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Review

Update on Mycochemical Profile and Selected Biological Activities of Genus *Schizophyllum* Fr. 1815

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Abstract: The aim of this systematic review was to investigate new research on the antioxidant, anti-acetylcholine, antimicrobial, and antitumor activity of genus *Schizophyllum*, as well as to describe the mycochemical profiles. A summary was made on the published studies in the five-year period from 2017 to 2022, with the focus on the most investigated species of this genus, *S. commune*. Data were obtained through various scientific online databases, including Google Scholar, Semantic Scholar, PubMed, Science Direct, Elsevier, and Wiley Online Library using specific keywords. Out of 918 records published between 2017 and 2022, a total of 44 peer-reviewed studies were included in qualitative synthesis. Most examined compounds were glucans isolated from the submerged cultivation of *S. commune*, even though many studies reported proteins, phenolics, and some other secondary metabolites such as flavonoids, saponins, steroids, tannins, triterpenoids, etc. Schizophyllan (SPG), one of the most studied β-glucans isolated from *S. commune*, has been utilized in clinical trials to treat patients receiving anticancer therapy as an immunopotentiator. Considering the enormous biopotential of genus *Schizophyllum*, specifically *S. commune* and *S. radiatum*, additional attention should be paid to identify the biomolecules more accurately and focus on their antitumor and anti-acetylcholinesterase properties, since they proved to have great prospects in the pharmaceutical and nutraceutical industries.

Keywords: *Schizophyllum*; *S. commune*; *S. radiatum*; antioxidant; antimicrobial; polysaccharides; phenolics

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1. Introduction

One of the most widely distributed fungal species on the Earth belongs to the genus *Schizophyllum* Fr *1815.* It is a member of the Schizophyllacea family, order Agaricales, and phylum Basidiomycota [1]. Within the family Schizophyllaceae, order Agaricales, we distinguish two genera, *Auriculariopsis* and *Schizophyllum*.

Schizophyllum Fr., a widespread genus, has a very easily identifiable macromorphology, with characteristic lamellar hymenophores whose radial eccentric lamellae are longitudinally split at the edges [2]. Within this fungal genus, 15 different species have been described so far in the Index Fungorum database [3], including *S. album* Rick, S. *amplum* (Lév.) Nakasone, *S. commune* Fr., *S. brasiliense* W.B. Cooke, *Sc. brevilamellatum* Linder, *S. fasciatum* Pat., *S. leprieurii* Linder, *S. murrayi* Massee, *S. palmatum* Jungh. ex W.B. Cooke, *S. umbrinum* Berk., *S. radiatum* Fr., *S. variabile* Sorokin, *S. lobatum* Went, *S. mexicanum* Pat, and *S. miia* (Scop.) Fr. According to Mycobank, the genera *Schizophyllum* includes 21 species [4]. However, ex-type strains for many of the described species do not exist, and only a small number of strains recognized by the experts have been deposited into several public culture collections (i.e., *S. commune, S. fasciatum, S. radiatum*, and *S. umbrinum*) [5]. *S. commune* and *S. radiatum* were earlier considered conspecific due to morphological and ITS rDNA genetic similarity; however, multigenetic analyses confirmed that both species are similar and closely related but of independent taxa [1,6].

Taking into consideration over ten species and their great morphological variability, most of the records presented are generally considered as synonyms of *S. commune,* which represents the most important, well-known, and most-researched species of this genus. A study from 1961 reported over 3714 specimens of genus *Schizophyllum*, where over 96% were attributed to *S. commune*, 2% were assigned to *S. fasciatum*, 2% to *S. umbrinum*, while *S. leprieurii* was represented only within four collections, *S. Brasiliense* within two, and *S. palmatum* within a single collection [7]. Other species have not been researched as much, considering that they are rarely found in nature and little attention was paid to them during field research [2,6,7]. There are only scarce data related to the morphology, taxonomy, phylogeny, and distribution of *S. brasiliense, S. fasciatum, S. leprieurii, S. lobatum, S. palmatum, S. umbrinum*, and *S. variabile* [7]. The species *S. fasciatum*, *S. umbrinum*, and *S. leprieurii* have limited distribution and were found mostly in countries near the Caribbean Sea and Gulf of Mexico, while *S. brasiliense* was recorded in Brazil and *S. palmatum* was recorded only in Japan [7]. During the phylogenetic analysis of genus *Schizophyllum* from Central Argentina, *S. umbrinum* and *S. leprieuri* were described in this country as well [2]. However, Carreño-Ruiz et al. [8], after an examination of the fungal collection (the Herbarium of the Biological Sciences Academic Division of the Juarez Autonomous University of Tabasco, Mexico) and fresh basidiomes collected during field investigations, recently determined that *S. radiatum* was the most abundant specimen (62), followed by *S. commune* (28) and *S. umbrinum* (3). At the same time, Sammut et al. [6] conducted a morphological and genetic study of *S. amplum* from Estonia and Malta, which is the first public record of this species in this part of Europe.

Among the research regarding the bioactivity of *Schizophyllum*, only one species—*S. commune*—has been studied in terms of its biological activities (Figure 1) and mycochemical characterization, with the exception of one publication that examined the antitumor activity of the polysaccharides (PSHs) of *S. radiatum* [1].

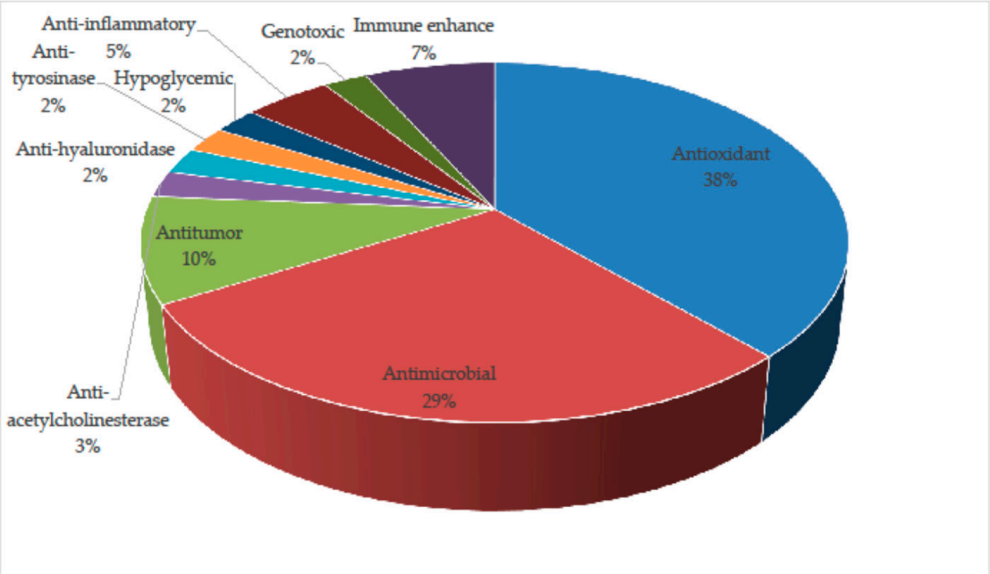

Figure 1. Percentage representation of bioactivities identified in *S. commune* from 2017 to 2022.

