

# Revisiting *Ramaria* species: the Coral Fungi as Food and Pharmaceuticals

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**Abstract:** With the advancement of the quality of life and the resultant increase in the frequency of life-threatening diseases, food is being viewed as a source of nutritional and functional benefits. Mushrooms have served as nutritious food from time immemorial along with useful medicinal properties. The genus *Ramaria*, coral fungi, is a potential group of culinarily acclaimed mushrooms with worldwide distribution. During the past two decades, studies on several species of the genus revealed high medicinal potency. In this review, we particularly aim to update this group's present status with respect to its importance as food and medicine, which will offer a new perception to researchers for its progress from dietary food to functional food.

**Keywords:** bioactive metabolites; functional food; mycomedicine; *Ramaria* sp.

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## 1. Introduction

Mushrooms are famous as therapeutic food since prehistoric times. A global population of about 140,000 mushroom species has been estimated, of which only 10% has been recorded well investigated [1]. It is believed that food and medicines share a common point of origin, and mushrooms are one of the most suitable manifestations of this idea [2]. They possess immense potential in bioprospecting based on their colossal roles in the production of ecologically beneficial bioactive metabolites, ethnomedical uses as well as enriched possibilities for genetic, pharmacological, and chemical analysis [3-5].

*Ramaria* Fr. ex Bonord is one of the most beautiful coralloid fungi with conspicuously colored basidiomata and circuitous branching pattern, bearing similarities with the genus *Clavaria*, because of which Persoon had described *Ramaria botrytis* and mistakenly placed it under the genus *Clavaria* [6, 7]. This genus contains 336 species, among which many species are distributed worldwide. From the Indian subcontinent, only 51 species have been reported to date [8]. However, the literature on this genus has been limited to its resource investigation and identification. Many species of this genus are ethnically edible such as *R. versatilis*, *R. aurea*, *R. botrytis*, and others. In contrast, a few species possess twofold traits as a consumable and ectomycorrhizal association [9-11].

The aim of this review is to compile recent data on the nutritional and medicinal properties of different species belonging to this genus.

## 2. Proximate composition of *Ramaria* species

The proximate composition of mushrooms is defined in terms of six parameters, among which moisture content is one of the essential factors that determine the freshness of tissue. Concerning *Ramaria* species, moisture content was relatively high in *R. botrytis* and *R. flava*, as reported in the literature [12, 13]. The proximate composition of *Ramaria* species is presented in Table 1.

Carbohydrates and crude protein are considered as such significant components that comprise the bulk of mushroom fruiting bodies. According to the table, the sugar content of *Ramaria* species varies with different regions of collections throughout the globe. The variability of carbohydrates and protein content among different *Ramaria* sp. seems to be associated with varying strains, substrate composition, and others. Mushrooms are a preferred source of nutrition because of their high-quality carbohydrate and protein and their low-fat content and high content of polyunsaturated fatty acids (PUFA) [14]. From the literature survey, it has been observed that the amount of lipids/fats in *Ramaria* sp. ranges from 0.14%-5.67% on a dry weight basis (Table 1). According to reports, *Ramaria* sp. contains many unsaturated fatty acids, especially MUFA and PUFA.

In contrast, linoleic acid (8.28%) and eicosadienoic acid (4.20%) were the most abundant PUFA in *R. botrytis*[15]. Thus, cumulatively, *Ramaria* species have significant nutritional attributes and can be listed in nutrition-rich food items. However, information about the digestibility and bioavailability of these mushroom nutrients has lacked a further in-depth study of these species.

**Table 1.** Nutritive property of different species of *Ramaria*.

Nutritional parameters (%)	<i>R. largentii</i>	<i>R. patagonica</i>	<i>R. rubripermanens</i>	<i>R. brevispora</i>	<i>R. flava</i>	<i>R. flavescens</i>	<i>R. aurea</i>	<i>R. stricta</i>	<i>R. botrytis</i>	
Carbohydrate	58.87	69.43	48.82	ND	46.54	45.26	43.82	40.50	50.25	5.12
Protein	28.8	19.68	16.32	24.1	15.8	14.60	13.30	10.81	21.65	4.08
Fat	5.67	2.51	1.49	1.30	1.26	1.18	0.91	0.37	0.22	0.14
Dietary fibres	ND	ND	1.06	8.8	1.02	0.90	0.82	0.28	1.33	ND
Moisture	ND	ND	ND	ND	93.3	ND	ND	ND	89.77	89.77
Reference	[53]	[21]	[15]	[54]	[15]	[15]	[15]	[15]	[15]	[12]

