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A Systematic Review of Human Trials on Mycoprotein - Way towards a Sustainable Ecosystem

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ABSTRACT

Rapidly increasing global warming and world population calls for exploring untapped elements of biodiversity in a much broader sense. Though there exists much evidence on the importance of livestock and animal-derived protein, escalating challenges related to sustainability have led to finding alternatives to animal-derived proteins. Mycoprotein is an eco-friendly sustainable product. This fungal-derived protein is high in fiber and protein content. For this review paper, literature was searched for human trials using PubMed, Google Scholar, and Cochrane Library. Fifteen trials, totaling 952 participants were included 5 solely reported on cholesterol response, 3 on glycemic response and 2 for serum uric acid concentrations, while 4 studies reported the combined effect of health markers such as cholesterol, glycemic response, and uric acid concentrations and 1 study on gut health. The Jadad scale was used to assess the quality of studies. Five trails were identified to be of good quality scoring 3 or more. The results showed the cholesterol-lowering percentage to be ranging between 4.3 to 13%. Similarly, a significant increase of (+0.02) ($P< 0.05$) was observed in *Lactobacillus spp* from the baseline value following mycoprotein consumption. Results however were inconclusive for glucose and insulin response. Overall, given the growing increase in sustainable proteins, this area should be explored further from a public health perspective.

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Introduction

Consumers today are much concerned about the nutritional, health-related and environmental characteristics of the food they eat (1). A rising demand exists for alternatives that make use of technology that is both cost-effective and eco-friendly(2). Over the years, production and utilization of plant-based meat alternatives (PBMA) have gained a momentous increase primarily because of their ability to improve health markers such as blood lipids, glycemic control in people with diabetes, uric acid levels and gut health when replaced for animal protein(3). The devastation caused by the global pandemic is undoubtedly a call to action for exploring environment-friendly and food-secure plant-based meat alternatives around the world(4). Thereafter, a new consumer group of "flexitarians" who reduce meat consumption in their daily diet is on the rise(5). Considering these concerns, numerous scientific organizations like the EAT-Lancet report(6) and various local and international agencies alike have emphasized the need to incorporate environmental sustainability and improved health factors in food consumption(7–10). While major emphasis has been placed on PBMA, other potential sources of vegan protein like fungal-derived protein have been overlooked.

Halal markets have faced the dilemma of animal protein replacement for many decades. However, in European regions, meat replacement gained much interest after the emergence of bovine spongiform encephalopathy, (the mad cow disease) in the 1980s (11). Fungal-derived proteins particularly are gaining popularity these days due to their healthy nutrition profile, environmental suitability and cost-effectiveness (12). Mycoprotein is a complete food protein, filamentous fungus biomass, and a well-known meat substitute.(13,14). It was first discovered in the 1960s and was extracted from the soil-dwelling non-pathogenic microfungus *Fusarium venenatum A3/5* (15). It was approved by the Ministry of Agriculture, Fisheries and Food in the United Kingdom after going through some rigorous lab testing (16). Later, following some further regulatory approvals, it has now reached all of the member EU states and countries like the USA, Australia and Japan(17). A variety of vegan and vegetarian products are being sold under the brand name Quorn(18). Toady mycoprotein is generated using fermentation processes resulting in a high-quality protein with a low carbon footprint (19). These environmental claims for example have been quantified by using techniques like life cycle analysis, conforming to international regulatory standards, the results of which are audited and certified by Carbon Trust(20).

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However, despite this growing popularity, health professionals are generally unaware of the wide scope of health benefits mycoprotein could provide across the lifespan(21). Though fungal proteins like *Fusarium* have been around for several years, their health benefits across the lifespan are only beginning to be fully acknowledged(22). Fungi are a significant and varied component of the Earth's biosphere(23). Interestingly, they are recognized as the third kingdom of organisms and a potentially useful food source in addition to the classic animal and plant kingdom (24,25).

