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Dietary supplements made from mushrooms

An overview of health-related aspects with a focus on cardiometabolic effects and an overview on food law regulations

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Abstract

Mushrooms (macromycetes) and their bioactive compounds are said to have health-promoting effects. These compounds include indigestible polysaccharides (e.g. β-glucans), mevinolin (which belongs to the group of statins), short-chain peptides, terpenoids and phenolic compounds. Most of the scientific findings regarding health-promoting effects come from *in vitro* and animal studies. There have been relatively few randomized controlled studies in humans regarding cardiometabolic effects; however, the studies that have been done in humans also show beneficial effects. Indications of protective effects explain the rising interest in and the booming market for fungi-based products. The potential preventive and therapeutic effects of several mushrooms and mushroom extracts raise the question of whether such products should be legally classified as dietary supplements or drugs for manufacturers, retailers, and consumers. This review discusses which criteria are decisive for legal classification. Blanket classification as either dietary supplements or drugs is not possible. Classification of such a product always requires the examination of all of the facts on a case-by-case basis.

Keywords: mushrooms, bioactive compounds, dietary supplements, food law regulations

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Introduction

Dietary supplements are very popular in Germany. According to a market analysis performed by the working group of the *Bund für Lebensmittelrecht und Lebensmittelkunde*, from April 2015 to March 2016, 177 million packages of supplements were sold in Germany, corresponding to annual sales of €1.175 billion. Vitamins and minerals accounted for around 70% of all packages sold, but products containing plant-derived ingredients still accounted for 18% of sales [1]. The category known as "botanicals" also includes mushrooms (macromycetes, cap mushrooms), even if these are not considered plants from a taxonomic point of view [2].

"Medicinal mushrooms" are gaining an ever larger share of the market for dietary supplements made from mushrooms. These products are crushed, powdered mushrooms or mushroom extracts, sold in the form of capsules, tablets, or powders. They contain bioactive substances that are said to have health-promoting effects. Some products (most of which are known only as part of traditional Chinese medicine [TCM]) are even said to have therapeutic effects [3]. The growing number of publications that have appeared in PubMed and Web of Science since the 1980s under the keyword combination "mushrooms" and "dietary supplements" testifies to the growing scientific interest in dietary supplements made from mushrooms.

This article will provide an overview of dietary supplements made from mushrooms and will highlight which mushrooms are currently being focused on, which bioactive substances they contain, and what health-promoting effects are ascribed to them, as well as what has been observed in randomized, controlled trials (RCT) in humans and how these products are categorized according to the relevant laws, including laws governing food.

The effects of medicinal mushrooms

◆ Table 1 provides an overview of the "top 10" medicinal mushrooms available on the market. These mushrooms have antibacterial, antiviral, and immunomodulatory effects. Some have antioxidant effects *(in vitro)* and anti-inflammatory effects. Some mushrooms reduce the glycemic effect of food and lower cholesterol levels and blood pressure. These effects have also been mentioned in other systematic reviews [4–7].

mushroom	effects
Agaricus blazei Murrill (ABM) *Agaricus brasiliensis* [a] (Brazilian fungus, almond mushroom)	antiallergenic, tumor-inhibiting, antibacterial, antiviral
Auricularia auricula-judae and *Auricularia polytricha* (cloud ear)	immunostabilizing, cholesterol-lowering, blood thinning, antioxidant, circulation-promoting
Corpinus comatus (shaggy ink cap)	antihypertensive and blood glucose-lowering
Cordyceps sinensis (Chinese caterpillar fungus)	immunomodulating, immune-strengthening, libido-strengthening, antibacterial
Ganoderma lucidum (reishi, glossy ganoderma)	antihypertensive, antibacterial, antiviral, analgesic
Grifola frondosa (maitake, hen of the woods)	antihypertensive, immune-strengthening, antibacterial, antiviral
Hericium erinaceus (lion's mane)	antibacterial
Lentinula edodes (Shiitake)	cholesterol-lowering, anti-inflammatory
Pleurotus ostreatus (oyster mushroom)	cholesterol-lowering, antioxidant, antibacterial
Polyporus umbellatus (lumpy bracket)	antihypertensive, antioxidant

