosidine synthase; T16H:Tabersonine 16-hydroxylase, D4H Desacetoxyvindoline 4-hydroxylase;16OMT: 16-hydroxytabersonine-O-methyltransferase; NMT: N-methyltransferase; DAT: deacetylvindoline 4-O-acetyltransferase.

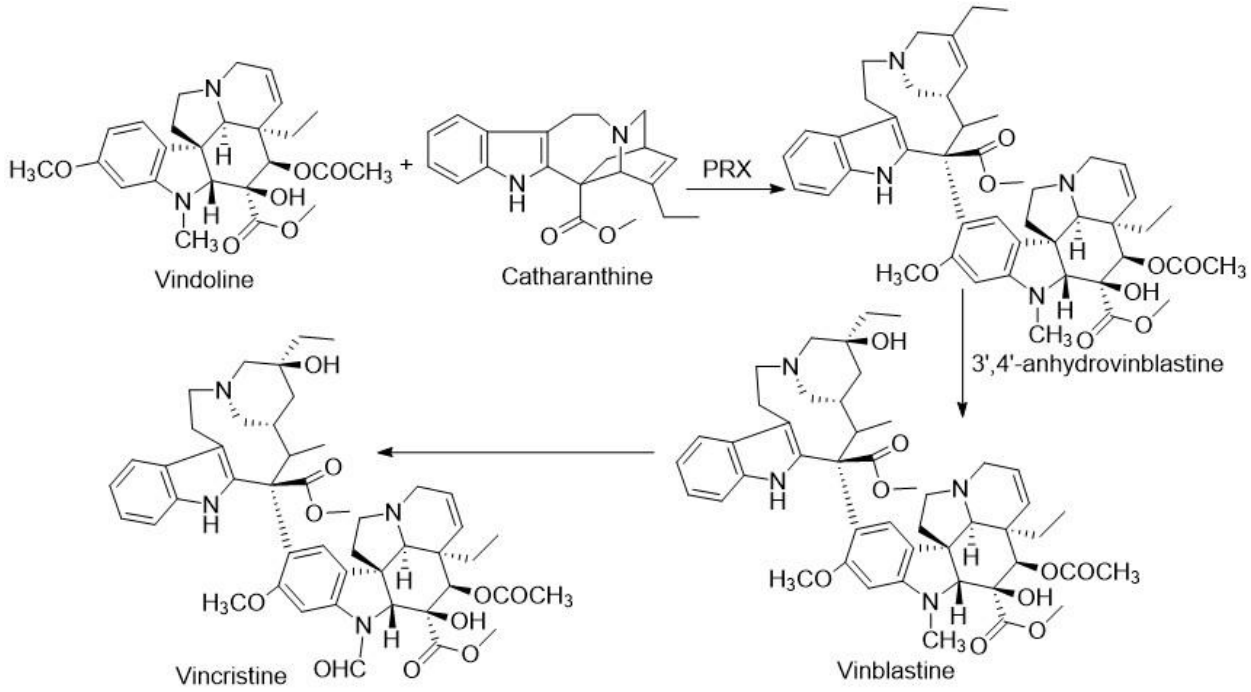

Figure 8. Biosynthesis of bis indolealkaloids, vinblastine and vincristine [PRX, vacuolar class III peroxidase] [143,144].

4. Application of the studied mushrooms in conjunction with traditional treatments

Traditional cancer treatments, including immunotherapy, radiation, and radiation therapy, are linked to downstream adverse reactions such immunosuppression or gastrointestinal problems that lower patients' quality of life [146]. In this regard, there is general agreement that complementary and alternative health care, is a viable therapy option [147]. Some study participants had multiple malignancies. *Lentinula edodes, Agaricus sylvaticus, Agaricus blazei, Coriolus versicolor, Antrodiacinnamomea*, and *Ganoderma lucidum* were the varieties of mushrooms employed in the various investigations. The type of mushroom that was used affected the dosage. The daily dosage utilized in all investigations with *Lentinula edodes* was 1800 mg. One dose of 2.1 g/day of *Agaricus sylvaticus* was provided [148]. Combining extracts from *Agaricus blazei* Murill Kyowa mushrooms with chemotherapy has been shown to reduce side effects like baldness and appetite loss. When *Antrodiac innamonomea* extracts were used as a chemotherapy adjuvant in adenocarcinoma patients, it was shown that while gastrointestinal symptoms were more common, they were less severe than in the group that did not get treatment [149]. Okuno et al. found that gastrointestinal cancer patients experienced nausea and abdominal symptoms over the first session of chemotherapy (without administering *Lentinula edodes* mycelia extract) but that these side effects did not occur during the second course of chemotherapy (using *Lentinula edodes* mycelia extract in conjunction with chemotherapy) in a preliminary study without a control group [149]. A fraction of *G. lucidum* that included fucose (FFLZ) reduced cell migration, tumor development, and the epithelial mesenchymal transition in breast cancer. Trastuzumab resistance was decreased by the combined action of FFLZ and trastuzumab [150]. In BALB/c mice with breast tumor xenografts, a Maitake d-fraction, decreased angiogenesis, carcinogenesis, invasiveness, and extended life were observed [151]. *In vitro*,