From a nutritional standpoint, mycoprotein can be considered a rich protein source, since it has a protein digestibility adjusted amino acid score of 0.996 and provides nine non-dispensable amino acids, indicative of high protein quality (26). According to the European Commission, mycoprotein is also high in fiber content, providing 6g of fiber per 100g (27). Mycoprotein fiber is naturally occurring and consists of roughly one-third chitin (N-acetylglucosamine) and two-thirds β-glucan (1,3- glucan and 1,6-glucan)(21). This fiber ratio can in turn be beneficial for minimizing the risk of type 2 diabetes and CVDs. One plausible explanation for this is the fact that delayed digestion by the consumption of resistant starches and dietary fiber in the cell wall can result in a lower glycemic response, reduced appetite and change in the gut/colonic microbiota(28). Moreover, the ratio of saturated fats and cholesterol contained in mycoprotein is close to negligible (29). The earliest study on the cholesterol-lowering effect of mycoprotein was conducted by Udall et al. (1984) who, whilst conducting a double-blinded, randomized controlled trial on 100 adults, reported a significant reduction (6.9%) in serum cholesterol following consumption of mycoprotein for 30 days (30). Moreover, myoprotein is also known to contain a wide variety of micronutrients like vitamin B12, riboflavin, folate, phosphorous, zinc and manganese(31).

The increased demand for nutritious and sustainable protein sources necessitates addressing common misconceptions regarding fungal protein. Excessive consumption of animal-based meat, especially red meat is largely associated with colorectal cancer, cardiovascular disorders, and potentially diabetes(32). Previous literature somewhat suggests that this can be minimized or induced at lower concentrations while health benefits can be achieved by combining cost-effective and sustainable approaches (33). Therefore, this paper aims to systematically review the evidence of mycoprotein consumption on human health primarily focusing on cholesterol, glucose, insulin levels, serum uric acid concentration and gut health throughout the last few years.

Materials and Methods

Relevant human trials were searched using PubMed, Google Scholar, and Cochrane Library database using the search terms "(mycoprotein OR fungi derived protein OR *Fusarium venenatum* OR Quorn) and (cholesterol OR lipids OR insulin OR glycemia OR glucose levels OR uric acid OR gut health) and (cholesterol reduction OR blood sugar levels OR human health OR cardiometabolic health) and (metanalysis OR randomized control trial)". A manual search of the reference list was also created to identify additional relevant articles. A cut-off time of March 2022 was applied. Moreover, search results were limited to English-language articles.

Approach

Human trials were looked up using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach(34). The PICOS criteria (patient, intervention, comparator, outcome, study design) were utilized to determine study eligibility(35). The studies included population (P): adults aged ≥ 20 years. The intervention (I) was the consumption of mycoprotein, the comparison (C) was the control or placebo group, and the outcome of interest (O) were markers of health including, cholesterol reduction, insulin and glucose levels, serum uric acid levels and gut/ cardiometabolic health.

Inclusion/Exclusion Criteria

The present systematic review included controlled human trials or observational studies. Studies comprising of participants (young people or adults ≥20 years) evaluating the effect of mycoprotein on health markers especially cholesterol profile, insulin, glucose levels, serum uric acid and markers of gut/cardiometabolic health were a prerequisite for the inclusion in this systematic review. Among the measures of effect calculated from the reported studies, the most used was found to be weighted mean differences and standard errors (Mean± S.D). Review papers as well as studies including animal trials and mechanistic studies were excluded. Furthermore, reviews and summaries of systematic reviews not including the primary outcome (cholesterol reduction, insulinemic, and serum uric acid concentration) were also excluded.

Primary screening yielded a total of 2060 articles ("Figure 1"). After excluding irrelevant, duplicate, and other studies not meeting the inclusion criteria,15 human-controlled trials were included in this systematic review.

Data extraction

Data extracted from the studies included the following details of the study (author, year, location), participants (number), intervention (type, amount), comparison group (diet), study outcomes with any reported (Mean± S.D) and significant *p*-values. Following the inclusion/ exclusion criteria authors identified, retrieved, and rechecked studies. Mean changes in health markers (serum cholesterol, glucose and insulin levels and serum uric acid levels) with 95% CI were extracted. The Jadad scale was used to develop quality scores for studies(36). Quality scores were graded between 1-5, with higher scores being indicative of better quality (Table 1).