ND: not detected

## 3. Bioactive secondary metabolites

Mushrooms are often considered a storehouse of bioactive metabolites that show immense potential as promising therapeutic agents [16]. These include phenolic compounds, terpenoids, sterols, and others, which play a vital role as scavengers of free radicals and thus stabilize lipid oxidation. Several studies have been conducted to ascertain the amount of bioactive secondary metabolites in different species of *Ramaria*.

The most extensively studied species is *R. flava*. The ethanolic extract of this mushroom contained higher phenolic content than methanolic extract [17-19]. Moreover, high-performance liquid chromatogram analysis of an ethanolic extract of *R. flava* from Mongolia revealed the presence of quercetin, chrysin, and pinocembrin. The hydromethanolic extract of *R. largentii* revealed the presence of protocatechuic and vanillic acids [20]. Furthermore, the methanolic extract of *R. patagonica* [21], *R. formosa* [22], and *R. subalpina* [23] was reported to contain phenolic compounds, including gallic acid, p-hydroxybenzoic acid, p-coumaric acid. Other than alcoholic extract, Khatua *et al.* [24] determined phenolic constituents of a heat-stable polyphenol-rich extract of *R. aurea* in which caffeic acid was found as the most abundant

phenolics followed by cinnamic acid and gallic acid. On the other hand, *Ramaria* sp. was also reported to contain carotenoids, ascorbic acid, anthocyanidins, and tocopherols [15].  $\beta$ -tocopherol was found to be present in a higher amount than  $\alpha$  tocopherol, the active form of Vitamin E.

#### 4. *Ramaria* species and their prospective medicinal properties

##### 4.1. Antioxidant activity.

A wide variety of reports regarding antioxidative properties of different *Ramaria* sp. have been published, which revealed the potentiality of these fungi as an effective antioxidant. The majority of reports showed radical scavenging activity of extracts tested in *in-vitro* systems; only two reports described *in-vivo* experiments (Table 2). *R. flava* [17-19] and *R. botrytis* [12, 15, 25] were the most extensively studied species of this group. The methanolic and ethanolic extracts of these two species were able to scavenge free radicals, which seem to occur because of synergistic effects of different phenolic compounds extracted through experiments. Besides scavenging free radicals, *Ramaria* species also showed positive results in lipid peroxidation inhibition assay, iron-chelating assay, reducing power assay, and 15-lipoxygenase inhibition (Table 2). The methanolic extract *R. botrytis* was also tested to determine its antioxidant potential in both *in vitro* and *in vivo* system. The extract was found to reduce superoxide dismutase (SOD), catalase, and glutathione peroxidase levels and inhibit lipid peroxide content in the liver of benzo- $\alpha$  pyrene treated mice [26].

