

THE ANTI-DIABETIC POTENTIAL OF MUSHROOMS: A REVIEW

Waill Elkhateeb¹, Galappaththi MCA², Dina El-Ghwas^{1,*} and Ghoson Daba¹

Received: July 21, 2023; Revised: September 22, 2023; Accepted: October 10, 2023

Abstract

It is crucial to discover new nutraceuticals or medications to cure or prevent diabetes because it is becoming a pandemic. Some mushrooms seem to have benefits in controlling blood glucose levels and correcting diabetes problems without any negative side effects. Only a few regions employ mushrooms as appetizing food, health-improving dietary supplements, or medicine because they contain immune-modulating polysaccharides. However, scientific or clinical research on mushrooms has not been sufficient to allow them to be used as recognized medicines or nutraceuticals worldwide. These functional fungi may have a greater impact on the prevention and diabetes treatment. This review focuses on prospective mushrooms that have demonstrated anti-diabetic effects in clinical or experimental studies and prevent or slow the progression of diabetes mellitus.

Keywords: Biological activities, Fungi, Medicinal mushrooms, Secondary metabolites

Introduction

Many researchers are interested in the use of secondary metabolites produced by microbes normally, and mushroom metabolites especially in different biotechnology fields, due to the bioactive properties of these metabolites, which have led to their use in pharmaceutical, industrial, and agricultural fields. Diabetes is a serious health problem that predisposes to a noticeable increase. Despite numerous prevention strategies and a range of drugs, the treatment of diabetes remains largely unsatisfactory (Perera and Li, 2011). Diabetes is one of the prominent non-communicable diseases at present. Diabetes is more common in developed

countries, but the highest growth rate of patients is in developing countries. Lifestyle changes directly relate to this problem (Sękowski *et al.*, 2022). Nowadays, there are many commercial hypoglycemic drugs that are effective in controlling hyperglycemia but have many side effects and are not sufficient to correct the complications of diabetes. Mushrooms and their bioactive compounds, especially polysaccharides and terpenoids from different mushroom species, have been used to treat diabetes for centuries. Some mushrooms have been found to be used in medical and/or experimental settings to control and reverse

¹ Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries Institute, National Research Centre, Dokki, Giza, 12622, Egypt. E-mail: dinaelghwas7781@yahoo.com

² Postgraduate Institute of Science (PGIS), University of Peradeniya, Peradeniya, Sri Lanka.

* Corresponding author

diabetes without side effects (Jovanović, *et al.*, 2021). Modern medicine treats type II diabetes utilizing anti-hyperglycaemic drugs with various mechanisms of action after the first-choice therapy, which is based on food modification and exercise (Ajith and Janardhanan, 2021). Abou Zaid *et al.*, 2017; Elkhateeb *et al.* 2021a described the mushrooms as macro-fungi with noticeable fruiting bodies, which may be hypogynous or epigeous and are large enough to be visible with one's own eyes and plucked by hand (Abou Zaid *et al.*, 2017; Elkhateeb *et al.*, 2021a).

Mushrooms were valued as palatable foods and as medicinal substances. In addition, because of their bioactive components, which have a variety of positive impacts on human health, mushrooms are regarded as functional foods (Elkhateeb *et al.*, 2019). A metabolic disorder called Diabetes Mellitus (DM) disorder is shown by high blood glucose levels by a fasting plasma glucose level >126 mg/dl or a casual plasma glucose >200 mg/dl. It is indicated by insulin insufficiency, receptor, or dysfunction that causes increased blood glucose levels and metabolic problems. Proteins, polysaccharides, fibers, and many other biomolecules isolated from mushrooms have been exhibited to help in the management of diabetes as biological anti-hyperglycaemic drugs (Daba *et al.*, 2020). Studies have shown that mushrooms display anti-diabetic properties, including antioxidants, blood glucose level reduction, insulin secretion through glucose stimulation, digestive enzymes, and inhibitory effects on tyrosine kinase (Du and Xu, 2014; Daba and Elkhateeb, 2020; Elkhateeb, 2020; Elkhateeb *et al.*, 2020; Thomas, 2020; Elkhateeb *et al.*, 2021b, Elkhateeb and Daba, 2021a; Elkhateeb and Daba, 2021b). Mushrooms in the phyla Ascomycota and Basidiomycota are much admired for pharmacological properties and their nutritional value. In traditional medicine, they have long been used to maintain health and prevent and treat various human diseases such as cancer, hypertension, metabolic syndrome and cardiovascular diseases. Many studies have documented the advantages of medicinal mushrooms for the management of diabetes (De Silva *et al.*, 2012; Patel *et al.*, 2012; Elkhateeb *et al.*, 2018; Badalyan *et al.*, 2019; Friedman, 2019).