Reports about these edible fungi, until recently considered inedible due to its small size and toughness, indicate that *S. commune* has antidiabetic, anti-inflammatory, antimicrobial (AM), antioxidant (AO), antitumor, anti-tyrosinase, immunomodulatory, neuroprotective activity, etc. [9–16]. Various extracts and isolated substances, including PSHs, polysaccharide–protein complexes, proteoglycans, protein, phenolics (PHs), and flavonoids from fungal fermentation broth, mycelia, and fruiting bodies, have been reported to contribute to these activities [9–11,15,16]. In particular, PSHs seem to be effective immunemodulators and anticancer agents in addition to having other positive effects (such as

wound healing, antinematode activity, and others) [17]. Moreover, schizophyllan (SPG), one of the most studied β-glucans isolated from *S. commune*, has been utilized in clinical trials to treat patients receiving anticancer therapy as an immunopotentiator and is currently being commercially developed by a number of Japanese pharmaceutical companies [1].

The purpose of this systematic review of the genus *Schizophyllum* is to systematize and describe the AO, anti-acetylcholinesterase, AM, and antitumor activity as well as thechemical characterization reported in the period from 2017 to 2022. This update is focused on *S. commune*, given that there is a lack of research data related to the activities and mycochemistry of other species belonging to this genus. Moreover, this review provides a baseline for future research studies.

2. Methodology

This study is a systematic review of the genus *Schizophyllum*, regarding the selected bioactivities and the mycochemical profiles published in the last five years (2017–2022), except 3 studies published prior to 2017, which were used as data source, given that data on the mentioned species are rare or nonexistent. Data were obtained through various scientific online databases, including Google Scholar, Semantic Scholar, PubMed, Science Direct, Elsevier, and Wiley Online Library using keywords such as *Schizophyllum*, *Schizophyllumamplum, Schizophyllum commune*, *Schizophyllumfasciatum, Schizophyllumradiatum, Schizophyllumumbrinum, schizophyllan, antioxidant*, etc. Only relevant studies that included the biochemistry and specifically selected bioactivities were included. A total of 918 records published between 2017 and 2022 were identified through the database search, and after duplicates and irrelevant research were removed, 256 studies were screened by title, abstract, and keywords. A total of 82 studies were assessed for eligibility by reading the full text, and afterwards, studies were removed due to detected activities not being the subject of this work. Furthermore, studies that were not peer-reviewed were also rejected, leaving a total of 44 studies which were included in the qualitative synthesis.

3. Mycochemistry

The majority ofthe research on the targeted activities of *S. commune* describes the effects of extracts while identifying the chemicals that are responsible for the activity. However, some studies lack this data, so it is difficult to determine which compounds are responsible for the testedactivities. Mycochemical screening of the ethanolic (EtOH) extracts of *S. commune* revealed the presence of saponin, tannins, alkaloids, flavonoids, terpenoids, proteins, and carbohydrates [18]. The same year, Karaman et al. [16] summarized that alkaloids, iminolactones, PHs, PSH, steroids, terpenoids, vitamins, and some other functional ingredients were found in *S. commune* (Figures 2 and 3). Debnath et al. [9] found that the moisture content of *S. commune* samples originated from India was determined at 87.76% d.w., ash (3.5%), while the nutrition profile was presented through the total carbohydrate content (TCC) (42.0%), followed by crude fiber (30.0%), crude protein (15.55%), crude fat (9.0%), and lipids (0.4%). In the study from 2022, proximate analysis results confirmed that this fungus was rich in moisture (60.60%), nitrogen-free (25.15%), and had a crude protein content of 7.63% and an ash content of 6.17%, while the crude fiber and fat materials were 0.18% and 0.27%, respectively [18]. Besides *S. commune*, a nutritional composition of *S. radiatum* was conducted as well [1]. The TCC was in the range of 73–79% for water-soluble exopolysaccharides (SEPSs) and water-soluble intrapolysaccharides (SIPSs), respectively. In addition, the protein content was quantified only in SIPSs, with an amount of $1 \pm 0.002\%$ [1].

3.1. Primary Metabolites

The biological activity of PSHs is closely linked to the structure, where β-glucans from *S. commune* play a major role [19]. SPG, β-1.3(1.6)-glucan (Figure 2), is an exopolysaccharide (EPS) isolated from *S. commune* and appreciated as a versatile metabolite that is useful in various industries, including the food industry and pharmaceutical industry, due to

a wide range of biological effects, including antitumor, immunomodulatory, and anti-inflammatory activities [20]. However, few studies have addressed the bioactivity and molecular structure of PSHs derived from *S. commune* [10–13,15,21,22].

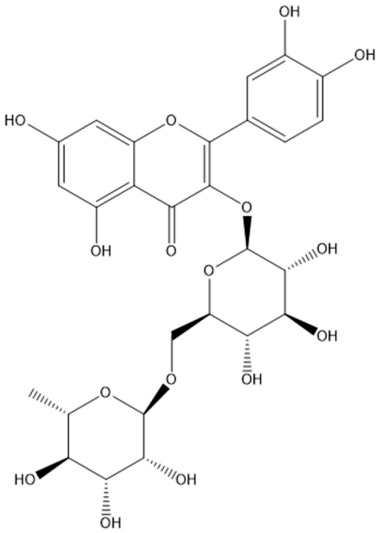

Figure 2. Schizophyllan from *S. commune*.

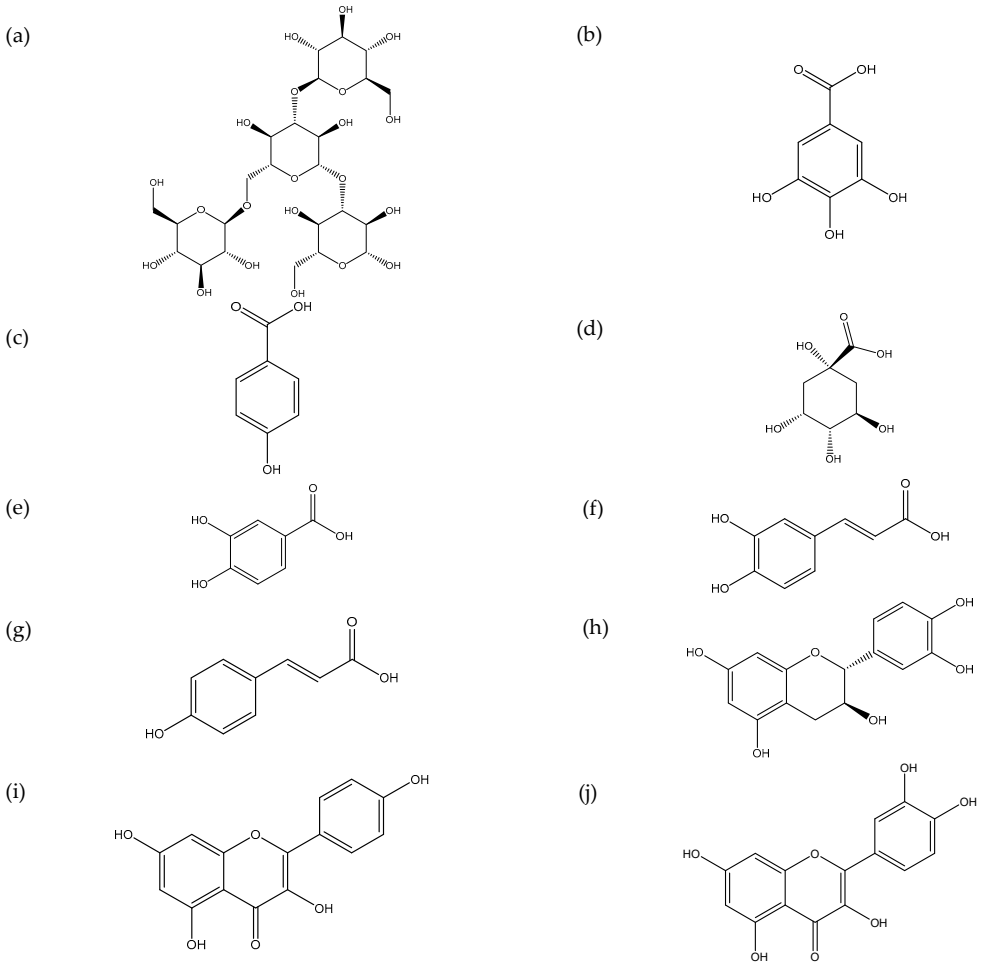

Figure 3. Phenolic compounds from *S. commune*: (**a**) rutin; (**b**) gallic acid; (**c**) p-hydroxybenzoic acid; (**d**) quinic acid; (**e**) protocatechuic acid; (**f**) caffeic acid; (**g**) coumaric acid; (**h**) catechin; (**i**) kaempferol; (**j**) quercetin.

