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REVIEWS: CURRENT TOPICS

Examining the health effects and bioactive components in *Agaricus bisporus* mushrooms: a scoping review☆

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Abstract

There is evidence from both *in vitro* and animal models that the consumption of edible mushrooms has beneficial effects on health. It is unclear whether similar effects exist in humans and which bioactive compounds are present. This review synthesises the evidence on the world's most commonly consumed mushroom, *Agaricus bisporus* to (i) examine its effect on human health outcomes; and (ii) determine the nutrient density of its bioactive compounds, which may explain their health effects. A systematic literature search was conducted on the consumption of *A. bisporus*, without date and study design limits. Bioactive compounds included ergosterol, ergothioneine, flavonoids, glucans and chitin. Two authors independently identified studies for inclusion and assessed methodological quality. Beneficial effects of *A. bisporus* on metabolic syndrome, immune function, gastrointestinal health and cancer, with the strongest evidence for the improvement in Vitamin D status in humans, were found. Ultraviolet B (UVB) exposed mushrooms may increase and maintain serum 25(OH)D levels to a similar degree as vitamin D supplements. *A. bisporus* contain beta-glucans, ergosterol, ergothioneine, vitamin D and an antioxidant compound usually reported as flavonoids; with varying concentrations depending on the type of mushroom, cooking method and duration, and UVB exposure. Further research is required to fully elucidate the bioactive compounds in mushrooms using vigorous analytical methods and expand the immunological markers being tested. To enable findings to be adopted into clinical practice and public health initiatives, replication of existing studies in different population groups is required to confirm the impact of *A. bisporus* on human health.

Keywords: Systematic review; *Agaricus bisporus*; Mushroom; Health; Human; Bioactive

Contents

Abbreviations: 25(OH)D_2, 25-Hydroxyvitamin D_2; 25(OH)D, 25-Hydroxyvitamin D; BBM, brown button mushrooms; CE, catechin equivalents; CG, comparator group; CGEs, cyanidin-3-glucoside equivalents; d, days; f, female; GAE, gallic acid equivalents; g, grams; Hb, haemoglobin; HDL, high density lipoprotein cholesterol; HMW, high molecular weight; H_2, hydrogen; IgA, immunoglobulin A; IgG, immunoglobulin G; IL, interleukin; IU, international units; IG, intervention group; kcal, kilocalorie; LDL, low density lipoprotein cholesterol; LMW, low molecular weight; MetS, metabolic syndrome; NA, not applicable; OR, odds ratio; ORAC, oxygen radical absorbance capacity; PCV, packed cell volume; iPTH, parathyroid hormone; PSA, prostate specific antigen; QE, quercetin equivalents; Qct, quercetin; RCT, randomised controlled trial; RBC, red blood cells; RE, rutin equivalents; sIgA, secretory immunoglobulin A; sCML, serum carboxymethyl-lysine; sMG, serum methylglyoxal; TNF, tumour necrosis factor; UV, ultraviolet; UVB, ultraviolet B; WBC, white blood cells; w/w, weight per weight; WBM, white button mushrooms

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1. Introduction

Although commonly regarded and consumed as a vegetable, mushrooms are members of the *Fungi* kingdom and offer a unique nutritional profile. Biologically distinct to both plants and animals, mushrooms are rich in micronutrients that are normally found in vegetables, meats and grains [1]. These include riboflavin, niacin, pantothenic acid, copper, phosphorus, selenium, fibre-associated monosaccharides and polysaccharides, and the sulphur-containing amino acid ergothioneine [1,2]. Mushrooms are one of the only natural vegetarian sources of both vitamin B_{12}, which is bacteria-derived [3], and vitamin D, which is produced by the conversion of ergosterol to ergocalciferol after exposure to ultraviolet (UV) light [4].

There is a growing body of evidence that suggests consuming several mushroom species, either as a food or as extracts, may improve physical and mental health [5,6]. Mushrooms are rich in bioactive compounds, particularly ergothioneine, ergosterol, vitamin D, beta-glucan and selenium, and these bioactive compounds have been favourably linked to immune function [7,8], glycaemic control [9,10], weight management [11], lipid profile [12,13], blood pressure [14], bone density [15], gut health [16], cancer [17,18] and cognitive function [19]. These health benefits are thought to be largely a result of the enhancement of cellular immunity to produce immunomodulatory, anti-carcinogenic, anti-microbial and hypocholesterolemic effects [5], and due to their effects on the gastrointestinal microbiota (19).

Despite the growing body of evidence linking mushrooms' nutritional uniqueness to beneficial health effects, existing narrative reviews have found limited evidence in human studies. In 2012, Roupas et al. [5] concluded that while mushrooms of many different species demonstrated numerous health benefits within *in vitro* and *in vivo* animal models, there was insufficient evidence to confirm similar effects in humans due to limitations in study design, sample size and the indirectness of the evidence [5]. Other narrative reviews investigating the role of beta-glucans in mushrooms [20] and immunomodulatory activities of mushroom polysaccharides [21] have also found limited research in humans. Since these narrative reviews were published, interest into the therapeutic properties of edible mushrooms in human models has grown. Therefore, a broad systematic synthesis of the evidence reporting the health effects of edible mushrooms in humans and their bioactive compounds that support these effects is warranted.

Due to the large variety of mushroom species available for human consumption, a focus on those that are most abundant and frequently consumed by humans will have the greatest translational value. The most commonly consumed mushrooms worldwide belong to the *Agaricus bisporus* species, which includes white button mushrooms (WBM), brown button mushrooms (BBM), portobello and cremini mushrooms [1]. Therefore, the aim of this scoping literature review was to synthesise the evidence on *A. bisporus* mushrooms to (i) examine its effect on human health outcomes; and (ii) determine the nutrient density of its bioactive compounds, which may explain their health effects.

2. Methods

The review protocol was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22], PRISMA Extension for Scoping Reviews (PRISMA-ScR) [23] and was prospectively registered at PROSPERO (still awaiting processing).

2.1. Eligibility criteria

Table 1 highlights the eligibility criteria for the study selection. Studies were deemed eligible if they were original primary research articles conducted in human populations, reported on whole or processed (*e.g.* dried extract) mushrooms from the *A. bisporus* species, were consumed orally, and reported a health outcome. All physical and mental health outcomes were considered for inclusion. Prospective cohort and cross-sectional studies on health outcomes in humans

Table 1
Inclusion and exclusion criteria for the selection of studies

Inclusion criteria	Exclusion criteria
Studies on *A. bisporus* mushrooms in human populations of any age and health effect, without date limits	Studies published in languages other than English
Studies using *A. bisporus* mushrooms in whole or processed (*e.g.* dried extract) form	Studies where *A. bisporus* mushrooms were not consumed orally
Studies conducted in any country	Studies in animals
Any study design	Studies in duplicate populations
Studies reporting data in a format that enabled data specific to mushrooms to be extracted	Lack of a random sample
Studies reporting ergosterol, ergothioneine, flavonoids, bioactive polysaccharides (alpha and beta glucans) and chitin in *A. bisporus* mushrooms	Studies solely reporting other bioactive compounds in *A. bisporus* mushrooms

were considered if the dietary intake from mushrooms was measured, even if the mushroom type (*e.g.* whole mushroom or extract) was unspecified. Studies reporting on bioactive compounds were also included if they reported on *A. bisporus* mushrooms and measured ergosterol, ergothioneine, flavonoids, glucans (alpha- or beta-glucans) or chitin.

2.2. Search strategy

A systematic search for publications was conducted (25th June 2019), using the electronic databases MEDLINE, EMBASE, Scopus, CINHAL and The Cochrane Library, without date limits (Table S1). To identify publications that reported on the consumption of *A. bisporus* mushrooms, the following keywords were searched (with special features in parentheses): Agaricus (exp/), Agaricus bisporus (exp/), A bisporus (exp/), white button mushroom (exp/), button mushroom (exp/), common mushroom (exp/), cultivated mushroom (exp/), champignon (exp/), cremini (exp/), cremini (exp/), portobello (exp/) (Table S1). Keywords were searched for as free text in the title, abstract and subject headings. Study population and outcomes records were combined using the Boolean operator "AND". Additional publications were identified from references in original papers.