Table 1: **Overview of the 10 most important edible and medicinal mushrooms and their effects**
Limited to the effects most commonly mentioned in the literature (according to [38–43])
[a] Designation according to new taxonomy

Bioactive substances in medicinal mushrooms

Mushrooms are rich in indigestible polysaccharides. These include β-glucans, xyloglucans, heteroglucans, chitin-containing substances and polysaccharide-protein complexes [6]. The focus is on β-glucans, which account for 15–22% of the dry matter [8]. Unlike the β-glucans in oats and barley, which have β-1,3- and β-1,4-glycosidic bonds and are therefore unbranched [9], the β-glucans in fungi mainly contain β-1,3-, β-1,4- and β-1,6-glycosidic bonds and have a branched structure [10].

β-glucans have excellent swelling properties that can delay gastric emptying, which can in turn delay the release of glucose from starch [11]. The dietary fiber in mushrooms inhibits the activity of α-amylase and α-glucosidase. This can also delay the breakdown of starch or maltose and sucrose into glucose and thus reduce the glycemic effect. In addition, mushrooms contain terpenoids that have antioxidant effects. These substances can protect the β-cells of the pancreas from oxidative stress and help to maintain normal insulin synthesis and secretion [6].

Mushrooms synthesize mevinolin [12], a metabolite that competitively inhibits hydroxymethylglutaryl-coenzyme A reductase, the rate-controlling enzyme involved in cholesterol biosynthesis [13]. Under the trade name Lovastatin, mevinolin is used as an active substance in medication for lowering cholesterol levels [14].

Mushrooms contain short-chain peptides that are broken down into stable dipeptides in the gastrointestinal tract and that competitively inhibit the angiotensin-I-converting enzyme, which hydrolyzes the prohormone angiotensin I into the biologically active angiotensin II. The antihypertensive effect of mushrooms could be explained by reduced synthesis of angiotensin II, which causes vasoconstriction, as well as by increased availability of nitric oxide, which intercepts free radicals and improves endothelial function, among other things [15].

Polysaccharides, especially β-glucans, activate natural killer cells and macrophages in the mucus, which could protect against tumors. It is also thought that they may have indirect effects on the immune system via the intestinal flora [5].

The polysaccharides, terpenoids, phenolic compounds and sterols contained in mushrooms also exhibit anti-inflammatory effects [7]. Bactericidal and antiviral effects are also ascribed to some polysaccharides. The underlying mechanisms of this are unclear [5].

The origins of reports of health-promoting effects

Most reports of mushrooms, mushroom extracts, or individual substances contained in mushrooms having health-promoting

mushroom	hit(s) (n)				
	Total	"Human"	"Animals"	"Clinical Trial"	
				"Human"	"Animals"
Agaricus blazei Murrill (almond mushroom)	46	13	26	2	1
Auricularia polytricha (cloud ear)	43	8	9	0	0
Corpinus comatus (shaggy ink cap)	125	33	49	0	0
Cordyceps sinensis (Chinese caterpillar fungus)	481	123	243	17	2
Ganoderma lucidum (reishi, glossy ganoderma)	148	40	66	3	0
Grifola frondosa (maitake, hen of the woods)	1,295	389	455	25	5
Hericium erinaceus (lion's mane)	290	63	135	2	1
Lentinula edodes (Shiitake)	415	51	56	23	0
Pleurotus ostreatus (oyster mushroom)	1,074	93	166	7	2
Polyporus umbellatus (lumpy bracket)	78	18	29	1	0