**Table 2.** Antioxidant activities of different species of *Ramaria*.

Species	Collection place	Methods used	Extracts used	Activity (EC <sub>50</sub> /% of inhibition)	References
<i>R. flava</i>	Turkey	$\beta$ -carotene linoleic acid assay	Methanol	95.02% at 20 mg/mL	[17]
		DPPH scavenging assay		94.78% at 12 mg/mL	
		Reducing power		1.91 at 20 mg/mL	
		Metal chelating effect		96.75 at 2 mg/mL	
<i>R. formosa</i>	India	DPPH radical scavenging activity	Methanol	EC <sub>50</sub> 5.8 mg/ml	[22]
<i>R. flava</i>	Turkey	DPPH scavenging assay	Ethanol	EC <sub>50</sub> 276 $\mu$ g/mL	[18]
		$\beta$ -carotene linoleic acid assay		94.7% at 160 $\mu$ g/mL	
<i>R. flava</i>	China	DPPH radical-scavenging activity	Ethanol	EC <sub>50</sub> 34.41 $\mu$ g/mL	[19]
			Petroleum ether	EC <sub>50</sub> 42.29 $\mu$ g/mL	
			Ethyl acetate	EC <sub>50</sub> 20.37 $\mu$ g/mL	
			n-butanol	EC <sub>50</sub> 46.80 $\mu$ g/mL	
			Water	EC <sub>50</sub> 5.86 $\mu$ g/mL	
	China	Hydroxyl radical-scavenging activity assay	Ethanol	EC <sub>50</sub> 41.46 $\mu$ g/mL	
			Petroleum ether	EC <sub>50</sub> 102.43 $\mu$ g/mL	
			Ethyl acetate	EC <sub>50</sub> 32.41 $\mu$ g/mL	
			n-butanol	EC <sub>50</sub> 116.55 $\mu$ g/mL	
			Water	EC <sub>50</sub> 18.08 $\mu$ g/mL	
<i>R. botrytis</i> (Pers.)	China	DPPH radical-scavenging activity	Purified polysaccharide (RBP)	44.33% at 1.4 mg/mL	[55]
			RBP1		
			RBP2	14.67% at 1.4 mg/mL	
			RBP3	74.01% at 1.4 mg/mL	
		RBP4	82.67% at 1.4 mg/mL		
		Hydroxyl radical scavenging activity	RBP1	~19% at 1.2 mg/mL	
			RBP2	~50% at 1.2 mg/mL	
			RBP3	90% at 1.2 mg/mL	
			RBP4	~70% at 1.2 mg/mL	
		Reducing power	RPB1	~0.2 absorbance at 1.5 mg/mL	

Species	Collection place	Methods used	Extracts used	Activity (EC <sub>50</sub> /% of inhibition)	References
			RBP2	0.8 absorbance at 1.5 mg/mL	
			RBP3	0.4 absorbance at 1.5 mg/mL	
			RBP4	0.56 absorbance at 1.5 mg/mL	
<i>R. botrytis</i>	Portugal	DPPH scavenging activity	Methanolic extract	EC <sub>50</sub> 0.66 mg/mL	[12]
		Reducing power		EC <sub>50</sub> 0.68 mg/mL	
		β-carotene bleaching inhibition		EC <sub>50</sub> 0.67 mg/mL	
		Lipid peroxidation inhibition		EC <sub>50</sub> 1.01 mg/mL	
<i>R. aurea</i>	India	DPPH scavenging activity	Polyphenol rich ethanolic extract	EC <sub>50</sub> 0.283 mg/mL	[24]
		Superoxide scavenging activity		EC <sub>50</sub> 0.384 mg/ml	
		Chelating ability		EC <sub>50</sub> 0.95 mg/ml	
		Reducing power		EC <sub>50</sub> 1.025 mg/ml	
<i>R. patagonica</i>	Argentina	DPPH scavenging activity	Methanol	EC <sub>50</sub> 770 µg/mL	[21]
		Reducing power		EC <sub>50</sub> 170 µg/mL	
		β-carotene bleaching assay		EC <sub>50</sub> 610 µg/mL	
		TBARS inhibition activity		EC <sub>50</sub> 60 µg/mL	
<i>R. formosa</i>	Korea	DPPH scavenging activity	Ethyl acetate	117 AsA/mg/mL at 500 µg/mL	[50]
		Peroxyl radical scavenging activity		7.8 µM trolox equivalent at 20 µg/mL	
		Reducing capacity		36% copper ion inhibition at 20 µg/mL concentration	
<i>R. botrytis</i>	Korea	DPPH scavenging activity	Ethanol	91.4%	[25]
			Methanol	92.1 %	
			Ethyl acetate	55.9%	
			Acetone	70%	
		ABTS scavenging activity	Ethanol	50.6%	
			Methanol	87.6%	
			Ethyl acetate	2.8%	
			Acetone	60.8%	
<i>R. botrytis</i>	India	DPPH radical scavenging activity	Ethanol	EC <sub>50</sub> 680 µg/mL	[15]
		ABTS radical scavenging activity		EC <sub>50</sub> 390 µg/mL	
		Ferric ion reducing power		EC <sub>50</sub> 920 µg/mL	
		Iron chelating ability		EC <sub>50</sub> 1120 µg/mL	
		Superoxide anion radical scavenging activity		EC <sub>50</sub> 869 µg/mL	
<i>R. rubripermanens</i>		DPPH radical scavenging activity		EC <sub>50</sub> 760 µg/ml	
		ABTS scavenging activity		EC <sub>50</sub> 430 µg/mL	
		Ferric ion reducing power		EC <sub>50</sub> 1150 µg/mL	
		Iron chelating ability		EC <sub>50</sub> 1220 µg/mL	
		Superoxide anion radical scavenging activity		EC <sub>50</sub> 1120 µg/mL	
<i>R. flava</i>		DPPH radical scavenging activity		EC <sub>50</sub> 880 µg/mL	
		ABTS radical scavenging activity		EC <sub>50</sub> 490 µg/mL	
		Ferric ion reducing power		EC <sub>50</sub> 1180 µg/mL	
		Iron chelating ability		EC <sub>50</sub> 1340 µg/mL	
		Superoxide anion radical scavenging activity		EC <sub>50</sub> 1350 µg/mL	
<i>R. flavescens</i>		DPPH radical scavenging activity		EC <sub>50</sub> 1520 µg/mL	
		ABTS radical scavenging activity		EC <sub>50</sub> 590 µg/mL	