2.3. Selection process

All records identified were first assessed for eligibility based on information contained in the title, abstract, and description/MeSH heading by two independent reviewers (KA, ED, TC or FFM), after

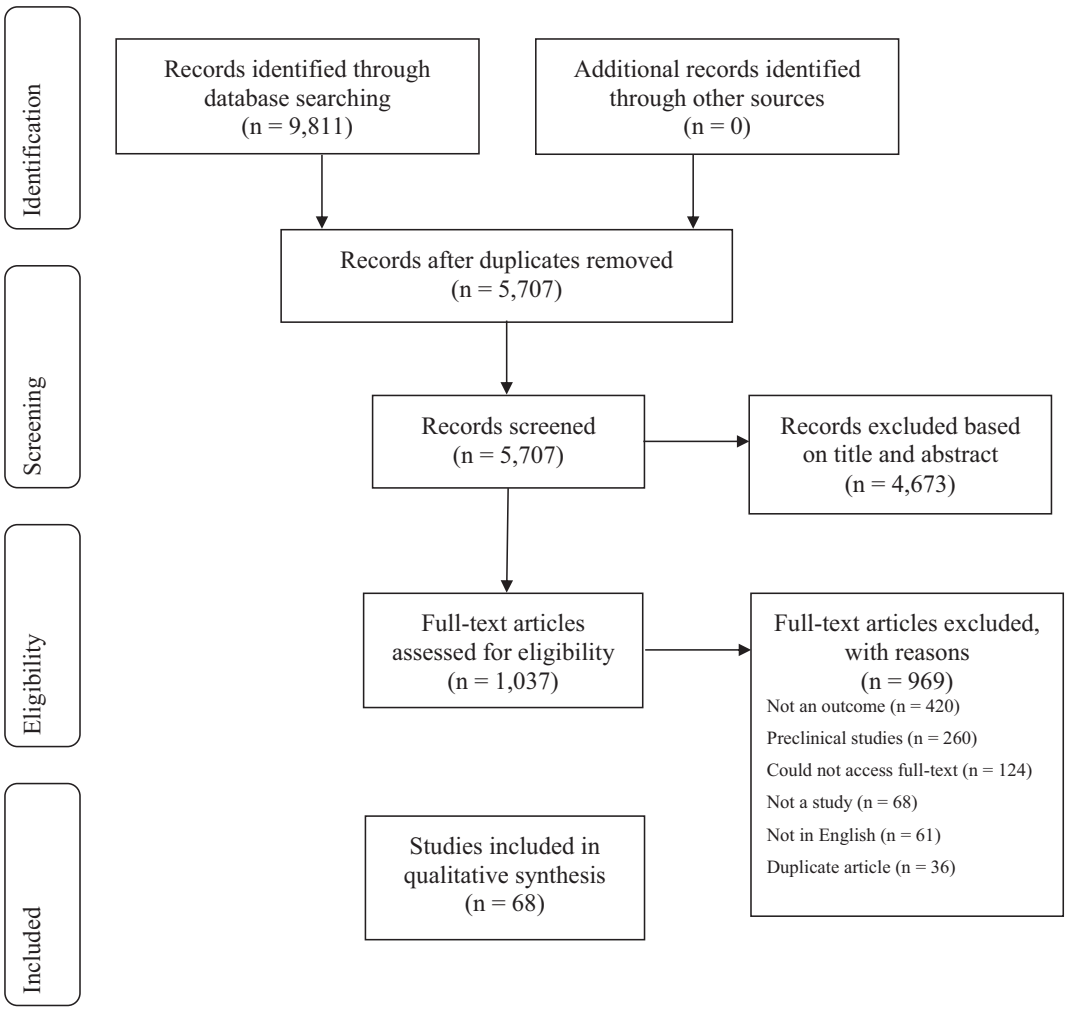

Fig. 1. PRISMA study flow chart.

Table 2
Studies using *Agaricus bisporus* mushrooms or extracts derived from *Agaricus bisporus* mushrooms and measuring health outcomes in humans

Author, year, country	Study aim	Study Design, sample size (n: IG/CG)	Study duration	Population (age, %female, health condition)	Exposure	Outcome/s Measured	Results (↑↓↔)	Adverse effects/ limitations	Conclusions	Study quality (+ Ø −)
Vitamin D										
Stephensen, 2012, USA	To evaluate the effects of consuming UV-exposed white button mushrooms (*A. bisporus*) on the vitamin D status of healthy adults.	Parallel, double-blind **n:** 9/10/10 (8.8 μg D_2/ 17.1 μg D_2/control) (3% attrition)	6 w	31±11 y 58% f Healthy	**Intervention:** UV-exposed cooked mushrooms (87.9 g/ day) delivering 8.8 μg OR 17.1 μg D_2/day **Comparator:** Non UV-exposed cooked mushrooms (87.9 g/day)	*8.8 μg D_2/day:* **Serum 25(OH) D_2** Serum 25(OH)D_3 Serum 25(OH)D (total) Serum 24,25 (OH)D_3 *17.1 μg D_2/day:* **Serum 25(OH) D_2** **Serum 25(OH) D_3** Serum 25(OH)D (total) Serum 24,25 (OH)D_3	↑ (**P<.05**) ↔ ↔ ↔ ↑ (**P<.05**) ↓ (**P<.05**) ↔ ↔	No adverse effects. No significant difference in the vitamin D_2 content of raw vs. cooked mushrooms (P=.41)	Ergocalciferol was absorbed and metabolised to 25 (OH)D_2 but did not affect vitamin D status, because 25OHD_3 decreased proportionally.	+
Keegan, 2013, USA	To compare effectiveness at increasing and maintaining vitamin D status of dried white button mushroom extract and supplemental vitamin D_3 and vitamin D_2.	Parallel, 3-arm (1IG, 2CG) **n**: 14/8/3 (17% attrition)	12 w	35 y 75% f Healthy	**Intervention:** Dried white button mushroom extract (2000 IU D_2/day) **Comparator:** Supplement 2000 IU D_2/ day OR 2000 IU D_3/day	**Serum 25(OH)D (total)** **Serum 25(OH) D_2** Serum 25(OH)D_3	↑ (**P<.001**)[a] ↑ (**P<.001**)[a] Not reported	No adverse effects.	Consumption of mushrooms containing D_2 was as effective at increasing and maintaining total serum 25(OH)D levels as supplemental vitamin D_2 and D_3.	−
Urbain, 2011, Germany	To investigate the bioavailability of vitamin D_2 from UV-exposed mushrooms in humans, in comparison to a vitamin D_2 supplement.	Parallel, single-blind, 3-arm (2IG, 1CG) n: 8/9/9 (8% attrition)	5 w	31 ± 6 y 65% f Healthy	**Intervention:** UV-exposed cooked mushrooms (28,000 IU D_2/day) OR Non-UV-exposed cooked mushrooms (60 IU D_2/day+28,000 IU D_2/day supplement) **Comparator:** Non-UV-exposed cooked mushrooms (60 IU D_2/ day + placebo supplement)	*28,000 IU D_2/day:* **Serum 25(OH)D (total)** Serum Calcium Serum iPTH *60+28,000 IU D_2/ day:* **Serum 25(OH)D (total)** Serum Calcium Serum iPTH	↑ (**P<.001**) ↔ ↔ ↑ (**P<.001**) ↔ ↔	No adverse effects.	Vitamin D_2-enhanced button mushrooms *via* UV exposure was effective in improving vitamin D status in young, healthy adults.	+
Shanely, 2014, USA	To determine if supplementation with mushroom powder would enhance skeletal muscle function and attenuate exercise-induced muscle damage in low vitamin D status high school athletes.	Parallel, double-blind, 2-arm (1IG, 1CG) **n**: 17/17 (3% attrition)	6 w	16± 0 y 0% f Vitamin D insufficient athletes	**Intervention:** UV-exposed powdered mushroom (600 IU D_2/day) **Comparator:** Placebo	**Serum 25(OH)D (total) Serum 25 (OH)D_2** **Serum 25(OH) D_3**	↑ (**P=.004**) ↑ (**P<.0001**) ↓ (**P<.0001**)	No adverse effects.	600 IU/d vitamin D_2 increased 25 (OH)D_2 with a concomitant decrease in 25(OH)D_3, with no effect on muscular function or exercise-induced muscle damage in high school athletes.	Ø

Inflammation										
Calvo, 2016, USA	To estimate the impact of adding white button mushrooms to daily diet on known T2D risk factors.	Parallel, 4-arm*** **n**: 37	16 w	48 y 65% f MetS	**Intervention:** UV-exposed cooked mushrooms (100 g/day) **Comparator:** Supplement 1242 IU D_3/day OR 7320 IU D_3/day	**Serum ergothioneine** **ORAC** 8-isoprostane **Adiponectin** Leptin **sCML** **sMG**	↑ (**P≤.01**) ↑ (**P=.03**) ↔ ↑ (**P=.03**) ↔ ↓ (**P≤.01**) ↓ (**P≤.01**)	No adverse effects.	Consuming white button mushrooms was associated with increased ergothioneine, lower circulating oxidative stress factors and higher serum adiponectin and ORAC.	+
Volman, 2010, Netherlands	To evaluate the effects of consuming α-glucans in hypercholestrolemic subjects.	Parallel, double-blind **n:** 26/30 (0% attrition)	5 w (2 w run-in)	57± 8 y 42.9% f	Hypercholesterolemic Ø *Th1 cytokines:* **IFNγ **IL-12 **IL-2 *Th2 cytokines:* **IL-13 **IL-4	**Intervention:** 200 mL juice/day containing 5 g/day α-glucans extracted from white button mushrooms **Comparator:** 200 mL juice/day with 0 g α-glucans	*IL-1β *IL-6 ***TNFα** *IL-10 *IL-17 ↔ ↔ ↔ ↔ ↔	↔ ↔ ↓ (**P=.017**) ↔ ↔	No adverse effects.	Consumption of A. bisporus a-glucans lowered LPS-induced TNFα production, whereas no effect on IL-1b and IL-6 was observed. No obvious Th1–Th2 skewing by PHA-stimulated PBMCs was observed. However, we observed a trend towards a decreased production of IL-12 and IL-10. No significant changes in kidney or liver function.
Serum creatinine	↔									
Serum ALT	↔									
Serum AST	↔									
Serum GGT	↔									
Serum APT	↔									
Serum Bilirubin	↔									
Weigand-Heller, 2012, USA	To evaluate the bioavailability of ergothioneine using a dose–response, postprandial time-course design.	Cross-over, 2-arm (1IG, 1CG) **n**: 10/10 (0% attrition)	3 d (3 d washout)	27± 3 y 0% f Healthy	**Intervention:** Powdered mushroom (8 g/day OR 16 g/day) **Comparator:** Placebo	CRP Cholesterol HDL LDL Triglycerides Glucose **ORAC (total)** **Ergothioneine**	↔ ↔ ↔ ↔ ↔ ↔ ↓ (**P<.05**) ↑ (**P<.05**)	No adverse effects.	Ergothioneine was bioavailable after consuming mushrooms and a trend in the postprandial triglyceride response indicated that there was a blunting effect after both the 8 g and 16 g doses. ORAC total values decreased after the 8 g and 16 g mushroom meal.	Ø
Satiety										
Hess, 2017, USA	To compare satiety and food intake differences between mushroom and meat consumption.	Cross-over, 2-arm (1IG, 1CG) **n**: 35/35 (9% attrition)	10 d (10 d washout)	23± 4 y 53% f Healthy	**Intervention:** Cooked mushroom meal (226 g/day) **Comparator:** Cooked beef meal (28 g/day)	**Satiety** Energy intake	↑ (**P=.05**) ↔	No adverse effects.	Mushroom meal had a positive effect on satiety, but no effect on energy intake.	Ø