In their study, Smirnou et al. [23] worked on the procedure for obtaining highly pure SPG cleaved into shorter fragments by using ultrasonication. The ultrasonicated SPG (uSPG) was obtained by the submerged cultivation of *S. commune* in a bioreactor. It contained less than 0.3% protein and 0.078 IU/mg endotoxin. Although the authors found that the β-glucan concentration in the medium continued to increase, cultivation longer than 144 h was not economically acceptable [23]. In addition, the authors highlighted that the application of ultrasound-assisted downstream processing was an efficient methodology for the manufacturing of low-MW SPG, which are applicable to cosmetics and medicine. Moreover, ultrasonication, when applied on a complete culture broth with mycelium, brought certain advantages to the SPG production. It reduced the product losses downstream and made the production of highly purified PSH possible due to the efficient usage of ultrafiltration [23].

In their research, Du et al. [10,11] characterized the EPSs of *S. commune*. In the first study, [10] used an ultrasonic treatment to produce EPSs with various molecular weights (MWs). The authors found EPSs with different MWs, including low MW (197 kDa), medium MW (936 kDa), and high MW (1437 kDa), respectively. In addition, it was found that high- and medium-MW EPSs had triple- and single-helix conformations, while the low-MW ESP exhibited the random-coiled conformation [10]. In the same year, Du et al. [11], using DEAE-52 cellulose and Sephadex G-150 chromatography, isolated, purified, and characterized an EPS with a molecular weight of 2900 kDa from a submerged mycelial fermentation of *S. commune*. It was found that the EPS was a type of heteropolysaccharide, β-(1→3)-D-glucan, based on the IR spectrum. It was composed of carbohydrates (89.0%), proteins (2.2%), and uronic acid (7.52%); therefore, the EPS could be observed as a protein-bound polysaccharide based on the protein content. In addition, it was found that glucose was the main monosaccharide in the EPS, consisting of arabinose, galactose, glucose, mannose, rhamnose, ribose, and xylose [11]. Moreover, the authors found that the elemental analysis of the C, H, and N content (% *w*/*w*) was: C, 25.84%; H, 5.45%; N, 0.65%. Based on the low amounts of N, it is obvious that polysaccharide-rich samples contain only small amounts of it, and the authors suggested that N may have its origins in either chitin or proteins from the EPS [11].

Phuket et al. [13] isolated β-glucan from a *S. commune* strain from Thailand to determine the AO and total phenolic content (TP) (284.41± 1.22 mgGAE/g). On the other hand, Yelithao et al. [21] documented the chemical composition, monosaccharide composition, MWs of the crude PSHs, and two fractions from *S. commune* in relation to the immune-enhancing activity. The PSHs obtained in this study contained carbohydrates (50.3–65.8%), proteins (1.46–20.1%), and sulfates (1.33–7.01%), while gas chromatography–mass spectrometry (GC-MS) confirmed the presence of glucose (17.0–88.2%), mannose (2.70–55.2%), galactose (6.2–19.1%), and xylose (0.90–8.57%). Additionally, Yelithao et al. [21] reported MWs of crude PSHs (710.3×10^3, 170.6×10^3, and 136.3×10^3 g/mol), as well as MWs of two fractions (255.0×10^3, 44.8×10^3; 533.7×10^3, 93.5×10^3, 79.8×10^3, respectively).

Since the presumed antiviral substances in the fungal extracts include PSHs, or proteins and PHs, a correlation study was made between the anti-dengue activity of the aqueous extracts (Aq) of *S. commune* and these components [12]. This study showed that the main chemical composition of the Aq were glucans, with a determined content of α-glucan (1.4 ± 0.1%) and β-glucan (34.4 ± 0.4%), and protein (15 ± 0.4%), while the PHs were detected in traces (0.31 ± 0.05%). The concentration and type of detected compounds varied based on the extraction method used, but no significant correlation for anti-dengue activity was reported [12].

Nonting et al. [19] evaluated the dependence of water-extraction conditions and β-glucan content due to the high demand in cosmeceuticals application, and determined that the β-glucan content from the extract with microwave-irradiation pretreatment was increased by 27.93%. Furthermore, Chen et al. [22] determined the influence of the four different extraction methods on the physicochemical properties, AO, and hypoglycemic activity of *S. commune* PSHs. This research showed that the highest PSH (67.96%), protein

(3.53%), and uronic acid (3.0%) content was obtained with hot-water extraction, as well as the highest MW (527.2 kDa). Another study confirmed these results, where the higher level of total PSH content (76.3 ± 1.2 mg GE/g extract) was observed in extracts subjected to hot-water extraction [24]. Meanwhile, Basso et al. [25] determined the β-glucan content of *S. commune* grown on different agro-industrial wastes, where substrates containing 94% grape residues showed the highest amount of PSHs (13.14%). The chemical composition of monosaccharides varied based on type of substrate used, with glucose from 8.53% to 30.03%, xylose from 4.13% to 10.95%, and arabinose from 0.24% to 0.60% [25]. Chen et al. [22] also detected ten monosaccharides, including ribose, rhamnose, glucuronic acid, galacturonic acid, glucose, galactose, xylose, arabinose, and fucose, in the PSHs extracted with hot water. However, due to the lowest AO activity obtained, hot-water extraction may not be the best choice for PSH extraction [22].

The submerged cultivation, extraction, and antitumor activity of the PSHs from *S. radiatum* were the focus of the study by López-Legarda et al. [1]. Elemental analysis of the dried mycelia of *S. radiatum* showed that the majority of the fungal biomass components were C and O (45.05% and 35.58%, respectively), followed by N and H (7.66% and 6.87%, respectively), while the presence of S was not determined. Extracts assigned as SIPS contained carbohydrates and total glucans in higher concentrations (79 ± 3% and 14 ± 2%, respectively) in comparison with SEPS (73 ± 6% and 11 ± 0.5%, respectively). Among the total detected glucans, β-glucans were the most represented in both PSH extracts (11–14%) in comparison with α-glucans (0.4–1.7%) (Table 1). Similar to some studies conducted on *S. commune*, the extracts have a larger concentration of β-glucans than of α-glucans, which supports the previously described link between α- and β-glucans seen in *S. commune* [15]. In addition, the high-performance liquid chromatography with the refraction-index-detection (HPLC-RI) technique showed that SIPS and SEPS are heteropolysaccharides composed mainly of arabinose, galactose, glucose, and xylose, similar to studies conducted on *S. commune* [10,22].

Table 1. Mychochemical profile of primary and secondary metabolites and bioactivities of genus *Schizophyllum* Fr. (species name, region, year of publication, identified primary and secondary metabolites, content, and used references).