Species	Collection place	Methods used	Extracts used	Activity (EC <sub>50</sub> /% of inhibition)	References
<i>R. aurea</i>		Ferric ion reducing power		EC <sub>50</sub> 1280 µg/mL	
		Iron chelating ability		EC <sub>50</sub> 1380 µg/mL	
		Superoxide anion radical scavenging activity		EC <sub>50</sub> 1480 µg/mL	
		DPPH radical scavenging activity		EC <sub>50</sub> 1580 µg/mL	
		ABTS radical scavenging activity		EC <sub>50</sub> 590 µg/mL	
		Ferric ion reducing power		EC <sub>50</sub> 1280 µg/mL	
		Iron chelating ability		EC <sub>50</sub> 1440 µg/mL	
		Superoxide anion radical scavenging activity		EC <sub>50</sub> 1550±0.0 µg/mL	
<i>R. stricta</i>		DPPH radical scavenging activity		EC <sub>50</sub> 1720±0.0 µg/mL	
		ABTS radical scavenging activity		EC <sub>50</sub> 920 ±0.0 µg/mL	
		Ferric ion reducing power		EC <sub>50</sub> 1320±0.0 µg/mL	
		Iron chelating ability		EC <sub>50</sub> 1580±0.0 µg/mL	
		Superoxide anion radical scavenging activity		EC <sub>50</sub> 1580±0.3 µg/mL	
		Reducing power		14.73%	
<i>R. aurea</i>	India	Hydroxyl radical scavenging activity	Ethanol	EC <sub>50</sub> 64.9 µg/mL	[56]
			Coldwater	EC <sub>50</sub> 300 µg/mL	
			Hot water	EC <sub>50</sub> 240 µg/mL	
		DPPH radical scavenging activity	Ethanol	EC <sub>50</sub> 87 µg/mL	
			Coldwater	EC <sub>50</sub> 160 µg/mL	
			Hot water	EC <sub>50</sub> 145 µg/mL	
		Nitric oxide synthase activity	Ethanol	620 gm mol NO produced/ mg d.w/hr	
			Cold water	310 gm mol NO produced/ mg d.w/hr	
			Hot water	400 gm mol NO produced/ mg d.w/hr	
		Inhibition of lipid peroxidation	Ethanol	EC <sub>50</sub> 100 µg/mL	
			Coldwater	EC <sub>50</sub> 380 µg/mL	
			Hot Water	EC <sub>50</sub> 360 µg/mL	
<i>R. subalpina</i>		Total antioxidant capacity	Methanol	230 µg ascorbic acid equivalent/mg of extract	[23]
		DPPH radical scavenging activity		EC <sub>50</sub> 0.3 mg/mL	
		Chelating ability		EC <sub>50</sub> 0.46 mg/mL	
		Reducing power		EC <sub>50</sub> 0.44 mg/mL	
<i>R. largentii</i>	Romania	ABTS radical scavenging activity Reducing power Chelating ability 15-Lipoxygenase inhibition assay	Methanol:water (1:1)	EC <sub>50</sub> 64.3 µg/mL	[20]
				EC <sub>50</sub> 61.54 µg/mL	
				EC <sub>50</sub> 2497 µg/mL	
				EC <sub>50</sub> > 833.34µg/mL	
<i>R. botrytis</i>	Korea	DPPH radical scavenging assay	Methanol	EC <sub>50</sub> 0.109 mg/ml	[26]
<i>R. botrytis</i>	Korea	DPPH radical scavenging assay Ferric reducing antioxidant power Reducing power	Hot water	33.8% at 1 mg/ml	[57]
				0.38 at 1 mg/ml	
				0.35 at 1 mg/ml	
<i>R. stricta</i>	Ukraine	Total antioxidant status Total oxidant status Oxidative stress index	Ethanol	4.223 ± 0.054 mmol/l	[58]
				8.201 ± 0.095 µmol/l	
				0.194 ± 0.001	