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Table 2 (*continued*)

Author, year, country	Study aim	Study Design, sample size (n: IG/CG)	Study duration	Population (age, %female, health condition)	Exposure	Outcome/s Measured	Results (↑↓↔)	Adverse effects/ limitations	Conclusions	Study quality (+ Ø −)
Cheskin, 2008, USA	To investigate how substituting mushrooms for beef in a test lunch affected energy intake, fat intake, palatability, appetite, satiation and satiety in normal weight, overweight and obese adults.	Cross-over, 2-arm **n**: 76/76 (29% attrition)	4 d (3 d washout)	36 y 67% f Healthy	**Intervention:** Cooked mushroom meal (339 kcal/day) **Comparator:** Cooked beef meal (783 kcal/ day)	Satiety Satiation **Fat intake** **Energy intake** Appetite	↔ ↔ ↓ (***P*<.0001**) ↓ (***P*<.0001**) ↔	No adverse effects.	Energy intakes were higher during meat lunches than mushroom lunches. Total daily energy and fat intake were greater in the meat than in the mushroom condition. Palatability, appetite, satiation and satiety did not differ.	Ø
Cancer										
Lee, 2013, China	To investigate the association between mushroom consumption and risk of epithelial ovarian cancer.	Case–control, retrospective **n**: 500/500	2 y	59 ± 6 y 100% f Healthy (controls) Ovarian cancer (cases)	**Exposure:** White button mushroom consumption	Ovarian cancer	↓ **(OR=0.68)**	N/A	Ovarian cancer patients consumed less mushrooms than controls. Apparent reductions in cancer risk were found at high levels of intake, especially for white button mushroom for women consuming>2 g/day.	+
Twardoski, 2015, USA	To evaluate the effects of white button mushroom powder on serum PSA levels and determine the tolerability.	Phase I, clinical dose-escalation **n**: 36	10 m (1–58 m)	68 y 0% f Elevated PSA	**Treatment:** Powdered mushroom (4,6,8,10,12,14 g/day)	**Serum PSA** Androgens MDSCs IL-15	↓ **(*n*=13, 36%)**	Abdominal bloating	White button mushroom powder therapy was associated with declining PSA levels in some patients.	+
Gastrointestinal										
Hess, 2018, USA	To assess mushroom consumption compared to meat on gastrointestinal tolerance, short chain fatty acid (SCFA) production, laxation, and faecal microbiota.	Cross-over, 2-arm (1IG, 1CG) **n**: 35/35 (9% attrition)	10 d (10 d washout)	23± 4 y 53% f Healthy	**Intervention:** Cooked mushroom meal (226 g/day) **Comparator:** Cooked beef meal (28 g/day)	Breathe hydrogen Stool frequency Stool consistency Faecal pH **Faecal wet weight** SCFA	↔ ↔ ↔ ↑ **(*P*=.002)** ↔	No adverse effects.	The mushroom diet resulted in higher average stool weight and a different faecal microbiota composition compared to the meat diet, with greater abundance of Bacteroidetes lower abundance of Firmicutes.	Ø
Nishihira, 2017, Japan	To investigate whether ingesting champignon extract daily improved halitosis and body and faecal odour.	Parallel, double-blind, 4-arm (3IG, 1CG) **n**: 20/20/20/20 (4% attrition)	4 w	64 ± 7 y 51% f Problematic halitosis, body or faecal odour	**Intervention:** Champignon extract (50 mg/day OR 500 mg/day OR 1000 mg/day) **Comparator:** 0 mg/day	*50 mg/day:* Halitosis **Pillow odour** Pyjama odour **Faecal odour** Bowel movement regularity **Strain during bowel**	↔ ↓ **(*P*=.003)** ↔ ↓ **(*P*=.001)** ↔ ↓ **(*P*=.005)** ↔	No adverse effects.	Ingesting champignon extract improved halitosis and body and faecal odour. Results suggest the effectiveness of champignon extract in alleviating odours is dose-dependent, *i.e.*, it increases with the dosage.	−

Author, year, country	Study aim	Study Design, sample size (n: IG/CG)	Study duration	Population (age, %female, health condition)	Exposure	Outcome/s Measured	Results (↑↓↔)	Adverse effects/ limitations	Conclusions	Study quality (+ Ø −)
						movements				
						Sensation of residual stools				
						500 mg/day:				
						Halitosis	↓ (***P*=.001**)			
						Pillow odour	↓ (***P*=.003**)			
						Pyjama odour	↓ (***P*=.004**)			
						Faecal odour	↓ (***P*=.001**)			
						Bowel movement regularity	↔			
						Strain during bowel movements	↓ (***P*=.005**)			
						Sensation of residual stools	↔			
							100 mg/day:			
							Halitosis			
							Pillow odour			
							Pyjama odour			
							Faecal odour			
							Bowel movement regularity			
							Strain during bowel movements			
							Sensation of residual stools			
							↓ (***P*=.001**)			
							↔			
							↓ (***P*=.004**)			
							↓ (***P*=.001**)			
							↔			
							↓ (***P*=.005**)			
							↔			
							Cholesterol			
Abd-alwahad, 2018, Iraq	To investigate the physiological and biological effects of eating mushrooms cooked in olive oil.	Parallel, non-randomised, 2-arm **n**: 25/25	30 d	Not reported.	**Intervention:** Cooked mushroom (2 g/kg body weight/day) **Comparator:** Usual diet	**Glucose**	↓ (***P*<.05**)	No adverse effects.	*A. bisporus* cooked in olive oil reduces harmful lipids, glucose and enhances the blood cells.	−
						Cholesterol	↓ (***P*<.05**)			
						HDL	↑ (***P*<.05**)			
						LDL	↓ (***P*<.05**)			
						Triglycerides	↓ (***P*<.05**)			
						Body weight	↓ (***P*<.05**)			
						Urea	↔			
						Uric acid	↔			
						WBC	↑ (***P*<.05**)			
						RBC	↑ (***P*<.05**)			
						Hb	↔			
						PCV	↔			
Weigand-Heller, 2012, USA	To evaluate the bioavailability of ergothioneine using a dose–response, postprandial time-	Cross-over, 2-arm (1IG, 1CG) **n**: 10/10 (0% attrition)	3 d (3 d washout)	27±3 y 0% f Healthy	**Intervention:** Powdered mushroom (8 g/day OR 16 g/day) **Comparator:** Placebo	Cholesterol	↔	No adverse effects.	Ergothioneine was bioavailable after consuming mushrooms and a trend in the	Ø
						HDL	↔			
						LDL	↔			
						Triglycerides	↔			

(continued on next page)

Table 2 (*continued*)

Author, year, country	Study aim	Study Design, sample size (n: IG/CG)	Study duration	Population (age, %female, health condition)	Exposure	Outcome/s Measured	Results (↑↓↔)	Adverse effects/ limitations	Conclusions	Study quality (+ Ø –)
	course design.								postprandial triglyceride response indicated that there was a blunting effect after both the 8 g and 16 g doses.	
T2D risk management										
Calvo, 2016, USA	To estimate the impact of adding white button mushrooms to daily diet on known T2D risk factors.	Parallel, 4-arm*** **n**: 37	16 w	48 y 65% f MetS	**Intervention:** UV-exposed cooked mushrooms (100 g/day) **Comparator:** Supplement 1242 IU D_3/day OR 7320 IU D_3/day	Serum 25(OH)D (total) **Serum ergothioneine** **ORAC** 8-isoprostane **Adiponectin** Leptin **sCML** **sMG**	↔ **↑ (*P*≤.01)** **↑ (*P*=.03)** ↔ **↑ (*P*=.03)** ↔ **↓ (*P*≤.01)** **↓ (*P*≤.01)**	No adverse effects.	Consuming white button mushrooms was associated with increased ergothioneine, lower circulating oxidative stress factors and higher serum adiponectin and ORAC and thus improved risk markers of diabetes.	+
Immunological										
Jeong, 2012, Australia	To investigate the effect of dietary intake of white button mushrooms on salivary IgA (sIgA) secretion in healthy subjects.	Parallel, 2-arm (1IG, 1CG) **n**: 12/8 (20% attrition)	7 d	42 ± 12 y 50% f Healthy	**Intervention:** Cooked mushrooms (100 g/day) **Comparator:** Usual diet	**sIgA: osmality** **sIgA secretion rate** **sIgA concentration** IgG secretion rate IgG concentration	**↑ (*P*=.0012)** **↑ (*P*<.0005)** **↑ (*P*<.0005)** ↔ ↔	No adverse effects.	Consuming white button mushrooms accelerates SIgA secretion, thereby indicating its potential health benefits for improving mucosal immunity.	+