Species	Region	Year of Publication	Primary Metabolites	Content/Molecular Weight	Secondary Metabolites	Content	Biological Activity	Reference
S. commune	India	2017	total carbohydrate crude fiber crude protein crude fat lipids	42.0% 30.0% 15.55% 9.0% 0.4%	-	-	Antimicrobial and antioxidant	[9]
S. commune	China	2017	low-MW EPS medium-MW EPS high-MW EPS	197 kDa 936 kDa 1437 kDa	-	-	Anti-inflammatory	[10]
S. commune	China	2017	EPS	2900 kDa	-	-	Anti-inflammatory	[11]
S. commune	India	2017	-	-	flavonoids saponins steroids tannins triterpenoids	qualitative mycochemical analysis	Antimicrobial	[26]
S. commune	Czech Republic	2017	ultrasonicated schizophyllan	-	-	-	Immunomodulatory	[23]
S. commune	India	2018	proteins	qualitative mycochemical analysis	glycosides flavonoids: catechin epicatechin rutin quercetin kaempferol phenolics: gallic acid chlorogenic acid caffeic acid coumaric acid triterpenoids	qualitative mycochemical analysis	Antioxidant, cytotoxic and genotoxic	[27]
S. commune	Korea	2019	-	-	nerolidol mannoside, (mannonerolidol) schizostatin nerolidol	-	Antibacterial and antifungal	[28]
S. commune	Malaysia	2019	α-glucan β-glucan protein	1.4 ± 0.1% 34.4 ± 0.4% 15 ± 0.4%	total phenolics	0.31 ± 0.05%	Antiviral (anti- dengue)	[12]

Table 1. *Cont.*

Species	Region	Year of Publication	Primary Metabolites	Content/Molecular Weight	Secondary Metabolites	Content	Biological Activity	Reference
S. commune	Thailand	2019	β-glucan	-	total phenolics	284.41 ± 1.22 mg GAE/g d.w.	Antioxidant	[13]
S. commune	Laos	2019	crude-PSH MWs fraction MWs carbohydrates proteins sulphates glucose mannose galactose xylose	710.3×10^3 g/mol 170.6×10^3 g/mol 136.3×10^3 g/mol 255.0×10^3 g/mol 44.8×10^3 g/mol 533.7×10^3 g/mol 93.5×10^3 g/mol 79.8×10^3 g/mol 50.3–65.8% 1.46–20.1% 1.33–7.01% 17.0–88.2% 2.70–55.2% 6.2–19.1% 0.90–8.57%	-	-	Immune enhancing	[21]
S. commune	Malaysia	2020	polysaccharides total glucan α-glucan β-glucan	66.7–76.3 mg GE/g extract 34.72 ± 1.94% 4.30 ± 0.40% 29.97 ± 1.55%	total phenolics	14.65 mg GAE/g extract	Antioxidant, anti-hyaluronidase, and anti-tyrosinase	[24]
S. commune	Brazil	2020	β-glucan	13.14%	total phenolics	299.31 ± 3.67 mg GAE/100 g	Antioxidant	[25]
S. commune	China	2020	polysaccharides protein uronic acid	45.09–67.96% 2.67–3.53% 1.92–3.0%	-	-	Antioxidant and hypoglycemic	[22]
S. commune	Indonesia	2020	-	-	-	-	Antibacterial	[29]
S. commune	Georgia	2020	-	-	-	-	Antibacterial	[30]
S. commune	Thailand	2020	β-glucan	5.04–32.94%	-	-	-	[19]
S. commune	Ukraine	2020	-	-	total flavonoids	0.64 ± 0.16 QE/g	Antioxidant	[31]
S. commune	India	2020	peptides MYSEKHGSGGT PGTRGAIAASSPQV MVSTLAVLGIREP EKEAAELGKGSF MSVTLLLLFISLVWVTISGLN	 1153.23 Da 1311.44 Da 1385.67 Da 1265.37 Da 2319.84 Da	-		Antioxidant	[14]

Table 1. *Cont.*

Species	Region	Year of Publication	Primary Metabolites	Content/Molecular Weight	Secondary Metabolites	Content	Biological Activity	Reference
S. commune	Thailand	2021	-	-	total phenolics	0.12–8.56 mg GAE/g d.w.	Antioxidant	[32]
					total flavonoids	53.06–577.35 µg CE/g d.w.		
S. commune	Thailand	2021	β-1,3-glucans	64.43–114.70 mg CE/g d.w.	total phenolics	15.15–18.92 mg GAE/g d.w.),	Antioxidant	[33]
			β-1,3-1,6-glucans	5.42–7.79 mg SE/g d.w	total flavonoids	422.54–910.54 CE/g d.w		
S. commune	Malaysia	2021	total protein total amino acid essential amino acid nonessential amino acid	1.30–2.17% 308.65–443.84 mg/g 51.44–88.56 mg/g 151.48–265.32 mg/g	-	-	-	[34]
S. commune	Italy and Serbia	2021	Polysaccharides	-	total phenolics phenolics: *p*-hydroxybenzoic acid protocatechuic acid gallic acid quinic acid	42.74–77.52 mg GAE/g d.w. (IT) 2.09–84.60 mg GAE/g d.w. (SRB) 1.87–22.19 µg/g.d.w. 1.90–5.41 µg/g.d.w. 75.77 µg/g d.w. 4.29–20.06 µg/g d.w.	Antioxidant antibacterial, and antiacetylcholinesterase	[15]
S. commune	Thailand	2021	α-glucan β-glucan	0.41–0.57% 47.94–49.20%	total phenolics	2.54–2.64 mg GAE/g d.w.	Antioxidant	[35]
S. commune	Germany	2021	-	-	sesquiterpenes: (-)-(1*R*,2*S*)-β-bisabolol β-bisabolene (*E*)-γ-bisabolene	-	Antibacterial and antifungal	[36]
S. commune	Japan	2021	-	-	volatile sulfur compounds: dimethyl disulfide dimethyl trisulfide dimethyl tetrasulfide methyl ethyl disulfide diethyl disulfide H_2S	-	-	[37]

Table 1. *Cont.*

Species	Region	Year of Publication	Primary Metabolites	Content/Molecular Weight	Secondary Metabolites	Content	Biological Activity	Reference
S. radiatum	Colombia	2021	total carbohydrate total glucans α-glucan β-glucan proteins	73–79% 11–14% 0.4–1.7% 11–14% 1%	-	-	Antitumor and immunostimulant	[1]
S. commune	Philippines	2022	proteins carbohydrates		saponins tannins alkaloids, flavonoids, terpenoids	-	Cytotoxic	[18]
S. commune	Malaysia	2022	-	-	-	-	Antioxidant and antimicrobial	[38]
S. commune	China	2022	-	-	fusidane-type antibiotics: (*E*)-4-(4-hydroxy-3-methylbut-2-en-1-yl) oxybenzoic acid methyl 4-(2,3-dihydroxy-3-methylbutoxy) benzoate ethyl 4-(2,3-dihydroxy-3-methylbutoxy) benzoate (*R*/*S*)-3-hydroxy-3-((*R*/*S*)-1-hydroxyethyl) indolin-2-one helvolinic acid 3,7-diketo-cephalosporin P_1 (24*R*)-6β-hydroxy-24-ethylcholest-4-en-3-one dankasterone A (22*E*,24*R*)-3β-hydroxyergosta-7,22-diene-6-one (3β,22*E*)-ergosta-5,7,22-trien-3-ol juglansnoid B *trans*-ferulic acid (*S*)-3-hydroxy-3-(2-oxopropyl) indolin-2-one schizostatin (13*S*)-8-oxo-(9*E*,11*E*)-8-oxo-octadeca-9,11-dien-13-olide	-	Antibacterial	[39]
S. commune	India	2022	total carbohydrate	0.597 ± 0.06 g/100 g d.w.	total phenolics	2.00 ± 0.05 mg GAE/g d.w.	Antioxidant and antibacterial	[40]
					total flavonoids	0.04 ± 0.00 mg QE/g d.w.		