However, there is not enough scientific data to draw conclusions on the efficacy of specific therapeutic mushrooms. Mushrooms belong to the genera *Ganoderma* (*G. lucidum*), *Auricularia* (*A. auricula-judae*), *Inonotus* (*I. obliquus*), *Morchella* (*M. conica*), *Coprinus* (*C. comatus*), *Tremella* (*T. fuciformis*), *Laetiporus* (*L. sulphureus*), *Lentinula* (*L. edodes*), *Agaricus* (*A. blazei*), *Lignosus* (*L. rhinocerotis*), *Grifola frondosa* and *Phellinus* (*P.*

linteus, *P. ribis*, *P. rimosus*, and *P. ignarius*) have shown considerable hypoglycaemic effect in experimental diabetic models (Wu and Xu, 2015; Elkhateeb *et al.*, 2018; Elkhateeb *et al.*, 2019; Badalyan *et al.*, 2019; Ajith and Janardhanan, 2021). This review focuses on mushrooms' antidiabetic effects and potential mechanisms of action in both in vitro studies by testing antioxidant activity and in vivo by evaluation of insulin levels, biological activity in rats and so on. Prospects in this field of research and limitations that may affect the development of potential drugs in mushrooms are also being considered.

Gill mushrooms (*Agaricus* and *Coprinus*)

The genus *Agaricus* is the globally grown edible mushroom (Figure 1). It contains bioactive compounds that may have valuable effects on patients with diabetes mellitus (Hsu *et al.*, 2007; Jeong *et al.*, 2010; Niwa *et al.*, 2011). The white button mushroom, *Agaricus bisporus*, contains high amounts of antioxidants and dietary fibers, including vitamins B12, D, and C; folates; and phytochemicals called polyphenols that may be good for treating diabetes and heart disease (Jeong *et al.*, 2010). Ekowati *et al.* 2018 determined the effects of *A. bisporus* extracts administration on the blood glucose, and Malondialdehyde (MDA) levels as well as superoxide dismutase (SOD) activity of alloxan-induced diabetic rats and showed that *A. bisporus* extract could lower blood glucose levels and malondialdehyde and also increase superoxide dismutase (Ekowati *et al.*, 2018). *A. bisporus* extract can be used as an alternative natural anti-diabetic agent and can be applied easily and on a more controlled industrial scale in the community (Ekowati *et al.*, 2018). Abou Zaid *et al.* 2017 concluded that *A. bisporus* has an anti-diabetic effect against streptozotocin-induced pancreatic islet damage. In addition, the repair/regeneration of β -cells in the islets of Langerhans induces insulin synthesis and secretion. Lectin-like molecule, high fiber content, polyphenols contained in *A. bisporus* that may play a role in preventing diabetic activity. (Abou Zaid *et al.*, 2017). The therapeutic effects of *A. bisporus* are dependent on its anti-oxidant properties and improving the action of the anti-oxidant system against the oxidative stress of Streptozotocin and its harmful effect (Abou Zaid *et al.*, 2017). The oxidative stress causes lipid peroxidation of cell membranes, which can lead to cell damage, and Streptozotocin induces the formation of nitric oxide radicals (Pizzino *et al.*, 2017).

Coprinus is also called shaggy ink cap, shaggy mane, lawyer's wig, or chicken drumstick mushroom. *Coprinus comatus* is widely grown for

eating and is recognized as an edible mushroom in Asian nations, but it is not used or recognized in many other nations despite its extensive distribution (Figure 1). Different studies have shown an antidiabetic effect of *C. comatus* (Elkhateeb and Daba, 2021a; Husen, 2021; Ratnaningtyas *et al.*, 2022). After treatment of *C. comatus* 80 mg/kg body weight to normal rats, blood glucose concentration decreased from 5.14 mM to 4.28 mM within 3 hours. resulted in *C. comatus* decreasing blood glucose levels and improving glucose tolerance in normal rats, and it also caused a slowly developing, moderate hypoglycaemic condition in those rats (Figure 1) (Ding *et al.*, 2010; Dotan *et al.*, 2011; Cao *et al.*, 2020; Nowakowski *et al.*, 2020).