Table 2: **Number of scientific publications on mushrooms in the literature database PubMed**
Literature search on 16 Dec 2017 in PubMed using the Latin name of the mushroom in question (e.g. „*Ganoderma lucidum*") in the free text and use of filters (such as "Human", "Human AND Clinical Trial", "Other Animals", "Other Animals AND Clinical Trial").

effects come from *in vitro* and animal studies [6, 7]. This is further demonstrated by the low number of clinical studies conducted in humans listed in the literature database PubMed (◆Table 2). Most of these studies were conducted using *Ganoderma lucidum* (reishi) and *Cordyceps sinensis* (Chinese caterpillar fungus), which are used in TCM, but are not edible mushrooms (◆Table 3). With the exception of *Lentinula edodes* (shiitake), clinical studies on the effects of edible mushrooms are relatively rare.

Randomized, controlled human studies on the cardiometabolic effects of mushrooms

The question of whether mushrooms have a positive effect on cardiometabolic risk factors is interesting because 65% of adults in Germany have a fat metabolism disorder [16], 7% have diabetes mellitus [17], and 36% have hypertension [18]. The prevalence of these diseases increases along with increasing age [19]; incidence will increase along with increasing life expectancy [20].

Some RCTs with mushrooms that are also edible mushrooms have demonstrated positive effects on cardiometabolic parameters. The administration of oyster mushrooms and abalone mushrooms in powdered form (50 mg/kg body weight [BW]) lowered glucose levels in healthy individuals, both after an oral glucose tolerance test and on an empty stomach after 14 days of intake. After bolus administration of both products (50 mg/kg BW) together with a defined glucose load in type 2 diabetics (T2D), the insulin increase was stronger and the glucose increase weaker than in the control [21]. When taken for 12 weeks, almond mushroom extract (3 × 500 mg/day in the form of capsules) reduced fasting insulin and adiponectin levels in the plasma and also reduced insulin resistance (HOMA-IR = Homeostatic Model Assessment Insulin Resistance) in T2D compared to placebo. Total LDL-cholesterol, HDL-cholesterol and triglycerides remained unchanged [22]. In patients with colon cancer, following administration of a button mushroom extract (30 mg/kg BW/day, administered in the form of capsules), fasting glucose levels were lowered for 6 months compared to the placebo group [23]. Triglyceride levels in fasting blood only increased in the placebo group. Cholesterol levels decreased following mushroom consumption and remained unchanged in the placebo group [24]. In healthy people with moderate, untreated hypercholesterolemia consuming a soup of freeze-dried oyster mushrooms every day for three weeks lowered triglyceride levels compared to tomato soup without affecting total, LDL and HDL cholesterol levels [25].

Similar effects were also observed in RCTs with "medicinal mushrooms", which are not edible mushrooms. Taking 100 mg of powdered *Inonotus obliquus* (chaga mushroom), administered in the form of capsules with a meal, reduced the postprandial glucose increase (area under the curve), but not the maximum concentration in T2D. Insulin, triglycerides, total and LDL cholesterol, blood pressure and endothelial function remained unchanged compared to placebo. However, when the intervention was performed in healthy people of the same age and sex, no changes were detectable compared to the placebo group [26]. In another RCT, daily administration of 5 mL of chaga extract for 8 weeks reduced blood pressure in healthy adults compared to the placebo group, but it increased triglyceride levels and the ratio of glycated hemoglobin to total hemoglobin (HbA_{1c}), whereas

mushroom	edible mushroom		mushrooms that are not edible mushrooms
	in Germany	in other countries	
Agaricus blazei Murrill (almond mushroom)	✓[a]	South America	
Auricularia polytricha (cloud ear)		Asia	
Corpinus comatus (shaggy ink cap)	✓[a]	Europe	
Cordyceps sinensis (Chinese caterpillar fungus)		✓[b]	✓
Ganoderma lucidum (reishi, glossy ganoderma)	✓[a]	China	
Grifola frondosa (maitake, hen of the woods)			✓
Hericium erinaceus (lion's mane)	✓	✓	
Lentinula edodes (Shiitake)	✓	✓	
Pleurotus ostreatus (oyster mushroom)	✓	✓	
Polyporus umbellatus (lumpy bracket)	✓[a]	✓	

Table 3: **Overview of the mushrooms most frequently used in dietary supplements**
✓ Check marks show which categories apply.
[a] Not known or not commonly known as an edible mushroom.
[b] Only a few varieties are edible mushrooms.