Table 1. *Cont.*

Species	Region	Year of Publication	Primary Metabolites	Content/Molecular Weight	Secondary Metabolites	Content	Biological Activity	Reference
S. commune	Thailand	2022	schizophyllan	-	total phenolics in schizophyllan, total phenolics in supernatant total phenolics in mushroom essence	6.22 ± 0.06 mg GAE/g 12.85 ± 0.12 mg GAE/g 14.07 ± 0.09 mg GAE/g of dry extract	Antioxidant	[41]
S. commune	Turkey	2022	-	-	-	-	Antimicrobial and anticancer	[42]
S. commune	Review	2022	hemolysin monomer ribonuclease schizophyllan	29 kDa 20 kDa	-	-	Antiviral	[43]
S. commune	Malaysia and Thailand	2022	total carbohydrate total proteins	229.95–596.22 mg carbohydrate/g extract 395.75–539.69 mg protein/g extract	total phenolics total flavonoids	6.43–37.87 mg GAE/g extract 5.77–84.55 mg RE/g extract	Antioxidant	[44]

—no data; EPS—exopolysaccharide; MW—molecular weight; d.w.—dry weight; PSH—polysaccharide; schizophyllan (SPG); GAE—gallic acid equivalents; GE—glucose equivalents; QE—quercetin equivalents; CE—catechin equivalents; SE—schizophyllan equivalents; IT—Italy; SRB—Serbia; amino acid abbreviations: M—Met; Y—Tyr; S—Ser; E—Glu; K—Lys; H—His; G—Gly; S—Ser; T—Thr; P—Pro; R—Arg; A—Ala; I—Ile; Q—Gln; V—Val; L—Leu; F—Phe; W—Trp; N—Asn.

On the other hand, Mongkontanawat and Thumrongchote [35] worked on five pure mycelial culture strains of *S. commune* (Thailand), whereas 1-day-old dried *S. commune* fruiting bodies were used as samples. The authors applied two different β-glucan extraction methods: hot-water and hot-alkali extraction, which were compared with the control (native-MR). Results indicated that the total glucan content varied from 48.51 to 49.76%, whereas β-glucans were the most present, with a content of 47.94–49.20%, and α-glucans were present in the range of 0.41–0.57% [35]. It was discovered that the yield of β-glucan was unaffected by the extraction techniques. Moreover, FT-IR spectroscopy was used for the structural analysis of the extracted PSHs and showed that extraction conditions such as heat and alkalinity had an effect on the structure and AO activity of β-glucan from *S. commune*. The PSHs extracted from the fungal fruiting bodies were impacted by the extraction process, whereas the extracted β-glucan was affected by the extraction heat or pH. Additionally, it was found that the analyzed samples contained some PHs besides glucans, whereas TP was in the range of 2.54–2.64 mg GAE/g d.w. [35].

Enzymatic hydrolysiscreates peptides fromamino acids in proteins, which may have the strong ability to quench free radicals, thanks to which peptides are investigated as natural antioxidants in plants, and recently in fungal species. The relationship among radical-scavenging activity and amino acid composition, sequence, and the MW of *S. commune* peptides (Table 1) was determined, but no correlation was found between the degree of hydrolysis and ABTS radical-scavenging activity [14].

Mišković et al. [15] used FTIR for the determination of the spectra of PSH and EtOH extracts from Italian (IT) and Serbian (SRB) strains of *S. commune*. The method showed peaks characteristic for the presence of predominantly PSH molecules, small quantities of proteins, and some aromatic compounds, while the EtOH showed absorption bands characteristic for the carbohydrate polymers, polyphenolics, and proteins. Moreover, the authors analyzed the monosaccharide composition and found the presence of a large amount of D-glucose, with lower amounts of D-galactose and traces of D-mannose [15].

Al Azad and Ai Ping [34] determined the total protein, total amino acid content (AAC), and amino acid profile of the Aq and organic extracts (50% acetone, 50% EtOH, and 50% methanol–MeOH) from two edible fungi, including *S. commune*. The different extraction solvents used in this study affected the yield of the examined extracts, whereas the selectivity was characterized by different strengths of the polarity. Based on the results, the Aq extracts obtained the highest dry extract yield in general, while the yield for the Aq extract of *S. commune* was 14.48 ± 1.2%. It was found that the amount of protein varied between the extracts of the same fungal species, whereas the Aq extract contained the highest amount of total proteins (2.17 ± 0.28%). Similar to total proteins, total amino acids were present in the highest amount in the Aq extract (443.84 mg/g) as well [34]. *S. commune* extracts contained a total of 17 different kinds of amino acids, with an AAC of 308.65–443.84 mg/g, and among them, glutamic acid was the most present in the acetone and EtOH extracts (150.65 ± 2.55 mg/g and 111.49 ± 1.36 mg/g, respectively). In addition, the authors revealed that these extract types contained the highest content of amino acids [34].

Debnath et al. [40] investigated seven distinct carbon and six different nitrogen sources to identify the ideal starting point for the synthesis of EPS using a submerged cultivation. It was found that *S. commune* produced higher levels of EPSs in the presence of xylose (4.100.26 g/L) and in the yeast-extract medium (4.26 ± 0.11 g/L), while the highest TCC was obtained in glucose (0.597 ± 0.06 g/100 g) [40]. Al-Salihi and Lau [44] determined that gamma irradiation increased the total sugar content due to the possible overexpression of genes encoding the PSH synthesis.

3.2. Secondary Metabolites

Essential mycochemicals in fungi, such asphenolics and flavonoids (Figure 3), have drawn increased attention because of their ability to prevent disease through their AO, anti-inflammatory, and AM activities. These biologically active compounds represent the main secondary metabolites found in fungi [13,16,45,46].

Deka et al. [26] analyzed the extracts of eight macrofungal species, including *S. commune*, and determined the presence of the following secondary metabolites: flavonoids, saponins, steroids, tannins, and triterpenoids (Table 1). Kaur et al. [27] documented the presence of flavonoids, triterpenoids, and PHs, while the ultra-high-performance liquid chromatography (UHPLC) analysis confirmed the presence gallic acid, catechin, chlorogenic acid, epicatechin, caffeic acid, coumaric acid, rutin, quercetin, and kaempferol PH compounds in the ethyl acetate extracts of *S. commune.*

Considering that earlier studies showed the antibacterial activity of *S. commune*, Woo et al. [28] isolated a new nerolidol mannoside from an AM chloroform:MeOH fraction of the submerged culture broth, designated as mannonerolidol, in addition to schizostatin and nerolidol.

On the other hand, some authors investigated the effect of different substrates or extraction methods on the TP and total flavonoid content (TF) [24,25,32]. *S. commune* grown in 94% cotton cake demonstrated the highest TP (299.31 ± 3.67 mg GAE/100 g substrate) compared to the other substrates from agroindustrial waste [25]. Furthermore, *S. commune* cultured onto wheat exhibited the highest levels of PH (8.56 ± 1.09 mg GAE/g d.w.), while the highest TP was detected on barley as a substrate (577.35 ± 29.93 µg CE/g d.w.), compared to other edible cereal media used as a substrate [32]. Abd Razak et al. [24] obtained slightly higher TPs in fruiting-body extracts subjected to hot-water extraction (14.65 ± 0.01 mg GAE/g extract) compared to cold-water extraction (14.22 ± 0.02 mg GAE/g extract).