IG, intervention group; CG, comparator group; UV, ultraviolet; PSA, total serum prostate-specific antigen; MetS, metabolic syndrome; 25(OH)D, 25-hydroxyvitamin D; IL, interleukin; iPTH, parathyroid hormone; TNFα, tumour necrosis factor alpha; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; WBC, white blood cells; RBC, red blood corpuscles; Hb, haemoglobin; PCV, packed cell volume; ORAC, oxygen radical absorbance capacity; sCML, serum carboxymethyl-lysine; sMG, serum methylglyoxal; sIgA, secretory immunoglobulin A; IgG, immunoglobulin G; d, days; w, weeks; m, months; y, years; f, female; IU, international unit; ↑, significant increase compared with control; ↓, significant decrease compared with control; ↔, no significant change compared with control; Study quality +, positive; Ø, neutral; –, negative; * *ex-vivo* LPS-stimulated cytokine production in peripheral mononuclear blood cells (PBMC); ** PHA-induced T-cell proliferation in PBMC; *** 4-arm pooled analysis; a, significant from baseline.

which the inclusion and exclusion criteria were applied (Table 1). This process was completed using Covidence systematic literature review software [Veritas Health Innovation, Melbourne, Australia] [24]. The full text of all studies that appeared to meet the eligibility screening were retrieved and subjected to a second assessment for relevance by the same two reviewers (Table 1). Any difference in assessments that arose between reviewers was discussed in the first instance or resolved by a third independent reviewer (FFM).

Human research studies were then assessed for methodological quality in duplicate by two independent reviewers (KA and ED) using the Quality Criteria Checklist for Primary Research in the Academy of Nutrition and Dietetics Evidence Analysis Manual [25]. The Quality Criteria Checklist included four relevance questions that addressed applicability to practice and 10 validity questions that addressed scientific reliability, including confounding, study quality and heterogeneity. The Quality Criteria Checklist enabled a systematic, objective rating (positive, negative or neutral) to be given to each study and was used to confirm agreement among independent reviewers. 'Positive' studies were of the highest quality, with most answers to the validity questions being positive, followed by 'neutral' studies. 'Negative' studies were of the lowest quality, with most of the answers to the validity questions being negative. Once again, any difference in assessments were resolved, if necessary, by a third independent reviewer (FFM). The internal validity of studies which reported biochemical analysis of mushrooms was not performed as critical appraisal tools do not exist for this study design.

2.4. Data extraction

Data were extracted from all included studies into a Microsoft Excel [Version 1908; Excel for Office 365] spreadsheet by one investigator (KA or ED) and checked for accuracy by another investigator (KA or ED). Data extracted were study and participant characteristics, baseline, follow-up, washout period, run-in period, test product, control product, dosage, measurement method, change in outcome, and *P*-value for between group comparisons. Data extracted for bioactive studies included source of mushrooms, whether mushrooms were cultivated or wild, storage conditions, extraction and measurement technique used, amount of the bioactive reported and units of measurement. For studies reporting ergosterol, vitamin D was also extracted if reported. Original authors were contacted to confirm any missing data [26–28]. If original authors could not be contacted, data were retrieved using manuscript figs. [27] or excluded [26,28].

3. Results

3.1. Description of studies

The systematic search strategy identified 9811 records, of which 68 were eligible for inclusion (n=15 human studies, n=53 biochemical studies; Fig. 1).

3.1.1. Health outcomes

A total of 15 human trials reported on consumption of *A. bisporus* mushrooms and physical health outcomes [29–43], and none reported on mental health or cognitive function. The study characteristics and methodological quality of these included studies are shown in Table 2. The majority (73%) of studies were randomised controlled trials (RCTs) [29–36,39,40,43]). Other study designs included a non-RCT [41], a secondary analysis of a RCT which presented pooled data from two intervention groups in a pre-post study design format [42], a Phase 1 Clinical trial [38], and a retrospective case–control study [37]. The reported health outcomes were vitamin D status (4 studies) [29–32], inflammation (2 studies) [33,34], satiety (2 studies) [35,40], cancer (2 studies) [37,38], gastrointestinal health (2 studies) [39,40], cholesterol [34,41], diabetes risk factors [42], and immunology [43]. Studies were mainly conducted in the United States of America (USA) (9 studies) [29,30,32,34–36,38,39,42], and others were from Germany [31], Netherlands [33], China [37], Japan [40], Iraq [41], and Australia [43]. Only one study reported minor adverse effects (abdominal bloating), but had no participant withdraw.

Studies were mainly conducted in adults, with one study on male teenage athletes [32]. Most of the intervention studies used 'healthy' populations (8 studies) [29–31,34–36,39,43], with the remaining conducted in adults with hypercholesterolemia [33], metabolic syndrome [42], insufficient Vitamin D levels [32], older adults with problematic halitosis and body odour [40], and cancer [37,38] (Table 2).

Using the Quality Criteria Checklist for Primary Research (Table 2), six studies received a positive quality rating (*i.e.* defined as having a high level of internal validity and low risk of bias across the study) [29,31,37,38,42,43], six studies received a neutral rating (*i.e.* unclear levels of internal validity and bias) [32–36,39], and three studies received a negative rating [30,40,41]. Interventions were generally well described with clearly defined outcomes. Objective biomarkers were utilised across studies, with the exception of studies that had self-reported measures of satiety [35,36] and gastrointestinal health outcomes [39,40].

3.1.2. Bioactive compounds

A total of 41 studies reported the concentration of bioactive antioxidant compounds (ergosterol, 16 studies [44–59]; ergothioneine, 4 studies [48,60–62]; flavonoids, 22 studies [63–84]) and 16 reported concentrations of polysaccharides (glucans, 9 studies [27,80,84–91]; chitin, 7 studies [27,87,90,92–95]) in *A. bisporus* mushrooms (Table 3**)**. From the 16 papers that reported ergosterol, five also reported Vitamin D_2 (25(OH)D_2) [46,48–51]. Mushroom varieties included WBM (47 studies) [27,46–56,59–66,68–87,89–95], portobello (8 studies) [49,57,58,60,61,85,87,88], BBM (7 studies) [47,48,54,55,67,79,89], and cremini (6 studies) [49,60,61,85,87,88] mushrooms. The majority of studies (79%) reported only one mushroom type, with WBM being the most common (68%), and two studies did not specify the type of mushroom used [44,45]. Mushrooms were mainly cultivated (51 studies) [27,46,48–58,60–83,86–95] and sourced from Europe (24 studies) [27,44,45,50,52,53,55–58,64,67,69,73,74,78,79,86,88–90,93–95] and Asia (19 Studies) [51,59,62,63,65,66,68,71,72,75–77,80–84,87,91]. Other regions included the Americas (6 studies) [48,49,60,61,70,85], Canada (3 studies) [46,47,54] and the United Kingdom (1 study) [92].

3.2. Impact of *A. bisporus* mushroom intake on human health

3.2.1. Serum vitamin D

Studies that reported on the bioavailability of vitamin D from UVB-exposed mushrooms used fresh mushrooms [29,31], dried mushroom extract [30] and mushroom powder [32]. Doses of vitamin D ranged from 8.8 μg/day (352 IU/day) [29], up to 28,000 IU/day (700 μg/day) [31], and study durations ranged from 5 to 12 weeks. A significant increase in serum 25(OH)D_2 was reported in all four RCT studies [29–32], alongside a decrease in serum 25(OH)D_3 reported in two studies [29,32], (P<.001 for all). Three studies showed a significant increase in total serum 20(OH)D (P<.001 for all) [30–32], and only one study specifically screened people for low levels of vitamin D at baseline [32]. When UVB-exposed mushroom extracts were compared to a daily vitamin D_2 or D_3 supplement (2000 IU/day; 50 μg/day) across a 12-week intervention, no significant differences in overall 25(OH)D levels between the groups were found [30]. At doses of 2000 IU/day, UVB-exposed mushrooms were equivalent to a supplement at increasing total 25(OH)D levels.