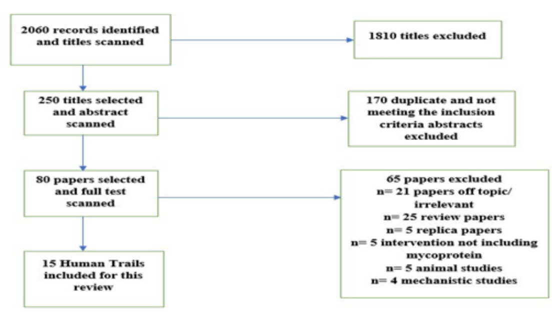

Figure 1. Flow diagram of literature search for evaluating the effect of mycoprotein on health through Human Trials.

Table 1. Jadad scale for quality assessment of studies.

Study	Randomization	Appropriate method of randomization	Blinding mentioned	Appropriate method of blinding	Withdrawal and dropouts of subjects	Total score
(30)	1	0	1	0	1	3
(37)	1	0	1	0	1	3
(38)	1	0	1	0	0	2
(39)	1	0	1	0	0	2
(40)	1	0	0	0	0	1
(41)	0	0	1	0	1	2
(42)	1	0	0	0	0	1
(42)	1	1	1	0	1	4
(43)	1	0	1	1	0	3
(44)	1	0	1	0	0	2
(45)	1	0	1	0	0	2
(46)	1	1	0	0	0	2
(47)	1	1	0	0	0	2
(48)	1	0	1	0	1	3

Assessment scale used to assess the quality of studies

Table 1. Jadad scale for quality assessment of studies.

Results

We identified controlled trials for cholesterol levels, serum insulin and glucose levels, uric acid concentrations and the effect of mycoprotein on gut health. Randomized controlled trials showing the effect of mycoprotein on protein synthesis and satiety were not included. Due to the heterogeneity of reported results and the scarcity of data on the subject, a statistical meta-analysis was not possible for all studies. Therefore, a systematic approach for critically appraising published systematic reviews and human trials was used(49). Results were reported according to outcome measures of studies.

Health Evidence

Effect of Mycoprotein on Cholesterol levels

Overall, seven human trials analyzing the effects of mycoprotein on cholesterol reduction were selected (37,40,50–53) (Table S1). The previous mentioned studies concluded that including a modest amount of mycoprotein in the diet could reduce cholesterol levels significantly. The duration of the trials varied between 30 days and 8 weeks. The results showed the cholesterol lowering percentage to be ranging between 4.3 to 13%.

The pioneering study done for testing the effect of mycoprotein on cholesterol levels was a 30 days trial conducted in the US that utilized a double-blinding method to minimize the risk of bias(30). Turnbull conducted two studies (1990; 1992). Participants in the first trial reported a 13% drop in plasma total cholesterol after consuming 191g of mycoprotein at lunch and dinner for three weeks (37). A prolonged 8-week study (38) reported a somewhat similar reduction of 8.2%, however, the (130g mycoprotein, wet weight) intervention was given as cookies. Later on, Carrie H. S. Ruxton and McMillan (2010) tested the cholesterol-lowering effect in consumer settings using (21 g dry-weight mycoprotein). They observed a significant reduction of serum lipids in the mycoprotein group, although blinding randomization was not applied in this trial.

More recently, Coelho demonstrated that meat/fish lunches (control group) or a diet containing 1.2 g of protein per kg of BW per day (intervention group) had a beneficial effect on various lipoprotein fractions. In the mycoprotein group (a 7 to27 % decrease $P < 0{\cdot}05$) was observed in comparison to the control group (55) giving rise to the idea that the cholesterol-lowering effect can be attributed to the type and amount of fiber contained in mycoprotein(56). Furthermore, researchers have also started exploring the cholesterol-lowering effects on CVDs risk. In a recent study, Farsi suggested that following a mycoprotein diet, CVDs risk was reduced from baseline by an average of 0.29% ($P = 0.19$) while there was a marginal increase of 0.05% in risk after meat consumption ($P = 0.99$). The difference in diet effects on CVDs risk was not significant (difference: 0.34, $P = 0.24$) (48). Further research is required to address these claims.