Comparison of the TFs in the fruiting bodies of confronting fungi *Hericiumcoralloides*, *Fomes fomentarius*, and *S. commune* showed that cocultivation is followed by the outstanding increase of the TFs (from 7- to 20.6-fold) compared to the monoculture conditions of *S. commune* as a response to stress factors [31].

The TFs of the *S. commune* hot-water extracts were lower than their TPs, while the gamma-irradiated strains showed higher levels of flavonoids compared to the parental strain [44]. The study demonstrated that the natural strain W possessed the highest TP and TF among the different *S. commune* strains from Malaysia and Thailand. In another study, Debnath et al. [40] determined the TP (2.00 ± 0.05 mg GAE/g) and TF (0.04 ± 0.00 mg QE/g) in *S. commune* from India. The same year, Saetang et al. [41] compared the TP in SPG, supernatant from the separation of SPG extraction, and fungal essence extracted with deionized water. The results showed the highest TP in the fungal essence (14.07 ± 0.09 mg GAE/g d.w.), followed by the supernatant (12.85 ±0.12 mg GAE/g d.w.) and the SPG (6.22 ± 0.06 mg GAE/g d.w.) [41].

Boonthatui et al. [33] determined the quantitative changes in the production of selected bioactive compounds (flavonoid, β-glucan, and PH) and their AO activities in the first and second harvests of *S. commune*. For two subsequent growing cycles, the authors divided fresh fungi samples into three groups and harvested them separately: (1) immature fruiting body (IF); (2) mature fruiting body with immature spores (MFISs); (3) mature fruiting body with mature spores (MFMSs). The findings showed that the PH compounds, flavonoids, and β-1,3- and β-1,3-1,6-glucans were considerably higher in fully grown fungi containing spores of each lifecycle. Regardless of the cycle, the fungal-bioactive-chemical content increased as it grew [33].

Four substances, gallic, *p*-hydroxybenzoic, protocatechuic, and quinic acids, were measured by liquid chromatography–mass spectrometry (LC-MS/MS) in the EtOH and PSH extracts of IT and SRB *S. commune* strains [15]. Among the quantified compounds, *p*-hydroxybenzoic acid was the most present (1.87–22.19 µg/g d.w.), and its presence was confirmed in all tested samples. Among the four quantified compounds, gallic acid was the

most abundant compound in the fermentation broth (F) extract of the SRB strain, with an amount of 75.77 µg/g d.w. The authors found that the EtOH extracts in general contained most of the quantified phenolic acids, whereas F contained a higher PH content than the mycelial biomass (M). Besides the LC-MS/MS profile, the authors measured the TP, although the TP levels in both strains were high and quite identical. In addition, the SRB extracts contained a higher amount (84.60 ± 1.64 mg GAE/g d.w. for F and 82.62 ± 0.99 mg GAE/g d.w. for M, respectively). Moreover, the authors showed that the F extracts of both strains contained a higher TP content compared to the M extracts [15].

In their study, Wirth et al. [36] claimed that volatile organic compounds (VOCs) such as ketones, sesquiterpenes, and ethanol are released by *S. commune*. Among them, sesquiterpene β-bisabolol and ethanol are involved in the *S. commune* biological activity against plant-pathogenic fungi that cause plant diseases [36]. Moreover, the *S. commune* strain *thn* produces large amounts of (-)-(1*R*,2*S*)-β-bisabolol, which makes it possible to analyze sesquiterpenes' role as AM metabolites. The sesquiterpenes (-)-(1*R*,2*S*)-β-bisabolol, β-bisabolene, and (*E*)-γ-bisabolene were dominant in GC-MS of different *S. commune* strains [36]. Volatile sulfur compounds were identified as the major VOCs produced by *S. commune*, and they can be helpful as biomarkers to diagnose different states, such as allergic bronchopulmonary mycosis caused by *S. commune* [37]. Among the identified compounds, dimethyl disulfide (DMDS), dimethyl trisulfide (DMTriS), dimethyl tetrasulfide (DMTetraS), methyl ethyl disulfide (MEDS), diethyl disulfide (DEDS), and H_2S were determined as the major VOCs of *S. commune* [37].

The constant search for new antibiotics within the secondary metabolites of fungi led to the discovery of fusidane-type antibiotics. These compounds are represented by fusidic acid, helvolic acid, and cephalosporin P1, and share similar core structures, but are produced by fungi [47]. Chen et al. [22] isolated sixteen active fusidane-type compounds from the ethyl acetate extract of the solid-state fermented *S. commune.*

When compared to current medicines for many disorders, metallic nanoparticle systems have a significant potential to offer effective treatment with few adverse effects [48]. In recent years, silver has grown in prominence as a crucial component for producing metallic nanoparticles, whereas silver nanoparticles (AgNPs) have undergone extensive assessment for the creation of future diagnostic and treatment systems [42]. In relation to this, Tosun et al. [42] synthesized AgNPs with green chemistry by microwave irradiation using the edible fungal species *Geoporasumneriana* and *S. commune*.

4. Biological Activities

4.1. Antioxidant Activity

Edible fungi represent a fantastic source of antioxidants due to the accumulation of different secondary metabolites, including PHs, flavonoids, steroids, terpenoids, carotenoids, polyketides, and quinones [46].

Debnath et al. [9] analyzed the AO activity of the MeOH extract of *S. commune* using a DPPH assay and showed the scavenging effect rapidly increased from 0.5 mg/mL to 8.0 mg/mL, showing an IC_{50} value at 1.4 mg/mL. The highest scavenging ability was determined at a concentration of 8.0 mg/mL (91.85%) [9], while a 2022 study of *S. commune* from a submerged culture determined the highest activity (92.59%) at a 16 mg/mL concentration, with a chelating effect of 91.11% [40]. In comparison with standard compounds (ascorbic acid and BHA), the extract showed a lower scavenging ability at a concentration of 0.125 mg/mL (inhibition of 95.37% and 97.83%, respectively) [9,40]. Moreover, the scavenging activity of β-glucan isolated from the *S. commune* strain from Thailand was confirmed by ABTS (IC_{50} = 0.829 ± 0.006 mg/mL) and DPPH (IC_{50} = 0.724 ± 0.021 mg/mL) assays [13]. Since, in this study, the TP in β-glucan extracts were documented [13], we can assume that the complexes of primary and secondary metabolites, in this case PSHs and PHs, are responsible for the obtained activity, which coincides with previously published research [15]. This is also supported by studies where peptides and PHs found in *S. commune* from India and Thailand positively correlated with ABTS scavenging activity [14,32].

Chen et al. [22] obtained a concentration-dependent trend of the reducing power, DPPH, and hydroxyl radical-scavenging abilities (range from 0.5 to 3.0 mg/mL) of the PSHs extracted using different extraction methods. Abd Razak et al. [24] demonstrated the AO activity of hot- and cold-water extracts by DPPH, SOA, and FRAP assays. Results of this study showed that the cold-water extract of *S. commune* had the highest DPPH (69.79 ± 0.13%) and SOA inhibition activity (94.82 ± 1.29%) [24]. Since the ultrasound-assisted hot-water extraction exhibited the highest PSH and TP, as well as cold extraction, they are proposed as the best extraction techniques due to the highest levels of AO activity [22,24]. The highest DPPH scavenging activity was recorded for *S. commune* grown on 94% cotton cake (60.74 ± 0.7%) and wheat substrate (IC_{50} = 3.83 ± 0.33 mg/mL), while the strongest FRAP activity was obtained from barley (IC_{50} = 2.14 mg/mL) [25,32].