15 mL of chaga extract caused no changes [27]. In patients with coronary artery disease, 12 weeks of administration of reishi extract (1,800 mg/day) reduced blood pressure, triglyceride levels, and the symptoms of coronary artery disease. No changes were detectable in the placebo group [28].

Legal categorization of drugs/foods/dietary supplements

Since various studies have shown that dietary supplements made from mushrooms have health-promoting effects, the question that arises is how these can be brought to market and made accessible to the consumer without violating the applicable legislation.

The legislation that dietary supplements made from mushrooms fall under is determined by definitions from food legislation and by the question of which rules apply to the scope of the legislation. There are differences here depending on whether preparations that contain substances derived from mushrooms are categorized as dietary supplements or drugs. Drugs can only be marketed if they have been approved by the competent authority (section 21 [1] *"Arzneimittelgesetz"* [AMG]). By contrast, German food legislation is generally characterized by market freedom [29]. The dosage form and advertising of dietary supplements is often the same as that which is typical for drugs; dietary supplements therefore belong to the category of "goods customarily offered at a pharmacy" in the sense of section 25 (6) of the *"Apothekenbetriebsordnung"* (ApoBetrO). They may be sold in pharmacies, but also in drugstores or supermarkets, provided that the relevant provisions of the *Verordnung über Nahrungsergänzungsmittel* [NemV] are observed. This applies in particular to section 2 of the NemV, which describes in which form dietary supplements may be marketed. However, dietary supplements do not need to meet the same strict requirements that apply to drugs in order to be dispensed to consumers.

Definition of drugs

The legal definition of the term "drugs" can be found in section 2 (1) (no. 1 and 2) AMG. In its current form, the definition is shaped by the European legal requirements of Council Directive 65/65/EEC[1]: "Drugs are substances or preparations made from substances which:

1. are intended for use on or in the human or animal body and are intended for use as remedies with properties for the curing, alleviating or preventing of human or animal diseases or disease symptoms ("medicinal product by presentation") [30, 31] or
2. can be used in or on the human or animal body or can be administered to a human being or an animal, either:
   a. to restore, correct or to influence the physiological functions through a pharmacological, immunological or metabolic effect ("drugs by function") [30], or
   b. to make a medical diagnosis."

In addition to this definition, certain objects, substances and instruments are regarded as drugs in the list in Art. 2 (2) (1–4), and certain prod-

[1] Council Directive 65/65/EEC of 16 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products ABl. EG No L of 09.02.1965, p. 369–373

ucts are excluded from the definition in the list in section 2 (3) (1–8).

Furthermore, section 2 (3 a) contains a conflict-of-law rule. This is a provision that describes which legislation must be applied when fundamentally different legal norms may apply to the same issue. According to this, in the case of doubt, if the requirements of section 2 (1 and 2) are met, the product should be considered a drug. Finally, section 2 (4) stipulates that a product is a drug if said product is authorized or registered as a drug under the AMG, or is exempted from the need for authorization or registration by ordinance. Therefore, according to the definition of a drug, drugs and foods are mutually exclusive – i.e. a drug can never be a food and vice-versa.

Definition of foods

There is also a legal definition of foods under the law. This can be found in Art. 2 (2) of the *Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch* (LFGB)[2]: "Food means food in the sense of Article 2 of Regulation (EC) No 178/2002."
In accordance with this reference to the Regulation laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety[3], food means "any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. 'Food' includes drink, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment."
According to this definition, the purpose for which a substance or article is consumed by humans is the decisive factor. If it is used for nutrition, i.e. to supply the body with substances that ensure its normal development and function [32], it is a food.