Effect of Mycoprotein on Glycemic Response

Seven human trials were selected to study the effect of mycoprotein on glycemic and insulin response in humans(40–43,55,57,58) (Table S2). The randomized controlled trials included 10-31 participants (Table S2). Oral mycoprotein dosage was between 20-132g per day with a study duration of 180 minutes to 6 weeks. Overall, the effects of acute mycoprotein consumption on glycemic response were less clear. Early research by Turnbul (1995) reported a significant decrease in glucose and insulin levels in both the intervention and control group by -1.94 (95% confidence interval:6.23 at 30 min to 4.29 mmol/L at 120 min) and -1.16(95% confidence interval:5.7 at 30 min to 4.54 mmol/L at 120 min) respectively. Similarly, insulin levels in both the intervention and control group declined by -224(95% confidence interval:406 to 182 pmol/L at 120 min) and -185(95% confidence interval: 330 to 145 pmol/L at 120 min) respectively(40).

Bottin (2011) reported glucose levels as Incremental Area Under the Curve (IAUC) values that showed significant reductions in insulin levels after 15, 30, and 45 minutes of 30g of mycoprotein (dry weight) versus the whey protein control consumption. Similar work by Bottin in the following years, which recruited obese adults did not report any significant reduction in glucose levels. (42). Recently two studies have been conducted by (45,58) each measuring glucose levels, reported no significant change between both groups.

Most of the trials regarding insulin levels showed mycoprotein to be effective in regulating insulin levels in overweight individuals at baseline (50,57). However, there is a strong need for large-scale randomized control trials as most of the results regarding glycemic control are heterogeneous (59).

Effect of mycoprotein consumption on serum uric acid levels

Four human trials were included to summarize the effects of mycoprotein consumption on levels of serum uric acid (43–45,47) (Table S3). Participant number ranged from 10 to 20 in these trials, with the trial duration between 240 minutes to 7 days. The summary of the studies indicated that serum uric acid concentrations remained unchanged in the control (CON) and low mycoprotein (L-NU) groups. On the other hand, these were raised by an average of 12% (from 284 ± 13 to 319 ± 12 μmol·L −1 after 210 min) and reverted to baseline concentrations after 24 hours in the high mycoprotein group (H-NU) (45,47). Previous research comparing mycoprotein consumption to meat/ fish consumption showed somewhat similar findings. If the mycoprotein ingested was high in dietary nucleotides, a persistent increase in blood uric acid concentrations occurred (44). However, further large-scale randomized control trials are needed to confirm the previous findings.

Effect of mycoprotein consumption on Gut Health

To date, one investigator-blind randomized crossover control trial (n=1) was identified that studied the effect of replacing a high red processed meat diet with mycoprotein on gut and cardiometabolic health(48). (Table S3). This study included a total of 20 participants and lasted for 8 weeks. It comprised three phases where participants consumed 240g (uncooked weight of red meat or mycoprotein). Results indicated a significant influence on the number of genera of *Lactobacillus spp.* after Mycoprotein (P = 0.05) consumption. Similarly, *Roseburia spp*, increased after Mycoprotein while it was significantly reduced following meat consumption (P < 0.001). Additionally, *Oscillibacter spp* increased after both study phases (Mycoprotein, P = 0.05; Meat, P =0.003), (Table S3).

Thus, it can be concluded that enrichment in the genus Lactobacilli following mycoprotein consumption may be a beneficial alternative to meat in the context of gut health. However, further large-scale randomized trials are needed to corroborate the present findings.

Discussion

The present systematic review elucidates the findings that fungal mycoprotein is a well-accepted food source with numerous health benefits. Fifteen human trials were identified to study the effect of mycoprotein on health markers. The main findings of the study were that mycoprotein had cholesterol-lowering effects in study subjects having higher baseline cholesterol levels. However, results were less convulsive for insulin and glucose levels. Furthermore, consuming mycoprotein with a high nucleotide content resulted in a sustained serum uric acid elevation. Finally, mycoproteins confer some beneficial effects on gut health by presumably increasing *Lactobacillus* concentration.