Additionally, the introduction of the stress of direct fungi confrontation led to an increased AO activity, as well as the levels of MDA detected by lipid peroxidation in the fruiting bodies of *S. commune* [31]. Boonthatui et al. [33] studied the AO potential of *S. commune* fruiting bodies at different stages of maturity in both generations and confirmed the scavenging activity of different maturity samples with the DPPH, ABTS, and ferric-reducing AO power assays. The highest DPPH, ABTS, and ferric-reducing AO power in the first cycle of harvesting was determined as IC_{50} = 0.69 ± 0.02 mg/mL, IC_{50} = 2.59 ± 0.13 mg/mL, and EC_{50} = 1.86 ± 0.17 mg/mL, respectively, while for the second cycle, it was measured as IC_{50} = 0.67 ± 0.08, IC_{50} = 2.18 ± 0.36, and EC_{50} = 1.15 ± 0.07 mg/mL, respectively.

Moreover, it was observed that fully grown cultivated fungi strongly correlated with their TP and TF, whereas bioactive compounds and AO activities of the second-harvest fungi were higher than for the first batch [33]. In the same year, Mišković et al. [15] worked on the examination of AO activity using six different in vitro assays (DPPH, ABTS, FRAP, OH, NO, and SOA). Among the analyzed extracts, the PSH extract after 7 days of submerged cultivation exhibited the most significant AO activity, opposite to the EtOH extracts, where the 14- and 21-day incubation periods stood out [15]. Moreover, it was found that there are statistically significant differences between the PSH and EtOH samples from the SRB strain in the DPPH and FRAP assays. The authors concluded that the majority of the submerged samples demonstrated significant AO activity, which is directly related to the traits of the strain's growth because it can indicate the point of entry into the secondary metabolism [15].

Mongkontanawat and Thumrongchote [35] measured the AO potential of β-glucan extracts using DPPH and ABTS assays, and found small differences between the activities of the five analyzed *S. commune* strains (Table 1).

One year later, the AO activity of the SPG, the supernatant from the separation of the extraction, and the fungal essence was examined [41]. Results revealed that the split-gill fungal essence exhibited prominent potential for the inhibition of the ABTS radical (98.18%) at 5.00 mg/mL (IC_{50} = 0.73 ± 0.02 mg of dry extract/mL) [41]. On the other hand, Al Azad and Ping [38] compared the AO activity of this fungi extracted in Aq and distinct organic solvents (acetone, MeOH, and EtOH). The highest DPPH scavenging activity was seen in the Aq extract (IC_{50} = 1.52 mg/mL), while the greatest reducing power was exhibited by the acetone extract (IC_{50} = 0.22 mg/mL) [38]. Furthermore, the results measured by the ABTS and DPPH assays in the Al-Salihi and Lau study [44] indicate the higher scavenging activities of hot-water extract of *S. commune* compared to the Aq extract of *P. pulmonarius*. The study suggested that PFs and flavonoids are the main contributors to higher activity since a positive correlation was observed. They also presented that gamma-irradiated strains exhibited a superior scavenging activity and reducing power in all assays other than the natural strain. The authors explained that mutation triggered by irradiation might have caused changes in the gene expression and led to the increased production of secondary metabolites with AO activity [44].

4.2. Anti-Acetylcholinesterase Activity

Free-radical production and quenching imbalance may result in a variety of illnesses, including neurodegenerative conditions such as Alzheimer's disease [15]. Acetylcholinesterase inhibitors have gained popularity among researchers because there is no cure for this condition or a way to stop or reverse its progression. As a result, a variety of organisms, including fungi, have been studied in an effort to develop a physiologically active substance that could replace the acetylcholinesterase inhibitors effectively. To the best of our knowledge, the anti-acetylcholinesterase activity of *S. commune* was only investigated in one study from 2021 [15]. Mišković et al. [15] demonstrated that the PSH extracts showed remarkable neuroprotective results, launching this type of research, and establishing *S. commune* as an important source of AChE inhibitors. In their study, the greatest AChE activity was seen in the M28 SRB PSH extract (IC_{90} = 79.73 ± 26.34 µg/mL), while the IT was more active in the case for the F14 EtOH extracts (IC_{50} = 0.8 ± 0.6 µg/mL). It is important to note that the activity of the M28 SRB PSH extract is comparable with the activity of a commercially approved Alzheimer's disease drug donepezil (IC_{90} = 87.92 µg/mL). Anti-AChE activity was documented for phenolic compounds and flavonoids [49], while results from our previous study strongly pointed out the possibility of the synergistic effect of both primary (mixture of polysaccharide fraction, probably SPG) and secondary metabolites (phenolics) [15].

4.3. Antimicrobial Activity

Medicinal fungi have great prospects in the drug and nutraceutical industries, as they possess a wide range of pharmacological properties, including antiviral (AV), antifungal (AF), and antibacterial (AB) activity [16]. Finding AB metabolites from various sources, including medicinal fungi, is crucial in the search for novel antibiotics that can fight the antibiotic resistance of a number of bacterial infections.

Debnath et al. [9] analyzed the AM activity of the MeOH extract of *S. commune* by using by the disc-diffusion method on Gram-positive bacterial strains (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacterial strains such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Xanthomonas campestris*. Based on the results, the MeOH extract showed the highest inhibition against *B. subtilis* and *X. campestris* in comparison with those of *E. coli* and *S. aureus*. *S. commune*'s MeOH extract had no effect on *P. aeruginosa,* which was confirmed in a 2022 study by Debnath et al. [40] as well. Meanwhile, the study by Deka et al. [26] analyzed the AM activity of the EtOH and Aq extracts of macrofungal species, including *S. commune*, against *B. subtilis*, *E. coli*, *P. aeruginosa*, *Salmonella typhi*, and *S. aureus*. The analyzed extracts showed various degrees of AM effects against the tested microorganisms, whereas the EtOH extract showed satisfactory results, with an MIC range of 10–25 mg/mL. In addition, the *S. commune* extracts showed wider inhibition zones in the disc-diffusion method. The activities of commercial drugs, when compared to the analyzed extracts, were found to be lower, whereas the microbial-inhibition activity was found to be in the range of 2.28–7.33 mm. The highest activity was shown against *E. coli* [26].

AB activity against *S. aureus* was confirmed in another study, together with AF activity against *Candida albicans*, as reported by Mandal [50]. The significant AF activity of schizostatin against *Rhizoctonia solani, Diaporthe* sp., *Botrytis cinerea,* and *Alternaria solani* was reported, while a new nerolidol mannoside (mannonerolidol) isolated from the same culture broth of *S. commune* displayed moderate AF activities against *R. solani* and *Diaporthe* sp., with clear zone diameters of 11.4 and 10.9 mm, respectively [28]. In the same study, schizostatin exhibited AB activity against *B. subtilis* and *S. aureus,* while nerolidol did not exhibit any AM activity.

Khardziani et al. [30] conducted AB screening of *S. commune* grown on agar plates in the submerged and solid-state fermentation of five lignocellulosic growth substrates. Strong activity against *S. aureus* (13 mm inhibition zone), *S. enteritidis* (11 mm), *E. coli* (12 mm), *P. aeruginosa* (19 mm), and *S. epidermitidis* (12 mm) was observed [30]. Moreover, *S. commune* filtrates inhibited the growth of *B. cereus* and *E. cloacae* [29]. The testing of the AB activity

after submerged and solid-state cultivation revealed that the highest inhibition activity against both Gram-negative and Gram-positive strains (94 and 98% growth inhibition, respectively) was in the presence of mandarin pulp in the substrate [30]. This study also documented the effect of the carbon and nitrogen source on the AB activity, where it was shown that xylose ensured the maximum inhibition for *S. aureus* and glucose for *E. coli*, as well as that KNO_3 supplementation enhancing the AB activity [30].