#### 4.2. Antimicrobial activity.

Despite the vast diversity of synthetic antibacterial compounds, bacterial resistance to conventional antibiotics has been substantially increasing [27]. Therefore, research of novel antibiotics that are resistant to the current remedy is urgently needed. Since ancient times,

natural resources have been exploited for humankind. Among them, mushrooms could be an alternative source of new antimicrobials[28-30]. In this context, different *Ramaria* sp. showed potential antibacterial activity against both gram-negative and gram-positive bacteria (Table 3). *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most sensitive strains to the extract of *R. botrytis* [25], *R. zippellii* [31], *R. aurea* [32], *R. flava* [19] and *R. Formosa* [22]. However, Bala *et al.* demonstrated water extracts of *Ramaria* sp. showed inhibitory action on fungal growth. In contrast, ethanolic extract showed a wider range of antimicrobial activity against the test organisms [33]. Besides, four butenolides (ramariolides A-D) isolated from coral mushroom *R. cystidiphora* showed strong antimicrobial effects against gram-positive bacteria as well as antimycobacterial effects, including *Mycobacterium tuberculosis* [34]. Later, Lehman *et al.* investigated the cellular mechanism of ramariolide A in mycobacteria and revealed that ramariolide A binds with a natively folded target protein resulting in amino acid anabolism. However, this fact requires further detailed analysis [35]. Thus it indicates that *Ramaria* sp. can become a source of antimicrobial leads in the times to come.

**Table 3.** Antimicrobial activities of different species of *Ramaria*.

Species	Extracts used	Methods Used	Bacteria that were inhibited		Fungi that were inhibited	References
			Gram-positive	Gram-negative		
<i>R. formosa</i>	Methanol	Inhibition zone assay	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>Candida albicans</i>	[22]
<i>R. formosa</i>	Ethyl acetate, methanol, and water	Percentage of inhibition	<i>S. aureus</i> , <i>B. subtilis</i>	<i>E. coli</i> , <i>K. pneumonia</i> , <i>P. aeruginosa</i> , <i>Proteus vulgaris</i>	Not tested	[59]
<i>R. zippellii</i>	Ethanol	96-well microplate bioassay	<i>S. aureus</i>	<i>E. coli</i>	No activity	[31]
	Water					
<i>Ramaria</i> sp. 1	Water					
	Ethanol					
<i>Ramaria</i> sp. 2	Water					
	Ethanol					
<i>Ramaria</i> sp.	Water		<i>Bacillus cereus</i> , <i>Listeria monocytogenes</i>	<i>P. aeruginosa</i> , <i>Acinetobacter baumannii</i>	<i>Geotrichum candidum</i> , <i>S. cerevisiae</i>	[33]
	Ethanol					
<i>R. botrytis</i>	Methanol	Disc diffusion method	No activity	<i>P. vulgaris</i>	No activity	[60]
<i>R. botrytis</i>	Methanol-water	Microdilution method	<i>Enterococcus faecalis</i> , <i>L. monocytogenes</i> , <i>Streptococcus agalactiae</i> , and <i>Streptococcus pyrogenes</i>	<i>Pasteurella multocoda</i>	No activity	[27]
<i>R. aurea</i>	Ethanol	Measurement of inhibition zone diameter	<i>S. aureus</i>	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>P. vulgaris</i>	<i>C. albicans</i>	[32]
<i>R. flava</i>	Ethanol	Inhibition zone assay	<i>S. aureus</i> and <i>B. subtilis</i>	<i>E. coli</i>	<i>Fusarium auneaceum</i> , <i>F. graminearum</i> and <i>Cercospora albomaculans</i>	[19]
<i>R. flava</i>	Ethanol	Agar-well diffusion method	<i>Salmonella enteritidis</i> , <i>Yersinia enterocolitica</i> and <i>K.pneumoniae</i>	<i>S. aureus</i> , <i>Micrococcus luteus</i> , <i>M. flavus</i> , <i>B. subtilis</i> , <i>B. cereus</i>	No activity	[18]