In order to determine the purpose of the product, the prevailing public understanding of the product for the average consumer must be determined. The criteria for this are: How the product is most commonly used by consumers, the composition of the product, scientific publications (if there are publications that are known to a broad section of the public that suggest a certain product characteristic, this can also have a formative effect), product presentation, product advertising, distribution and manufacturer's name [33].

Definition of dietary supplements

Originally, there was no definition for the term "dietary supplement" in either European or German food law [34]; dietary supplements were classified as food[4]. This has remained the case. In principle, dietary supplements are foods. However, we now have the definition in section 1 (1) of the *Verordnung über Nahrungsergänzungsmittel* [NemV]. Under this ordinance, dietary supplements are foods:

1. whose purpose is to supplement the normal diet,
2. that are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, and
3. that are marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop-dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.

The distinction is based on function and the food (in this case the mushroom product) must meet the three criteria above in order to qualify as a dietary supplement.

Legal definition

From a legal point of view, the distinction between drugs, foodstuffs and food supplements is initially governed by the legal definitions contained in the applicable special laws or ordinances, and by "conflict-of-law" rules.
Thus, in cases of doubt, section 2 (3a) of the AMG first requires a positive determination (in accordance with the current state of science) of the drug characteristic. According to prevailing opinion (cf. further evidence in Kügel et al. [34]) it can be deduced from this that the AMG takes priority. After that, the next step is to check whether the product may fall into another product category. Only if this check shows that the product is a drug does the AMG take priority. However, if the check shows that the preparation has no effect in the sense set out in the definition of a drug, another product law shall apply, along with its particular provisions.[5]
Dietary supplements and drugs exhibit some very close similarities, so the definition alone cannot be decisive. For example, it was previously assumed that certain dosage forms, e.g. capsules, were an indication that the product in question was a drug, but now, such dosage forms are prescribed by the *Verordnung über Nahrungsergänzungsmittel* [NemV] and can therefore under no circumstances be used as a differentiation criterion [34].
A mushroom extract in tablet form can therefore be classified as a

[2] in the version promulgated on 3 June 2013 (BGB I p. 1426), which was amended by Article 10 of the Act of 10 March 2017 (BGB I p. 420).
[3] ABl. No L 31 1.
[4] e.g. Verwaltungsgerichtshof München [VGH München], NJW 1998, 845
[5] Also Oberverwaltungsgericht Nordrhein Westfalen [OVG NRW], Decision of 15 March 2010–13 A 2612/09 and 23 April 2010–13 A 622 /10, DÖV 2011, 165

drug, and as a dietary supplement; the boundaries are often blurred. Therefore, when dealing with gray areas, the legal prerequisites of both product categories must be checked [34]. If the nutritional aspect is the dominant aspect of the mushroom product, and if this is reflected in its composition and properties, as well as in its labeling and manner of distribution, it is likely to be a dietary supplement. If the focus is on an effect in the sense of drug, it is a drug (by function).

The European Court of Justice stated in its Judgment of 09 June 2005 (ref no.: C-211/03) that: "For the purposes of determining whether a product must be classified as a drug or as a foodstuff within the meaning of the Community regulations, the competent national authority must decide on a case-by-case basis, taking account of all the characteristics of the product, in particular its composition, its pharmacological properties, to the extent to which they can be established in the present state of scientific knowledge, the manner in which it is used, the extent of its distribution, its familiarity to consumers and the risks which its use may entail."

Dietary supplements in German law and European law

Legal sources/legal foundations

Since food supplements are foods in principle, the provisions of German food law apply to these products. German food law is shaped by European law [35]. Within the European Union, it was recognized that there are dietary supplement preparations on the market in every member state, but the legislation in each member state was very different. This was seen as an obstacle to trade that risked hindering the free movement of these products, leading to an uneven playing field in terms of competition. This led to a proposal from the Commission[6], suggesting that Community legislation should be drafted for products placed on the market as foods.