In their study, Mišković et al. [15] examined AM activity, measuring the minimal bactericidal concentration (MBC) and MIC of EtOH extracts. Only two extracts among all the tested SRB-strain samples exhibited AB activity, while the IT strain was not active. It was found that the F extract of the SRB strain after 21 days of cultivation expressed the highest AM activity, with MIC and MBC values lower than 0.31% against three bacterial strains (*B. cereus*, *E. coli*, and *S. aureus*), while the lowest was exhibited against *P. aeruginosa* (with MIC and MBC values of 5%). At the same time, Wirth et al. [36] determined that the presence of the bisabolene mixture from *S. communethn* mutants was considered potentially responsible for the growth inhibition of the analyzed bacteria and fungi based on the fact that their absence in *S. commune* wildtype monokaryon correlated with reduced effects. It was found that used mixture led to growth inhibition in *Flammulinavelutipes*, *Ganoderma lucidum*, and *Kuehneromycesmutabilis*, whereas the influence of (-)-(1*R*,2*S*)-β-bisabolol was even stronger on growth reduction for all analyzed mushrooms. The (-)-(1*R*,2*S*)-β-bisabolol and the mixture of bisabolenes did not show an effect on bacterial growth that would mimic the effect of the VOC of *S. commune* thn. In addition, the bisabolene mixture and (-)-(1*R*,2*S*)-β-bisabolol significantly reduced the swarming motility in the experiments on the analyzed Gram-negative bacteria *Serratia marcescens*.

Al Azad and Ping [38] compared the AB activity of *S. commune* extracted with Aq and three types of organic solvents. All tested extracts inhibited *Vibrio harveyi* growth, with an MIC lower than 1.25 mg/mL, while the MIC values of 2.5 mg/mL and 5 mg/mL in *V. parahaemolyticus*, as well as of 5 mg/mL and 10 mg/mL in *V. anguilarium*, were observed [38].

Fusidane-type active compounds, helvolinic acid and diketo-cephalosporin P1, isolated from *S. commune* ethyl acetate extracts, exhibited strong AB activity against *Stenotrophomonas maltophilia*, with MIC values of 4 μg/mL and 16 μg/mL, respectively [39].

In summary, *S. commune* exhibited a significant AB response; however, a stronger effect was observed against Gram-positive bacteria as opposed to Gram-negative ones [9,30,40,50]. Moreover, *S. aureus* and *B. subtilis* were more sensitive to MeOH extracts [40], which indicates that further research should be based on this type of solvent.

The prominent anti-dengue serotype 2 activity of the Aq soluble extracts of *S. commune* was documented in vitro with simultaneous (IC_{50} = 424.9 μg/mL) and penetration (IC_{50} = 279.3 μg/mL) assays [12]. Zhang et al. [43] summarized that hemolysin monomer and ribonuclease extracted from *S. commune* fruiting bodies inhibit the activity of HIV-1 reverse transcriptase, while SPG was associated with regulation of humoral immune response and improving antibody levels in patients with chronic hepatitis B. Furthermore, this polysaccharide (SPG) enhanced shrimpimmune levels against white spot syndrome virus [43].

In addition to the most common application of fungal extracts, AgNPs have a big potential in designing next-generation anticancer and AM agents. Tosun et al. [42] analyzed synthesized AgNPs nanoparticles as potential AM and anticancer agents. The AM potential of the AgNPs was determined as AB against pathogenic bacterial (*Enterococcus faecalis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*) and fungal (*Candida albicans*, and *C. utilis*) strains, while the anticancer activities were studied on the four cancer cell lines (breast (MCF-7), lung (A549), colon (HT-29), and liver (HUH-7) cancer cells). The authors pointed out the fact that nanoparticles synthesized from fungi have great potential for the treatment of cancer and infectious diseases [42].

4.4. Antitumor Activity

Due to the diversity of their physicochemical properties and the intricacy of their antitumor effects, natural PSHs' anticancer effectiveness has been challenging to compare with manufactured medicines [51]. Different fungal PSHs showed varying degrees of antitumor activity, and typically, were in correlation with the immunomodulatory activities of the identified compounds [51]. The antitumor activity of *S. commune* was analyzed in studies conducted before 2017, while in the period covered in this paper, we did not find studies that examined the mentioned activity of this species.

The submerged cultivation, extraction, and antitumor activity of PSHs from *S. radiatum* were the focus of the study by Lopez-Legarda et al. [1]. Different cancer cell lines (EL-4, MDA-MB-231, RAW 264.7, and U937) were analyzed for antitumor and immunostimulant activities. The findings imply that these PSHs both directly and indirectly inhibit tumor growth by stimulating immune cells such asmacrophages [1]. The highest antitumor activity was determined for the SIPS extract, while the best immunostimulant activity was obtained for the SEPS extract. The researchers concluded that, although the *S. commune* PSHs studied did not have a strong and direct antitumor effect as with other anticancer drugs, they had a considerable impact on the in vitro activation of macrophages. Probably, the in vivo the antitumor activity of SIPS and SEPS could be enhanced with the help of all the immunological machinery and gut microbiota [1].

5. Conclusions

In conclusion, research on the described bioactivites and mycochemistry identification has expanded in a five-year period, particularly in terms of the *S. commune* species, except for the antitumor activity. The most examined bioactivites were AO and AM, while the anti-AChE and antitumor activities received only passing consideration. Moreover, the most examined compounds were glucans, isolated from *S. commune*, even though many studies reported PHs and other secondary metabolites, including alkaloids, terpenoids, and steroids, detected as well. These findings suggest that the synergism of primary and secondary metabolites is responsible for the detected bioactivities of genus *Schizophyllum*. In general, more attention should be paid to the antitumor and anti-AChE activity, together with more accurate compound identification of genus *Schizophyllum*, specifically *S. commune* and *S. radiatum*, considering their huge biopotential. Nevertheless, *S. commune* should be considered as one of the first choices for functional food and pharmaceutical production.

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Abbreviations

AAC	total amino acid content
AB	antibacterial
ABTS	and 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid
AChE	acetylcholinesterase
AF	antifungal
AM	antimicrobial
AO	antioxidant
Aq	aqueous, water
AV	antiviral
BHA	butylated hydroxyanisole
DPPH	2,2-diphenyl-1-picrylhydrazyl
EPS	exopolysaccharide
EtOH	ethanolic
F	fermentation broth
FRAP	ferric reducing–antioxidant power
GC-MS	gas chromatography–mass spectrometry
HPLC-RI	high-performance liquid chromatography with refraction index detection
IR	infrared
IT	Italy
LC-MS/MS	liquid chromatography–mass spectrometry
M	mycelial biomass
MBC	minimum bactericidal concentration
MeOH	methanol
MIC	minimum inhibitory concentration
MW	molecular weight
NO	nitric oxide radical
OH	hydroxyl radical
PH	phenolic
PSH	polysaccharide
SEPS	water-soluble exopolysaccharide
SIPS	water-soluble intrapolysaccharide
SOA	superoxide anion radical
SPG	schizophyllan
SRB	Serbia
TCC	total carbohydrate content
TF	total flavonoid content
TP	total phenolic content
VOC	volatile organic compounds

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