Species	Extracts used	Methods Used	Bacteria that were inhibited		Fungi that were inhibited	References
			Gram-positive	Gram-negative		
<i>R. botrytis</i>	Acetone Ethanol Ethyl Acetate Methanol	Measurement of inhibition zone diameter	<i>S. aureus</i>	<i>P. aeruginosa</i> <i>E. coli</i> <i>Enterobacter cloacae</i>	No activity	[25]
<i>R. botrytis</i> <i>R. rubripermanens</i> <i>R. flava</i> <i>R. flavescens</i> <i>R. aurea</i> <i>R. stricta</i>	Methanol	Measurement of minimum inhibitory concentrations	<i>S. aureus</i>	<i>E. coli</i> , <i>K. pneumonia</i> , <i>Vibrio cholera</i> , <i>P. aeruginosa</i> , <i>V. aglinolyticus</i>	No activity	[15]

In addition to antibacterial activity, mushrooms also can cure several infectious diseases caused by viruses. Zhang *et al.* isolated a novel ribonuclease from fruiting bodies of *R. formosa* and checked its ability to inhibit the HIV-1 reverse transcriptase enzyme [36]. Results showed that the ribonuclease exhibited 93% inhibition at the maximum concentration tested (30 μM) with an IC<sub>50</sub> value of 3 μM. The enzyme possessed certain novel features, including its unique N-terminal sequences, temperature-resistance, and optimum acidic pH value suggesting this ribonuclease might have a unique role in the prevention of HIV diseases.

#### 4.3. Anticancer activity.

Cancer is ranked as the second-largest cause of death after cardiovascular diseases. Despite many treatment strategies that have come up with the advancement of science, most of them are target-unspecific and with several side effects as well as costly [37]. Therefore, there is an urgent need to develop nature-based, cost-effective anticancer agents. As such, mushrooms have been reported to show anticancer activity, and many mushrooms derived compounds have already been tested for clinical trials [38-41].

In 1982, Yoo *et al.* tested the antitumor activity of a protein-bound polysaccharide fraction of *R. formosa* and in sarcoma 180 implanted mice [42]. It was found to inhibit 66 % of a tumor at the dosage of 50 mg/kg/day. The tumor in two out of eight mice wholly degenerated. Alcohol extract and acid hydrolysates of *R. botrytis* displayed an antiproliferative effect on the HeLa cell line [43]. Further, Kim *et al.* investigated the cytotoxic effects of water, methanol, and ethyl acetate extract of the same mushroom against human colon adenocarcinoma (HT-29) and hepatocarcinoma cell (HepG2) [44]. It was found that HT-29 cells were susceptible to methanol and ethyl acetate extract. In contrast, moderate activity was shown by water extract. Recently, a novel ubiquitin-like protein, RBUP was isolated from *R. botrytis*, which exhibited apoptosis-mediated cell death in lung cancer cell lines (A549) [45]. The ethanolic extract of *R. flava* was able to inhibit the proliferation of the human breast cancer cell line (MDA-MB-231), and ergosterol peroxide was recommended to be responsible for the anticancer properties of this mushroom [19]. Likewise, methanolic and aqueous extracts of *R. flava* also showed potent antiproliferative activity against the human liver carcinoma HepG2 cell line, which could be due to the presence of gallic acid and p-coumaric acid as suggested by the authors [46]. Water extracts of fermented mycelia and culture supernatant of *R. botryoides* also showed antitumor activity against the Human HCC cell line (SMMC7721) with an IC<sub>50</sub> value of 0.284 and 0.593 mg/ml, respectively [47]. Recently, a novel polysaccharide (RF1) was isolated from an edible species of *Ramaria*; *R. flaccida* (Fr.) Quél. and found to inhibit mouse sarcoma S180 tumors