Since 21 February 2002, the "Regulation laying down the general principles and requirements of food law", Regulation (EC) No 178/2002[7] has been in force. For dietary supplements, the more specialized provisions of Directive 2002/46/EC take priority [36].

Directive 2002/46 EC[8] of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements was adopted on 10 June 2002. This means that dietary supplements are now regulated on a Europe-wide basis for the purpose of the approximation of laws with the aim of the free movement of goods [37]. Where the Directive does not contain any provisions, the other directly applicable Community provisions, e.g. the EC Regulation on organic production and labeling of organic products[9] and the regulations on residues and contaminants[10], are also applicable to dietary supplements [36]. In addition to these provisions under European law, there are also some sources of law from the national legislators. Pursuant to Article 74 (1) (20) of the Regulation laying down the general principles and requirements of food law, the German Federal Government has legislative competence for "the law governing foodstuffs, including animals used for their production, the law governing alcoholic beverages and tobacco, consumer goods and animal feed (...)".

Based on this, the German Federal Government has issued various ordinances, such as the 2004 *Verordnung über Nahrungsergänzungsmittel* [NemV][11], which was based on Directive 2002/46/EC. The term "dietary supplement" [in German: *NEM – Nahrungsergänzungsmittel*] is defined in section 1 of the Ordinance under "Scope". Regulations on labelling (section 4) and notification (section 5) appear further on in the text. Finally, the provisions of the NEMV are enforceable by penalty (cf. section 6).

The regulations of the NEMV govern the particularities of the composition and labeling of dietary supplements. Where the European Regulation does not apply, national regulations, such as the *Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch* (LFGB) apply.

Conclusion

Mushrooms are said to have many health-promoting effects. Even where this is plausible, most of the current evidence is based on *in vitro* and animal studies. The evidence of cardiometabolic effects should be evaluated as *potential* evidence due to the low number of RCTs in humans and due to the fact that in some cases, potential "confounders" (nutrition habits, lifestyle, nutritional status) have either not been taken into account or have not been sufficiently taken into account.

Whether powdered mushrooms are dietary supplements or drugs must be determined by checking them against the criteria of European and national laws on a case-by-case basis. Either the product's health-promoting effect must be proven or its properties in terms

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[6] ABl No C 311 E of 31.10.2000, p. 207 and ABl No C 180 E of 26.06.2001, p. 248

[7] ABl No L 31/1 of 01.02.2002

[8] Directive 2002/46/EC of ABl No L 183/51 of 12.07.2002

[9] Council Regulation (EC) No 834/2007 of 28 June 2007 on organic production and labelling of organic products and repealing Regulation (EEC) No 2092/91, ABl No L 189 of 20.07.2007, p. 1

[10] Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food ABl No L 37/1

[11] Verordnung über Nahrungsergänzungsmittel [NemV] dated 24 May 2004 (BGB I, p. 1011)

of curing, alleviating or preventing human or animal diseases or disease symptoms must be established, as must how it is used to achieve this (in which case it is likely a medicinal product). Or the product's primary purpose is to supplement the diet (in which case it is likely a dietary supplement). Where there is a gray area, however, it should not simply be assumed that priority should be given only to the AMG because the extensive interpretation and application of the definition of the term "drug" carries with it some disadvantages. Products that are not classified as drugs based on their nature and effects should also not be subject to the specific regulations of the AMG in order to avoid jeopardizing the free movement of goods, for instance. Furthermore, it must be borne in mind that in the event of incorrect classification of a dietary supplement as a drug, the distributor of the product is liable to prosecution (section 96 [5] AMG). If classification is based solely on a dogmatically prioritizing the German Medicinal Products Act, this would conflict with the applicable presumption of innocence in criminal law.

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Conflict of Interest
The authors declare no conflict of interest.

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