3.2.2. Inflammatory markers

Three studies reported on inflammatory markers [33,34,42]. In healthy young women, both 8 g and 16 g doses of mushroom powder

Table 3
Bioactive components in *Agaricus Bisporus* mushrooms

Reference	Type	Mushroom source (wild/cultivated, country)	Mushroom part	Compound (glucan/flavonoid/ ergosterol etc.)	Amount
Babu, 2013	WBM	Cultivated, India	Cap	Flavonoids	2.173±0.0007 μg/g
			Stipe	Flavonoids	1.533±0.005 μg/g
Akyüz, 2012	WBM	Cultivated, Turkey	Whole	Myricetin	11.75 μg/g
				Quercetin	0.25 μg/g
				Kaempferol	0.25 μg/g
				Catechin	396.00 μg/g
				Naringenin	1.75 μg/g
				Resveratrol	0.50 μg/g
Tajalli, 2015	WBM	Cultivated/wild, Iran	Whole (wild)^	Flavonoids	3.72 (0.0020) mg CE/g
				Anthocyanins	4.7 (1.2) mg CGEs/100 g
				Flavonoids	4.24 (0.0016) mg CE/g
				Anthocyanins	7.7 (0.5) mg CGEs/100 g
				Flavonoids	2.78 (0.0004) mg CE/g
				Anthocyanins	1.13 (0.2) mg CGEs/100 g
				Flavonoids	5.11 (0.0044) mg CE/g
				Anthocyanins	0.15 (0.01) mg CGEs/100 g
			Whole (cultivated)	Flavonoids	3.98 (0.0004) mg CE/g
				Anthocyanins	1.7 (0.2) mg CGEs/100 g
				Flavonoids	4.12 (0.0020) mg CE/g
				Anthocyanins	0.087 (0.1) mg CGEs/100 g
				Flavonoids	4.15 (0.0016) mg CE/g
				Anthocyanins	'very low' (almost 0) mg CGEs/100 g
				Flavonoids	4.94 (0.0028) mg CE/g
				Anthocyanins	4.6 (0.9) mg CGEs/100 g
Singla, 2010	WBM	Cultivated, India	Whole (raw)	Flavonoids (free)	37.12 mg/100 g
				Flavonoids (bound)	64.69 mg/100 g
			Whole (processed)	Flavonoids (free)	35.42 mg/100 g
				Flavonoids (bound)	63.72 mg/100 g
Mircea, 2015	BBM	Cultivated, Romania	Whole	Flavonoids	1.09 (0.02) mg CE/g
					0.97 (0.01) mg CE/g
					1.52 (0.01) mg CE/g
Guizani, 2012	WBM	Cultivated, Oman	Whole	Flavonoids	0.76 (0.05) mg
Jaworska, 2014	WBM	Cultivated, Poland	Whole (fresh)	Flavonoids	142 (8) mg/100 g
			Whole (blanched)	Flavonoids	53 (3) mg/100 g
			Whole (culinary treated)	Flavonoids	35 (5) mg/100 g
Gan, 2013	WBM	Cultivated, Malaysia, Brazil	Extract (60% ethanol)	Flavonoids	1.75 (0.26) mg GAE/g
			Extract (aqueous)	Flavonoids	1.36 (0.11) mg GAE/g
Ganguli, 2006	WBM	Cultivated, India	Whole (raw)	Flavonoids	0.079% (0.004)
			Whole (fried 4 min)	Flavonoids	0.050% (0.002)
			Whole (fried 5 min)	Flavonoids	0.041% (0.004)
			Whole (fried 6 min)	Flavonoids	0.038% (0.006)
Singla, 2012	WBM	Cultivated, India	Whole (raw)	Flavonoids	37.12 mg/100 g
			Whole (2% treated)	Flavonoids	31.54 mg/100 g
			Whole (4% treated)	Flavonoids	31.53 mg/100 g
Öztürk, 2011	WBM	Cultivated, Turkey	Whole	Flavonoids	5.12 (0.55) μg QE/mg
Ozen, 2010	WBM	Cultivated, Turkey		Flavonoids	0.106 (0.006) mg QE/g
				Anthocyanins	0.17 (0.01) mg/mL
Rezaeian, 2015	WBM	Cultivated/wild, Iran	Whole (cultivated)	Flavonoids	6.46 (0.13) mg CE/g
			Whole (cultivated)	Flavonoids	1.11 (0.24) mg CE/g
			Whole (wild)^	Flavonoids	4.48 (0.05) mg CE/g
Ng, 2019	WBM	Cultivated, India	Whole (raw)	Flavonoids	78.67 (8.80) mg QE/100 g
			Whole (boiled)	Flavonoids	46.89 (1.25) mg QE/100 g
			Whole (microwaved)	Flavonoids	43.39 (4.66) mg QE/100 g
			Whole (steamed)	Flavonoids	32.83 (4.51) mg QE/100 g
			Whole (pressure-cooked)	Flavonoids	59.11 (10.30) mg QE/100 g
Ng, 2017	WBM	Cultivated, Malaysia	Whole (raw)	Flavonoids	20.2 (2.9) mg Qct/100 g
			Whole (boiled 1.5 min)	Flavonoids	12.2 (2.8) mg Qct/100 g
			Whole (boiled 3 min)	Flavonoids	11.3 (2.7) mg Qct/100 g
			Whole (boiled 4.5 min)	Flavonoids	10.7 (0.7) mg Qct/100 g
			Whole (boiled 6 min)	Flavonoids	9.8 (0.4) mg Qct/100 g
			Whole (microwaved 1.5 min)	Flavonoids	14.3 (2.4) mg Qct/100 g
			Whole (microwaved (3 min)	Flavonoids	7.5 (1.0) mg Qct/100 g
			Whole (microwaved 4.5 min)	Flavonoids	6.1 (1.1) mg Qct/100 g
			Whole (microwaved 6 min)	Flavonoids	4.2 (0.5) mg Qct/100 g
			Whole (steamed 1.5 min)	Flavonoids	11.2 (3.4) mg Qct/100 g
			Whole (steamed 3 min)	Flavonoids	14.4 (5.0) mg Qct/100 g
			Whole (steamed 4.5 min)	Flavonoids	12.0 (1.0) mg Qct/100 g
			Whole (steamed 6 min)	Flavonoids	13.8 (1.0) mg Qct/100 g
			Whole (pressure-cooked 15 min)	Flavonoids	12.7 (0.3) mg Qct/100 g
Barros, 2018	WBM	Cultivated/wild, Portugal	Whole^	Flavonoids	1.73 (0.11) mg/g
Buruleanu, 2018	WBM	Cultivated, Romania	Cap	Flavonoids	6.54 (0.00) mg QE/g
				Flavonoids	7.83 (4.18) mg QE/g
			Stipe	Flavonoids	5.23 (0.02) mg QE/g

Table 3 (*continued*)

Reference	Type	Mushroom source (wild/cultivated, country)	Mushroom part	Compound (glucan/flavonoid/ ergosterol etc.)	Amount
				Flavonoids	3.26 (0.04) mg QE/g
	BBM		Cap	Flavonoids	8.43 (0.02) mg QE/g
				Flavonoids	3.5 (0.14) mg QE/g
			Stipe	Flavonoids	8.05 (0.04) mg QE/g
				Flavonoids	5.22 (0.06) mg QE/g
Khan, 2016	WBM	Cultivated, India	Whole	Flavonoids	56.76 μg RE/g
Jagadish, 2009	WBM	Cultivated, India	Whole (raw)	Flavonoids	16.4 (0.5) mg QE/g
			Whole (boiled)	Flavonoids	15.2 (0.2) mg QE/g
Dhamodhara, 2013	WBM	Cultivated, India	Whole	Flavonoids	10.3 (1.0) mg QE/g
Um, 2014	WBM	Cultivated, South Korea	Whole	Flavonoids	1636.8 (17.5) mg naringin/100 g
Palanisamy, 2014	WBM	Cultivated, Spain	Whole (25 °C)*	α-Glucan	27%[a]
				β-Glucan	25%[a]
			Whole (50 °C)*	α-Glucan	26%[a]
				β-Glucan	27%[a]
			Whole (100 °C)*	α-Glucan	32%[a]
				β-Glucan	29%[a]
			Whole (150 °C)*	α-Glucan	35%[a]
				β-Glucan	0%[a]
			Whole (200 °C)*	α-Glucan	50%[a]
				β-Glucan	44%[a]
			Whole	Chitin	4.9 mg/100 g
Choi, 2010	WBM	Korea	Whole	Total Glucan	8.97 (0.21) % w/w
				α-Glucan	1.13 (0.52) % w/w
				β-Glucan	7.83 (0.74) % w/w
			LMW	Catechin	15.07 (0.83) mg/g
				Tannic acid	11.58 (0.65) mg/g
				Gallate	9.51 (0.52) mg/g
			HMW	Catechin	14.98 (0.34) mg/g
				Tannic acid	11.50 (0.27) mg/g
				Gallate	9.45 (0.22) mg/g
Dikeman, 2005	WBM	Cultivated, USA	Raw immature	β-Glucan	0.1%
			Cooked immature	β-Glucan	0.1%
			Raw mature	β-Glucan	0.1%
			Cooked mature	β-Glucan	0.1%
	Crimini		Raw immature	β-Glucan	0.1%
			Cooked immature	β-Glucan	0.1%
			Raw mature	β-Glucan	0.1%
			Cooked mature	β-Glucan	0.1%
	Portabella		Raw immature	β-Glucan	0.1%
			Cooked immature	β-Glucan	0.1%
			Raw mature	β-Glucan	0.0%
			Cooked mature	β-Glucan	0.2%
Nitschke, 2011a	WBM	Cultivated, Germany	Whole	β-Glucan	2.60 g/100 g
Khan, 2017	WBM	Cultivated, India	Whole	Total glucan	10.045 (0.21) g/100 g
				α-Glucan	1.534 (1.56) g/100 g
				β-Glucan	8.511 (2.45) g/100 g
Singh, 2017	WBM	Cultivated, India	Whole	Total glucan	0.78 g/10 g
				Chitin	0.12 g/10 g
				Chitin-glucan complex	1.8 g/10 g
	Portobello			Total glucan	3.96 (0.64)
	Crimini			Total glucan	3.94 (0.08)
				β-Glucan	19.20%
Mirończuk-Chodakowska, 2017	Portobello	Cultivated, Poland	Whole	Total glucan	3.96 (0.64)
	Crimini			Total glucan	3.94 (0.08)
				β-Glucan	19.2%
Sari, 2017	WBM	Cultivated, Germany	Cap	Total glucan	10.051±2.228 g/100 g
				α-Glucan	1.547±0.378 g/100 g
				β-Glucan	8.605±2.373 g/100 g
			Stipe	Total glucan	14.963 (4.979) g/100 g
				α-Glucan	2.667 (1.224) g/100 g
				β-Glucan	12.296 (4.077) g/100 g
	BBM		Cap	Total glucan	12.348 (4.514) g/100 g
				α-Glucan	3.511 (2.383) g/100 g
				β-Glucan	8.837 (3.046) g/100 g
			Stipe	Total glucan	14.647 (4.874) g/100 g
				α-Glucan	4.568 (2.845) g/100 g
				β-Glucan	10.079 (2.230) g/100 g
Taofiq, 2016	Unknown	Portugal	Extract	Ergosterol	44.79±0.37 mg/g
Stojkovic, 2014	Unknown	Netherlands	Cap	Ergosterol	138.74± 0.61 mg/100 g
Simon, 2011	WBM	Cultivated, Canada	Whole	Ergosterol	578.2±29.8 mg/100 g
				Vitamin D	5.5±4.6 μg/100 g