growth *in vivo* mice model. The administration of 20 mg/ kg polysaccharide dosage inhibited the tumor growth rate to 48.4% and triggered Wnt and MAPK signaling pathways followed by the downregulation of interleukin levels [48].

## 5. Other bioactivities of *Ramaria* species

Only a few numbers of other beneficial properties have been determined in *Ramaria* species. Kim *et al.* evaluated the hepatoprotective activity of methanol extract of *R. botrytis* against liver toxicity in mice induced by benzo( $\alpha$ )pyrene [26]. Results revealed that the extract reduced the increased enzyme activities such as glutathione S-transferase and  $\gamma$ -glutamylcysteine synthetase due to the induction of benzo( $\alpha$ )pyrene. The low EC<sub>50</sub> value (0.109 mg/ml) for DPPH radical scavenging assay also pointed towards the high antioxidant potential of the extract, which might have contributed to the hepatoprotective property of this mushroom.

A pure water-soluble glucan was obtained from fresh fruiting bodies of *R. botrytis* collected from hilly areas of Darjeeling, which consisted of (1 $\rightarrow$ 6)-linked- $\beta$ -D glucopyranosyl residues with the branching of (1 $\rightarrow$ 3)-linked- $\beta$ -D-glucopyranosyl at O-3 position demonstrated excellent immunostimulatory potential in a murine macrophage cell line (RAW264.7 cell) as well as in splenocyte and thymocyte cells. The glucan was found to enhance nitric oxide level and stimulate splenocyte and thymocyte proliferation rates. Hence this glucan can be developed into a potent immunostimulatory [49].

Two novel sesquiterpene derivatives named ramarin A and B, along with three known compounds, were purified from methanol extract of *R. Formosa* and represent one of the very rare mushrooms derived inhibitor of human neutrophil elastase, which can be utilized for the treatment of skin aging [50].

Öztürk *et al.* studied the effect of baking on the bioactivity of *R. flava* collected from a local market in Muğla-Turkey and reported that the baking process influenced higher nutrient contents and bioactivities than unbaked ones. Both baked and unbaked extracts, namely hexane and methanolic fraction, showed potential *in vitro* acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities. However, the efficacy should be evaluated with purified components and in an *in vivo* experimental system [51].

Recently, Bhanja *et al.* prepared bio metallic composite nanoparticles from *R. botrytis* polysaccharide. They tested for its antioxidant potential against different highly reactive free radicals as well as antibacterial activity towards *Pseudomonas aeruginosa*. The bio-nano particles showed excellent radical scavenging efficacy towards DPPH radical, nitric oxide radical, and hydrogen peroxide. It also catalyzed the reduction of p-nitrophenol, thus indicating a new direction in the field of nanotechnology-mediated biomedicine [52].

## 6. Conclusion

The updated knowledge about *Ramaria* sp. studied to date made available in this comprehensive review shows that coral mushroom harbors the potential as a functional therapeutic food. However still, it requires more advanced approaches for profound exploration. Most of the research works had focussed on different extracts of species. Only a few species such as *R. formosa*, *R. botrytis*, *R. cystidiphora*, and *R. madagascariensis* have been studied to identify novel compounds from their fruiting bodies. Therefore the further investigation is needed to find out their activities and mechanisms of action. The nutritional values of the genus *Ramaria* studied so far are entirely satisfactory. However, there is limited

information regarding their bioavailability, mineral, and vitamin compositions. Therefore, this review recommends further exploration of this group in nutrition and mycomedicine for its up-gradation from diet food to holistic mycomedicine.

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## Conflicts of Interest

The authors declare no conflict of interest.

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