There are several mechanistic explanations for the association between cholesterol lowing effects of mycoprotein. One explanation for this effect could be attributed to the unique dietary fiber composition of its cell wall(21). Chitin and β-glucans produce a fibrous, 88% insoluble matrix that delays the absorption of BCAAs or glucose and impairs the absorption of cholesterol and bile. Additionally, the gut microbiota's role in the intestinal fermentation of these insoluble dietary fibers also lowers plasma cholesterol levels (63). Short-chain fatty acids (SCFA), mainly acetate, propionate, and butyrate, are the primary end products of fiber fermentation (64). Propionate, in particular, has been shown to decrease hepatic cholesterol production (65). It has also been observed that propionate inhibits β-hydroxy β-methylglutaryl coenzyme A (HMG-CoA) reductase, which is rate-limiting in cholesterol production (66). Despite previous findings, it remains unclear whether the cholesterol-lowering effects are caused by limiting production or by other unidentified mechanisms like decreased cholesterol absorption or increased peripheral clearance. This necessitates further large-scale human trials.

The findings for glucose and insulin levels were less compelling. While some trials revealed reduced glucose levels, the results were not statistically significant (41,42,57,58). Recent systematic reviews found that the effects of mycoprotein ingestion on postprandial glucose levels may not always translate to long-term benefits on insulin sensitivity (24). Despite these findings, the reduction in fasting blood glucose levels following a mycoprotein diet was noteworthy(40). This could be explained by the fact that mycoprotein ingestion decreased glucagon sensitivity (perhaps owing to the high fiber content of mycoprotein)(67), or due to improvements in β- cell function(68). Therefore, further large-scale trials studying the effect of mycoprotein ingestion in diabetic patients would further clarify the results.

Besides studying the effect of mycoprotein on cholesterol and glucose levels, trials have also looked into the fluctuations in serum uric acid concentrations in human subjects (43–45,47). Fungi like mycoprotein are a rich source of protein and various vitamins and minerals(69). Moreover, they have a nucleic acid concentration ranging from 6% to 11%. Purine bases in nucleic acids are converted to insoluble uric acid in humans, which can potentially lead to metabolic disorders like gout, kidney stones, or gall stones. The United Nations Protein Advisory Group suggests that individuals should not consume more than 2 g of nucleic acid per day. As a result, the fungi are often heat treated to lower RNA levels to a safe level (70). The mechanistic explanation for why a nucleotide-rich meal raises uric acid levels is most likely linked to increased uric acid generation as a metabolic end product with no urinary excretion (71). Several in vitro tests have revealed uric acid to be a pro-oxidant that contributes to metabolic dysfunction by increasing oxidative stress (72). However, earlier experiments in this regard primarily studied the acute response to bolus ingestion, and findings are not supportive of the idea that a nutritionally induced elevation in uric acid concentration impairs metabolic health markers(45). Thus, human trials with a large sample size are needed to further elucidate the link between the two variables.

The role of mycoprotein intake on gut health is also gaining attention since numerous fungi have been shown to benefit gut health (73). The high meat, low fiber western diets are somewhat damaging to gut health(74). In this regard, an investigator-blind, randomized, cross-over dietary intervention trial conducted at Northumbria University, Newcastle found that higher meat intake increases fecal genotoxicity along with a higher number of putrefactive bacteria like (*Oscillobacter* and *Alistipes*). On the other hand, mycoprotein consumption increased the abundance of good bacteria like (*Lactobacilli* and *Roseburia)* (48). These intestinal bacteria in turn exert anti-cancerous effects on the heath. Further microbially produces SCFA feeds intestinal epithelial cells and in turn, promotes healthy barrier function or a protective mucus layer between epithelial cells and luminal mutagens(75–77). Despite reporting sound results, this trial had some limitations like applicability to the larger population as the cohort comprised mainly of male participants. Thus, further larger-scale randomized trials are needed to corroborate findings.

Conclusion

Our review concluded that a minute consumption of 18g to 24g dry weight/day of mycoprotein could lead to significant blood cholesterol reduction. Moreover, mycoprotein is one of the better and more sustainable meat alternatives available to consumers. Researchers have been investigating biodiversity concerns for thousands of years, and it is reasonable to argue that no period in history has been more vital than now to further the investigation of how we may use the kingdom fungi as a source of healthy and sustainable food source.

Author Contribution

Conceptualization: A.I., U.F. and Z.P.; Literature Search: A.I. and J.A.; Writing Original Draft: A.I.; Writing Critical Analysis: S.I., S.A. and A.M.R.A.; Review and Editing: S.Z., A.I and A.M.R.A.; Validation: S.I.

Conflict of interest

The authors declare no conflict of interest.

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