(continued on next page)

Table 3 (*continued*)

Reference	Type	Mushroom source (wild/cultivated, country)	Mushroom part	Compound (glucan/flavonoid/ ergosterol etc.)	Amount
			Whole (UV light exposed)	Ergosterol	579.5±20.7 mg/100 g
				Vitamin D	579.5±20.7 μg/100 g
			Whole (sunlight exposed)	Ergosterol	633.4±17.4 mg/100 g
				Vitamin D	633.4±17.4 μg/100 g
Shao, 2010	WBM	Canada	Stage 1	Ergosterol	3.41 mg/g
			Stage 2	Ergosterol	3.32 mg/g
			Stage 3	Ergosterol	3.01 mg/g
			Cap (Stage 3)	Ergosterol	3.30 mg/g
			Stipe (Stage 3)	Ergosterol	2.33 mg/g
	BBM	Canada	Stage 1	Ergosterol	4.66 mg/g
			Stage 2	Ergosterol	2.93 mg/g
			Stage 3	Ergosterol	2.49 mg/g
			Cap (Stage 3)	Ergosterol	2.71 mg/g
			Stipe (Stage 3)	Ergosterol	2.03 mg/g
Sapozhnikova, 2014	WBM	Cultivated, USA	Extract	Ergothioneine	0.81–0.92 mg/g
				Ergosterol	4.6–5.2 mg/g
				Vitamin D	179 ± 5 IU/g
			Extract (Low UV)	Vitamin D	2156± 43 IU/g
			Extract (High UV)	Vitamin D	4739± 61 IU/g
	BBM	Cultivated, USA	Extract	Ergothioneine	0.37–0.48 mg/g
				Ergosterol	4.6–6.2 mg/g
				Vitamin D	179± 4 IU/g
			Extract (Low UV)	Vitamin D	1942± 30 IU/g
			Extract (High UV)	Vitamin D	6292±109 IU/g
Phillips, 2011	WBM	Cultivated, USA	Whole	Ergosterol	56.3 mg/100 g
				Vitamin D	0.11 μg/100 g
	Crimini	Cultivated, USA	Whole	Ergosterol	61.4 mg/100 mg
				Vitamin D	0.06 μg/100 g
	Portabella	Cultivated, USA	Cap	Ergosterol	62.1 mg/100 g
				Vitamin D	0.25 μg/100 g
			Cap (UV treated)	Ergosterol	51.1 mg/100 g
				Vitamin D	11.2 μg/100 g
Mattila, 2002	WBM	Cultivated, Finland	Whole	Ergosterol	654 mg/100 g
				Vitamin D	0 mg/100 g
		Wild, Finland	Whole^	Vitamin D	4.7–194 μg/100 g
Jasinghe, 2005	WBM	Cultivated, Singapore	Whole	Ergosterol	7.80±0.35 mg/g
				Vitamin D	12.48±0.28 μg/g
Heleno, 2017	WBM	Cultivated, Portugal	Extract	Ergosterol	36.72±0.01 mg/g
Hammann, 2016	WBM	Cultivated, Germany	Whole	Ergosterol	443± 44 mg/100 g; 90% free sterols
Guan, 2016	WBM	Cultivated, Canada	Cap	Ergosterol	6.12±0.09 mg/g
			UV dose:		
			0.5 kJ/m^2		6.05±0.37 mg/g
			1.0 kJ/m^2		6.11±0.20 mg/g
			2.0 kJ/m^2		5.96±0.16 mg/g
			Stem	Ergosterol	5.2±0.13 mg/g
			UV dose:		
			0.5 kJ/m^2		5.4±0.29 mg/g
			1.0 kJ/m^2		5.25±0.22 mg/g
			2.0 kJ/m^2		5.2±0.18 mg/g
	BBM		Cap	Ergosterol	7.59±0.13 mg/g
			UV dose:		
			0.5 kJ/m^2		7.61± 0.61 mg/g
			1.0 kJ/m^2		7.64±0.31 mg/g
			2.0 kJ/m^2		7.69±0.19 mg/g
			Stem	Ergosterol	7.56±0.41 mg/g
			UV dose:		
			0.5 kJ/m^2		7.22± 41 mg/g
			1.0 kJ/m^2		7.35±0.29 mg/g
			2.0 kJ/m^2		7.60±0.18 mg/g
Gasecka, 2018	BBM	Cultivated, Poland	Extract (Hollander Spawn C9)	Ergosterol	26.4± 1.5 mg/100 g
	WBM		Extract (Sylvan 767)	Ergosterol	9.5± 1.2 mg/100 g
			Extract (Amycel 2600)	Ergosterol	21.7± 1.2 mg/100 g
			Extract (Kanmycel 3–1)	Ergosterol	36.1± 3 mg/100 g
			Extract (Italspawn F599)	Ergosterol	4± 0.7 mg/100 g
			Extract (Kanmycel K2)	Ergosterol	18.4 mg/100 g
			Extract (Sylvan A15)	Ergosterol	1.1±0.2 mg/100 g
Cardoso, 2017	WBM	Cultivated, Portugal	Cap	Ergosterol	17.4±0.1 mg/g
Cardoso, 2019	Portobello	Cultivated, Portugal	Whole	Ergosterol	216–250 mg/100 g
Barreira, 2014	Portobello	Cultivated, Portugal	Extract	Ergosterol	352 ± 1 mg/100 g
					77 ± 1 mg/100 g
Alshammaa, 2017	WBM	Wild, Iraq	Extract^	Ergosterol	27.6675% (w/w)
Chung, 1998	WBM	Cultivated, UK	Stipe	Chitin	42%
Hassainia, 2018	WBM	Cultivated, France	Cap	Chitin	7.4± 1.2%

Table 3 (*continued*)

Reference	Type	Mushroom source (wild/cultivated, country)	Mushroom part	Compound (glucan/flavonoid/ ergosterol etc.)	Amount
			Stipe	Chitin	6.4±1.4%
			Gills	Chitin	5.9± 1.2%
Manzi, 2001	WBM	Cultivated, Italy	Whole (fresh, raw)	β-Glucan	1.4±0.2 mg/100 g
				Chitin	0.6±0.04 g/100 g
			Whole (fresh, cooked)	β-Glucan	4.2± 0.3 mg/100 g
				Chitin	0.7±0.04 g/100 g
			Whole (deep frozen, raw)	β-Glucan	1.2± 0.6 mg/100 g
				Chitin	0.34±0.01 g/100 g
			Whole (deep frozen, cooked)	β-Glucan	3.2±0.8 mg/100 g
				Chitin	0.52±0.02 g/100 g
			Whole (canned, raw)	β-Glucan	1.7±0.2 mg/100 g
				Chitin	0.61±0.05 g/100 g
			Whole (canned, cooked)	β-Glucan	0.8± 0.4 mg/100 g
				Chitin	0.74±0.06 g/100 g
Nitschke, 2011b	WBM	Cultivated, Germany	Extract	Chitin	4.69±0.90 mg/100 g
Vetter, 2007	WBM	Cultivated, Germany	Cap (1st flush)	Chitin	7.21±0.51%
			Cap (2nd flush)	Chitin	7.16±1.0%
			Cap (3rd flush)	Chitin	5.63±1.02%
			Stipe (1st flush)	Chitin	7.61±0.90%
			Stipe (2nd flush)	Chitin	7.29±1.34%
			Stipe (3rd flush)	Chitin	6.94±2.23%
Kalaras, 2017	WBM	Cultivated, USA	Whole	Ergothioneine	0.41±0.18 mg/g
	Crimini				0.47±0.16 mg/g
	Portobello				0.15 mg/g
Dubost, 2007	WBM	Cultivated, USA	Whole	Ergothioneine	0.21±0.01 mg/g
	Crimini				0.40±0.03 mg/g
	Portobello				0.45±0.03 mg/kg
Chen, 2012	WBM	Cultivated, Taiwan	Whole	Ergothioneine	932.7±5.0 mg/kg

WBM, white button mushroom; BBM, brown button mushroom; LMW, low molecular weight; HMW, high molecular weight; * pressurised-water extraction temperatures; ^ wild mushrooms may naturally receive UV exposure from sunlight compared to cultivated mushrooms unless otherwise specified; a, values estimated from figures; μg, micrograms; CGEs, cyanidin-3-glucoside equivalents; CE, catechin equivalents; QE, quercetin equivalents; GAE, gallic acid equivalents; Qct, quercetin; RE, rutin equivalents; w/w, weight per weight.

increased serum ergothioneine and decreased oxygen radical absorbance capacity (ORAC) [34]. Alternatively, in a 16-week uncontrolled pre-post study using a cooked mushrooms intervention (100 g/day), both serum ergothioneine and ORAC increased (P=.03) [42]. When cytokine production was measured after 5 g/day of α-glucans from mushroom extract consumed across a 5-week intervention, tumour necrosis factor (TNF)-alpha decreased compared to the control (P=.017) [33]. However, there were no effects on any other inflammatory markers measured (*i.e.* interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, interferon-γ, serum creatinine).