Figure 1. Medicinally important mushrooms. A. *Agaricus campestris* (The photograph was taken by photographer andreagrossi, at Provincia di Ferrara, Italia); B. *C. comatus* (The photograph was taken by photographer gugmag, at Via Calore Variante, Mirabella Eclano, Campania, Italy).

Ganoderma is a fungus that causes a wood rot infection through tree injuries. It strikes large roots and the base of the trunk but can expand several feet. *Ganoderma* is a rot fungus widely distributed in Asian countries, and many species are used as tonics to increase longevity and health as illustrated in (Figure 2). *G. lucidum* extracts have been identified as a possible supplemental treatment for diabetes (Wińska *et al.*, 2019). Polysaccharides, proteins, proteoglycans, and triterpenoids of *G. lucidum* exhibited hypoglycaemic effects (Xiao *et al.*, 2012; Rašeta *et al.*, 2020). By lowering mice's blood glucose levels and raising their plasma insulin levels, *G. lucidum* polysaccharides have been proven to have hypoglycaemic action. Diabetes is a promising candidate for protein tyrosine phosphatase 1B therapy, and *G. lucidum* proteoglycan can inhibit this enzyme in vitro. Triterpenoids from *G. lucidum* have also shown an inhibitory impact on aldose reductase and α -glucosidase, which can prevent postprandial hyperglycaemia (Ma *et al.*, 2015). Jung

et al. 2005 proved that the bioactive polysaccharide components of *G. applanatum* are responsible for anti-diabetic properties (Jung *et al.*, 2005).

Grifola frondosa (Maitake), belonging to phylum: *Basidiomycota*, class: *Agaricomycetes*, order: *Polyporales*, and family: *Meripilaceae* (Figure 2) has been verified to possess compounds that have anti-diabetic properties. A genetically diabetic mouse (KK-A^y) was given 1 g/d of powdered fruit body of maitake, and in contrast to the control group, blood glucose levels decreased. In addition, plasma insulin and triglyceride levels showed a similar change to blood glucose levels when maitake was administered (Kubo *et al.*, 1994). High-value medicinal mushrooms like *G. frondosa* are widely used as traditional medicine and health foods in China and Japan. It is an herbal remedy that has traditionally been used to treat cancer, diabetes, and inflammation. (Wu *et al.*, 2020). Kou *et al.* 2019 also indicated *G. frondosa* polysaccharides exhibited hypoglycemic activities against diabetic rats (Kou *et al.*, 2019).

In the last decade, several investigations have documented the biological activities of *Inonotus obliquus* fruiting bodies, such as anti-cancer, anti-oxidation, anti-inflammatory, anti-diabetic, and immune-enhancing activities (Abou Zaid, 2017; Peng and Shahidi, 2020; Szychowski, 2021). (Figure 2). The medicinal benefits of *I. obliquus*, known as 'Chaga' have recently been demonstrated with strong anti-cancer, anti-oxidation, anti-inflammatory and anti-diabetic effects (Thomas *et al.*, 2020). Extracts of Chaga (*I. obliquus*) act as an anti-diabetic by lowering blood glucose levels. One of the essential elements is polysaccharides of Chaga extracts, are able to inhibit α -glucosidase, an enzyme that hydrolyzes carbohydrates. Thus, Chaga extracts act as a hypoglycemic agent by slowing glucose uptake in the digestive tract, thereby preventing hyperglycemia (Chen *et al.*, 2010; Wang *et al.* 2017). Sun *et al.* 2008; Thomas *et al.* 2020 reported that polysaccharides of *I. obliquus* are capable of reducing the level of glucose triglycerides, fatty acids, and cholesterol levels in the blood (Sun *et al.*, 2008; Thomas *et al.*, 2020). *Laetiporus sulphureus* species commonly known as chicken of the woods, sulfur shelf, or sulfur polypore. It belongs to family Polyporaceae, phylum Basidiomycota that edible (Figure 2). It is widespread in Europe, North America, and Asia. On hardwoods or conifers, this fungus is frequently observed. The distinctive yellowish or orange shelf-like fruit bodies of *L. sulphureus* make it simple to identify. The amazing size (up to 40 cm wide) and dazzling bright sulfur yellow to orange-colored porous basidiocarps of this mushroom make it easy to identify in woodlands and