Gou et al.'s investigation found that *Trametes robiniophila* Murr polysaccharides dramatically reduced human HepG2 and Bel-7404 survival rates at 48 and 72 hours in a dosage-dependent way. Additionally, they demonstrated that the combination of *T. robiniophila* Murr polysaccharides and oxaliplatin resulted in a stronger inhibitory effect than the medication used alone. The analysis for clone development revealed that the number of replicas in the population obtaining combined therapy was much lowercompared to those in the group obtaining oxaliplatin alone. This suggests that the group receiving merged attitudes had more diminished cell growth than the oxaliplatin-alone group [152]. According to Xu et al., cisplatin alone decreased tumor development by 35.5%, whereas *Pleurotus pulmonarius* solely lowered it by 22.6%. *Pleurotus pulmonarius* and cisplatin, in conjunction, produced an amazing 88.5% reduction rate because of their synergistic effects. These results imply that *P. pulmonarius* and cisplatin used concurrently greatly increase the anti-proliferative benefits of chemotherapy. As a result, combination therapy has a great impact on reducing the rate at which cancer cells divide [153]. In SKOV3 and SKOV3/DDP ovarian cancer cell populations, Cen et al. demonstrated that cisplatin and SBSGL (Sporoderm-Broken Spores of *Ganoderma lucidum*) both had notable destructive and anti-proliferative properties. For SKOV3/DDP, cisplatin was administered at a dosage of 200 μM, whereas SBSGL was administered at a dose of 40 μM. In comparison to the population treated with cisplatin solely the group that received a cocktail of SBSGL and cisplatin had more marked inhibitory effects on tumor development in terms of tumor dimensions and weight. Furthermore, a measure of the rate of cell growth, Ki-67, was discovered to be substantially reduced in the tumors in the group receiving combination treatment. This finding implies that a mixture of SBSGL and cisplatin further inhibited the growth of ovarian cancers and promoted their death *in vivo*[154]. Employing a 4T1 triple-negative mice breast carcinoma model, it was found that an amalgam of therapeutic mushrooms that were taken orally and were high in β-glucans had a clear and specific cancer-preventing effect on cerebellar metastases while also improving locomotor abilities. This additive of medicinal mushrooms is used as an adjuvant medication in conjunction with traditional therapy because it inhibits the metastatization process, causes a considerable rise in cell death, and reduces the growth of cells [155].

It is crucial to remember that further study is required to fully comprehend the effects and possible hazards of medicinal mushrooms, even if the studies show that they could have value as a supplemental remedy for cancer sufferers. According to the research, medicinal mushrooms may be able to stop lymph node metastases, increase overall survival, lessen side effects from chemotherapy (such as nausea and diarrhoea), influence the immune system, and support the preservation of systemic the standard of life and immunological function in people with particular cancers. To guarantee reliable results, more human subjects are needed to employ a bigger sample of RCTs. A thorough study must be done on other lethal tumors as well, such as lung cancer, which progresses swiftly [12].