3.2.3. Satiety

Two studies assessed the impact of dietary mushrooms on satiety, and findings were inconsistent [35,36]. In 35 young adults (age 23±4 years), mushroom consumption was associated with lower hunger (P=.045), greater fullness (P=.05) and decreased prospective food consumption (P=.03) compared with a protein-matched beef portion [35]. However, no change in energy intake was observed [35]. Alternatively, in a different sample of mixed-race adults from the USA (n=47; age mean (range) 35.5 (18–62) years) mushroom intake was not associated with changes in subjective satiety when compared to a volume-matched, rather than energy-matched, portion of beef [36]. The replacement of mushrooms for beef resulted in a decrease in the total fat and energy intake (total fat 41.1 ±0.4 g vs. 10.2±0.2 g, P<.001; energy 2012±70 kcal vs. 1640±65 kcal, P<.001) of the meal, and the lower energy intake from the meal was only partially compensated for at the other eating occasions (11.4±12.0% energy; 7.4±7.7% total fat) [36].

3.2.4. Gastrointestinal health

Consumption of fresh mushrooms [39] and a mushroom extract [40] both showed beneficial effects on stool weight, microbiota, bowel strain, faecal odour and halitosis (Table 2). No changes were observed in markers of bacterial fermentation (breath H_2, faecal pH and faecal short chain fatty acids) [39] or bowel regularity [40], compared to the control.

3.2.5. Cancer

The association between human consumption of *A. bisporus* mushrooms and cancer was assessed in a case control study [37] and a Phase 1 Clinical Trial [38]. In the case–control study of 1000 females from China (age 59±6 years), consumption of more than 2 g per day of WBM reduced the odds of ovarian cancer by 32% (adjusted OR 0.68 (95% CI, 0.52–0.89) [37]. In a sample of prostate cancer patients, mushroom extract at increased doses (4–14 g extract daily; equivalent to 40–140 g fresh WBM) was associated with decreased total prostate specific antigen (PSA) levels in 36% of patients, with stable PSA levels or no effect in the remaining patients [38]. Minimal side effects were reported and mostly limited to Grade 1 abdominal bloating [38].

3.2.6. Metabolic markers

Two studies reported on metabolic markers of health [41,42]. WBM cooked in olive oil (2 g/kg body weight/day) were associated with significantly lower glucose, total cholesterol, low-density lipoprotein, triglycerides and body weight, and higher high-density lipoprotein, compared to the control (P<.05 for all) [41]. However, baseline values were not reported, and the olive oil was only delivered to the treatment group. In a second sample of adults with at least two features of the metabolic syndrome, adiponectin increased after daily consumption of 100 g of cooked mushrooms over the 16-week intervention (7.9±3.2 μg/mL baseline; 8.8±3.5 μg/mL 16 weeks, P=.03) [42].

3.2.7. Immune function

The effect of cooked WBM (100 g/day for 7 days) on salivary IgA secretion was measured in 24 healthy adults (age 41.4±11.3 years) [43]. Compared to their usual diet, 100 g of cooked WBM intake for 7 days was associated with increased serum IgA osmolarity ($P<.0001$), secretion rate ($P<.0005$), and concentration ($P<.0005$) [43]. These findings indicate a potential benefit for mucosal immunity.

3.3. Concentration of bioactive compounds in A. bisporus

3.3.1. Flavonoids

The majority (95%) of studies reported the total flavonoid content of whole mushrooms, and one study reported individual flavonoids [64] (Table 3). Two studies measured the cap and stipe (*i.e.* the stalk) separately for WBM [63,79] and BBM [79], and five studies investigated the effect of cooking on flavonoid content [69,71,76,77,81]. WMB had the highest concentration of catechins (396.00 μg/g) and myricetins (11.75 μg/g), and low to negligible quantities of quercetin, kaempferol, naringenin and resveratrol present (0.25–1.75 μg/g) [64]. Cooking mushrooms reduced flavonoid concentrations and flavonoid concentration for raw mushrooms was the highest across all studies [69,71,76,77,81]. Cooking methods assessed included blanching [69], frying [71,76], boiling [76,77,81], microwaving [76,77], steaming [76,77] and pressure cooking [76,77]. Only two studies measured the effect of cooking time, on flavonoid content [71,76]. For both boiling and frying, flavonoid content was reduced with cooking time (6 min) [71,76]. For shorter cooking times (1.5 min), microwaving retained the most flavonoids compared to boiling or steaming (70.8%, 60.4% and 55.4% respectively) [76]. When cooking time was extended to 6 min, microwaving retained the least flavonoids compared to other cooking methods (20.8% microwaving, 48.5% boiling, 68.3% steaming) [76].

The mushroom cap had a greater concentration of flavonoids than the stipe. Four out of five analyses from two studies reported a mean of 28.1% greater flavonoid concentration in the WBM cap (range: 4.5–58.4%), compared to the stipe [63,79]. For BBM, the difference between the cap and stipe differed according to the solvent used for the analysis, with the water solvent showing a greater concentration in the cap, and the 50% water-ethanol showing a greater concentration in the stipe [79]. Only one study reported on flavonoids in both WBM and BBM, with the water solvent showing higher concentrations of flavonoids in the BBM, and water-ethanol solvent showing a greater concentration in WBM [79]. Majority of studies (75%) used colorimetric assays [63,65–68,70–76,78,79,81], while the remainder used spectrometry (15%) [69,77,80], high performance liquid chromatography (5%) [64] or an unspecified method (10%) [82,83]. None of the studies reported on flavonoid concentrations by mushroom maturity (*e.g.* WBM compared to Portobello).

3.3.2. Ergosterol and vitamin D

Ergosterol was measured in 16 studies [44–59]. In addition to ergosterol, vitamin D_2 was also measured in five of those studies [46,48–51]. Most studies (67%) that reported on ergosterol and vitamin D content used UVB-exposed mushrooms [46,48–50]. The range of ergosterol concentrations in UVB-exposed whole WBM and BBM were 579.5 mg/100 g–633.4 mg/100 g [46,54] and 722.0 mg/100 g – 769.0 mg/100 g [54], respectively (Table 3). No studies reported ergosterol in UVB-exposed extracts. In non-UV-exposed whole WBM and BBM, the average ergosterol concentration was 714.3 mg/100 g (range 56.3–1740 mg/100 g) [45–47,49–51,53,54,56] and 334.5 mg/100 g (range 203.0–466.0 mg/100 g) [47,54], respectively. In non-UV-exposed WBM and BBM extracts, the range of ergosterol concentration was 4–3672 mg/100 g [44,48,52,55] and 26.4–620 mg/100 g [48,55], respectively. Exposure to UVB light over time consistently increased vitamin D_2 content and decreased ergosterol concentrations [49,54].

Both BBM and cremini mushrooms had a marginally higher quantity of ergosterol compared to WBM in two studies (BBM 466 mg/100 g vs. WBM 341 mg/100 g [47]; cremini 61.4 mg/100 g vs. WBM 56.3 mg/100 g [49]. None of the studies investigated the effect of cooking method or mushroom maturity on ergosterol content. Except one study which compared the portobello cap against whole WBM [49] and found a marginally higher concentration of ergosterol in the portobello cap (62.1 mg/100 g) compared to the WBM (56.3 mg/100 g) [49].

3.3.3. Ergothioneine

Four studies measured ergothioneine content [48,60–62]. One used both WBM and BBM extracts [48], while the remaining studies used whole mushrooms [60–62]. Whole mushrooms contained an average ergothioneine content of 0.43±0.25 mg/g. There were no clear trends among the two studies that compared the ergothioneine content by type of whole mushroom (whole WBM, cremini and portobello mushrooms) [60,61]. However, WBM extract had a greater concentration of ergothioneine (0.81–0.92 mg/g) than BBM extract (0.37–0.48 mg/g) [48]. None of the studies reported on the effect of cooking method or the part of the mushroom body (*i.e.* cap vs. stipe) on ergothioneine concentrations.

3.3.4. Glucans

Nine papers measured and reported on glucans as either total [80,84,87–89,91], alpha- [27,80,84,87–89,91], and/or beta- [27,80,84–89,91]. Glucans were reported using a variety of methods (% w/w, %, and g/100 g), making direct comparisons across studies difficult. When total, alpha- and beta-glucans were compared across the cap and stipe of WBM and BBMs, a higher concentration of glucans was reported in the stipe [89]. Studies which measured both alpha and beta-glucans reported that the most prevalent glucans present in mushrooms are beta-glucans, which account for (mean ± SD) 75.0± 17.8% of the total glucan concentration [80,84,89,91]. BBM had a marginally higher concentration of glucans than WBM [89]. No differences in beta-glucan concentration were reported by mushroom maturity or cooking method [85], and all studies used whole mushrooms.