Despite the integration of fungal and mushroom-derived compounds into cancer treatment strategies due to their therapeutic potential, some have exhibited toxicity or adverse effects, leading to their exclusion from clinical trials. As an instance, early clinical testing has indicated that orellanine, a nephrotoxin present in mushrooms such as *Cortinarius orellanus*, may be used to treat metastatic clear cell renal cell carcinoma. Despite difficulties with its geometric optimization and the intricacy of its biological assessment because of active compounds, it has advanced to phase I/II human trials as of early 2022 [156]. Ergosterol peroxide, a significant bioactive component of

Ganoderma lucidum, has been well-received by mice and suppresses the proliferation of tumors in mouse cancer scenarios. When mice were given increasing dosages up to a specified maximum of 500 mg/kg, the highest tolerated dosage was examined. Plasma chemistry and tissue examination revealed no symptoms of toxicity. Ergosterol peroxide's hepatotoxicity and cardiotoxicity tests, among other additional organ damage tests, showed no adverse reactions [157]. Even though orellanine is undergoing clinical studies, its well-established nephrotoxic effects provide serious obstacles to its potential therapeutic application. Rats are more tolerant to orellanine then humans, which is a significant disadvantage of using them as models for orellanine toxicity. In males, inner cortex injury was less common and invariably associated with permeates in the outer medulla, but in females, it was seen to be the only histological sign. A hepato-renal disorder, which was also noted in a number of the first documented cases of orellanine toxicity in humans, is one of the tissue-dependent toxicities that mice exhibit that rats do not. The toxicity of the chemical, especially its preference for the kidney's proximal tubular cells, is still a serious worry that, if left unchecked, may affect its clinical feasibility [156].

5. Safety considerations and adverse effects

With the exception of limited trials, unexpected complications that occur after taking mushrooms are typically not reported in detail [149]. It is important to read this cautiously because a number of the undesirable effects may be brought on by an underlying health issue or ongoing medical therapy. Hence, double-blinded assessment and placebo-controlled categories are required for accurate interpretation of side effects [158]. The adverse consequences on the overall wellness of those suffering from breast cancer receiving endocrine therapy combined with *G. lucidum* were examined; only modest discomforts were recorded, with 12.0% of patients with mouth dryness and 16.0% with dizziness being the most prevalent. In addition, 8.6% of those diagnosed reported having slight intestinal discomfort and diarrhoea [159].

6. Conclusions

For thousands of years, people have valued mushrooms for their culinary and health virtues. More recently, research indicates that mushrooms may be crucial to cancer treatment. Despite considerable advances in cancer treatment, many patients search for alternatives that offer fewer side effects, immune system support, and improved quality of life. Medicinal mushrooms, with their abundant array of bioactive substances, offer promising potential in this regard.

Although there is mounting evidence of mushrooms' anti-cancer effects from *in vitro* research and traditional medical practices, comprehensive *in vivo* and clinical studies are necessary to confirm their effectiveness and reliability. For instance, orellanine, which has been addressed, has advanced to stage I/II clinical investigations and has demonstrated promise in treating metastatic clear cell carcinoma of the kidney. However, a major obstacle to its therapeutic use is its well-established nephrotoxicity. Its evaluation is made more difficult by species-dependent differences in toxicity, especially the greater tolerance seen in rats as opposed to humans. Concerns regarding the compound's clinical viability are raised by its preferential toxicity to kidney cells in the proximal tubule and related hepato-renal diseases. However, even at high dosages of up to 500 mg/kg, ergosterol peroxide isolated from *Ganoderma lucidum* has shown potent anticancer action in animal

models without any discernible harm. Its worth as a safer curative option is highlighted by the lack of liver damage, cardiac toxicity, or other organ damage. Although ergosterol peroxide offers a promising therapy option for cancer, orellanine's impact on the kidneys is a significant barrier that needs to be overcome before it can be regarded as a practical clinical agent. The challenge of exactly identifying and naming medicinal mushrooms also needs to be addressed, especially as new species with potential therapeutic properties continue to be discovered, particularly in underexplored regions.

To fully investigate these natural chemicals' potential, including their metabolism, modes of action, and appropriateness for therapeutic development, more research is necessary. Large-scale, high-quality clinical trials are necessary to confirm the curative potentials of compounds obtained from mushrooms. Overall, the exploration of medicinal mushrooms represents a promising frontier in the search for new, effective cancer treatments.

Author contributions

ND, TS and MR designed the study; MR and CP performed data collection and literature analysis; NP prepared figures and schemes; MR and CP prepared the initial draft; ND, NP and TS contributed to review and editing. All authors approved the final version of the manuscript.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare that they have no conflict of interest.

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