3.3.5. Chitin

Chitin was measured in seven studies using WBM [27,87,90,92–95], with high variability in reported values. Chitin content ranged from 0.005 g/100 g to 1.2 g/100 g for whole mushroom [27,87,90], 6.4% to 42% in the stipe [92,93,95], 7.2% to 7.4% in the cap [93,95], 5.9% gills [93] and 0.005 g/100 g for the extract [94]. Cooking increased chitin content regardless of preparation technology, with comparable values in fresh and canned samples (fresh: raw 0.6±0.04 g/100 g vs. cooked 0.7±0.04 g/100 g; deep frozen: raw 0.34±0.01 g/100 g vs. cooked 0.52±0.02 g/100 g; canned: raw 0.61±0.05 g/100 g vs. cooked 0.74±0.06 g/100 g) [90]. No studies measured chitin in other mushroom types.

4. Discussion

This scoping literature review systematically summarised the evidence from human intervention trials and biochemical studies that reported on the health effects and bioactive compounds in *A. bisporus* mushrooms. Results confirmed that *A. bisporus* mushrooms are a rich source of beta-glucans, antioxidants and vitamin D, with a wide variability in values reported by mushroom type, cooking time and method, and exposure to UVB across studies. Several beneficial effects of *A. bisporus* consumption exist for metabolic syndrome, gastrointestinal health and cancer, with the strongest evidence of a health effect on improving vitamin D status of individuals. All studies reported that the consumption of UVB-exposed mushrooms was as effective at increasing and maintaining total serum 25(OH)D levels as

vitamin D supplements, in individuals with and without vitamin D deficiency at baseline. Despite the wide range of health benefits reported, the evidence is still quite limited and further research is warranted, specifically for inflammatory and immune function where results are promising.

The biologically distinct and nutritionally unique properties of mushrooms make them a powerful food choice to improve human health. Unlike plants, mushrooms have high concentrations of ergosterol in their cell walls [4], and when both fresh and dried varieties of mushrooms are exposed to UVB radiation, ergosterol is transformed to pre-vitamin D_2, then converted to vitamin D_2 [30,96]. Findings confirm UVB-exposed mushrooms contain vitamin D_2 in a very bioavailable form that is relatively stable during storage and cooking, making them an ideal non-animal food source of vitamin D. Mushrooms also contain significant proportions of beta-glucans. We found that beta-glucans accounted for approximately 75% of total glucan concentrations in *A. bisporus* mushrooms with a volume of 8–12 g/100 g dry weight, which is substantially higher than the 3–8 g/100 g dry weight found in oats, 1.3–2.7 g/100 g dry weight in rye, and 2–20 g/100 g dry weight in barley. A number of international food governing bodies (including Food Standards Australia New Zealand, U. S. Food and Drug Administration, European Food Safety Authority, Health Canada's Food Directorate, and Singapore Food Agency) have approved a high level health claim based on the relationship between the consumption of 3 g of beta-glucans (from oats or barley) and blood cholesterol, with no such claim available for mushrooms. Given the significant proportions of beta-glucans reported in mushrooms, further research in this area is warranted to confirm the potential health effects induced by beta-glucans from mushrooms specifically.

Studies identified by this review suggest that the consumption of *A. bisporus* mushrooms may improve both components of the metabolic syndrome and gastrointestinal health. However, the only study that measured markers of metabolic syndrome provided mushrooms alongside olive oil, which exerts its own beneficial effect on human health [97]. The impact of mushrooms on satiety was inconsistent, which is likely a result of the lack of consistent comparator groups used (*i.e.* volume matched vs. energy matched portion of beef). While whole mushrooms and extracts were associated with bowel function, further research is required to explore if these effects are linked to any further health improvement as existing research did not identify any change in short chain fatty acids or bacterial fermentation.

Two included studies reported that *A. bisporus* mushrooms reduced the risk and progression of ovarian and prostate cancers, respectively. This suggests that these mushrooms may have a role as adjuvant therapy for cancer treatment. The mechanism of action for this effect may be related to the immunomodulating and anti-tumour effects of beta-glucans, ergothioneine and ergosterol [5]. Beta-glucans have been shown to have immune-stimulating effects [20,21], and ergothioneine is an immune modifier with antioxidant and cytoprotective properties [98,99]. This review found that consumption of whole WBM improved mucosal immunity in one study *via* increased serum IgA osmolarity and adiponectin [42], which may have a role in the prevention of malignancy and improved prognosis [100]. Decreased levels of ergothioneine in both blood and plasma have been observed in neurogenerative, cardiovascular and kidney diseases [99], while increased ergothioneine concentrations may beneficially modulate the tumour microenvironment [101]. Similarly, ergosterol is an immunologically active lipid that can induce pyroptosis [102]. Although included studies regarding the effect of human *A. bisporus* mushroom consumption on immunity and cancer had high internal validity, further robust RCTs are required to confirm their cancer preventative and treatment effects in diverse samples alongside traditional therapies.

A large number of published studies reported the presence of flavonoids in *A. bisporus* mushrooms. These highlight large variability in the measurement of total flavonoids, ranging from as little as 5.68 mg rutin equivalents per 100 g [80], up to 1636 mg per 100 g [83] in whole WBM. Estimates of daily flavonoid intake from across USA, European and Australian databases range from 209 mg to 1017 mg per day [103]. Recent evidence suggests that mushrooms may not contain flavonoids at all due to (i) the absence of genes required for their biosynthesis, and (ii) the lack of flavonoids detected when using analytic methods with higher levels of sensitivity and specificity such as high-performance liquid chromatography *versus* colorimetric assays [104]. Currently, there are no validated methods for the identification and quantification of flavonoids in foods and plants, and thus quantification of flavonoids has been inconsistent between studies [105]. Gil Raminez et al. (2016) provide convincing evidence to suggest that another compound is being detected by assays claiming to detect flavonoids [104]. They showed that ergosterol demonstrated cross-reactivity with quercetin in a colorimetric assay, giving a positive reading in the detectable range when no quercetin was present [104]. As the majority (75%) of studies in this review measured flavonoids using colorimetric assays, caution is required when interpreting these values. Although flavonoids may or may not be present in mushrooms, a strong correlation between total flavonoids and antioxidant activity has been found [61]. Therefore, whatever the measured compound/s is, it has biological activity similar to that of flavonoids *in vitro*. If not a flavonoid, the compound could be ergosterol, as ergosterol from BBM and WBM has been highly correlated with total antioxidant activity (R^2=0.89) [47] and could account for the antioxidant activity previously observed [61]. In turn, it may further contribute to the cancer preventative effects of *A. bisporus* mushrooms.

4.1. Implications for future research

Opportunities exist for future research to confirm the causative relationship between the consumption of whole WBM *versus* extracts on human inflammatory and immune function, and its anti-cancer effects. Prior to being adopted into clinical practice and public health initiatives, replication of existing studies in other population groups is required to confirm the impact of *A. bisporus* mushrooms on human health including satiety, gastrointestinal function including its effect on the microbiota, and metabolic syndrome. Initial human studies are required to replicate findings from *in vitro* and animal studies which suggest *A. bisporus* mushrooms may improve mental health and cognitive function, as none conducted in humans have reported on these health outcomes. Further research is required to fully elucidate the bioactive compounds in mushrooms using vigorous analytical methods, such as nuclear magnetic resonance spectroscopy, and expand the immunological markers and bioactive compounds being tested.

4.2. Limitations

The strengths of this review relate to the broad systematic literature search strategy used to identify the available evidence to answer the research question. This is the first review to systematically synthesise the evidence from published human trials on *A. bisporus* mushroom specifically, and its consumption on health outcomes, while further reporting on the bioactive compounds that may explain these effects. This review is further strengthened by the development of and adherence to an evidenced based protocol and comprehensive evaluation of the methodological quality of included human studies. It is limited by many studies that reported inadequate details related to sample size or power calculations. The lack of such details may confound data particularly relating to the reliability of effect sizes. There was large variability in bioactive measurements reported in mushrooms, which may be due to differing analytic methods with

varying degrees of sensitivity and specificity. Lastly, despite a growing interest in the relationship between mushrooms and health, only a small number of studies (<4 studies) have been published for each health outcome, despite over 300 narrative reviews having been published on mushrooms and health using *in vitro* and animal models. This reduces confidence in the reported effects and limits the generalisability of the conclusions to the general population.

5. Conclusion

A. bisporus mushrooms are sources of beta-glucans, ergosterol, ergothioneine, vitamin D and an antioxidant compound usually reported as flavonoids; with varying concentrations depending on the type of mushroom, cooking method and duration, and UVB exposure. UVB-exposed mushrooms increase and maintain serum 25 (OH)D levels to a similar degree as vitamin D supplements. Further, the evidence shows *A. bisporus* may lower the risk of cancer, and could potentially improve metabolic syndrome, immune function and gastrointestinal health. Due to the small number of studies examining each health outcome and the lack of replication of reported results, further research is required to confirm these effects on health to enable findings to be adopted into clinical practice.

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Appendix A. Supplementary data

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