urban settings. *L. sulphureus* species is rich in several bioactive compounds like triterpenes, polysaccharides, lectins, phenolic compounds, α -glucans, and laetiporic acids (Figure 2). *L. sulphureus* has a longer history of consumption than other polypores, particularly in North America, Thailand, and Japan. As a source of anti-oxidant, anti-diabetic, anti-viral, anti-tumor, anti-coagulant, anti-bacterial, anti-inflammatory, and other qualities, this mushroom has also long been employed in Asian herbal medicine (Patocka, 2019; Elkhateeb and Daba, 2021a).



Figure 2. Medicinally important mushrooms. A. *Ganoderma applanatum*; B. *G. lucidum*; C. *I. obliquus*; D. *L. sulphureus*; E. *G. frondosa* (Maitake); F. *Phellinus igniarius* (Photographs were taken by Dr. Waill Elkhateeb, Prof. T.C Wen, and Dr. Paul W. Thomas).

The mushroom *Lignosus rhinocerotis* belongs to phylum: *Basidiomycota*, class: *Agaricomycetes*, order: *Polyporales*; and family: *Polyporaceae*, which is natural to tropical regions such as Malaysia, the Philippines, and Indonesia (Figure 2), contains a very large amount of potential anti-oxidants and anti-diabetic agents. By dramatically bringing high blood glucose levels to a normal range, biological components discovered in the freeze-dried *L. rhinocerotis* powder have been found to have anti-diabetic activities (Nyam *et al.*, 2017). The *Phellinus* mushroom, also known as "Sanghuang" in China, is a unique edible mushroom that has long been valued as a food source in a number of East Asian nations, including Korea, China, and Japan (Figure 2). *P. baumii* has a variety of biological effects, including decreasing blood lipids, anti-tumor, anti-influenza, anti-oxidation abilities, and blood glucose regulation (Huang *et al.*, 2015). Previous research has shown that some phenolic compounds and extracts from wild

Phellinus have a hypoglycaemic impact. Nevertheless, Gilvsins A, B, C, Hispidin, 7,8-dihydroxy coumarin, chlorophyllin C, and 7,3'-dihydroxy-5'-methoxyiso-flavone, inoscavin C, D,3,4-dihydroxybenzalacetone, are phenolic substances isolated from the fruit body of wild *Phellinus* that have been demonstrated to have a hypoglycaemic effect which is characterized by a disordered metabolism and abnormal high blood glucose (Jang *et al.*, 2010; Kim *et al.*, 2010).

In the previous studies by Yang *et al.* 2020, Jang *et al.* 2010, diabetes can be helped by the fruit body of wild *P. baumii*, and antioxidants are helpful because they shield the β -cell from oxidative stress damage (Jang *et al.*, 2010, Yang *et al.*, 2020). β -cell dysfunction results from a lack of glucose to stimulate insulin production. The fruit body of the grown *P. baumii* was extracted using 80% ethanol extracts, and various fractions were produced using n-butanol (n-BuOH), petroleum ether, water, and ethyl acetate (EtOAc). The results revealed that the highest level of inhibition of α -glucosidase activity was seen in the ethyl acetate fraction, which was higher than the positive control. By using liquid chromatography-mass spectrometry (LC-MS), with a purity of 79.45% It was composed mainly of phenolic compounds it was identified as 2,5-bis (4,7-dihydroxy-8-methyl-2-oxo-2H-chromen-3-yl) cyclohexa-2,5-diene-1,4-dione, inoscavin A, and hypholomin B. In addition, insulin-resistant HepG2 cells consumed more glucose when the ethyl acetate fraction was present. The hydroxyl radical (OH) $^{\cdot}$ scavenger activities of the ethyl acetate fraction and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic) diammonium salt also displayed antioxidant properties. Due to its high concentration of specific phenolic chemicals, the ethyl acetate fraction of the grown *P. baumii* fruit body demonstrated anti-diabetic benefits. As a result, the grown fruit body of *P. baumii* may provide a reliable source for the management of diabetes. (Yang *et al.*, 2020).

Jelly mushrooms (*Auricularia* and *Tremella*)

The edible mushroom *Auricularia auricula-judge*, often known as the jelly ear edible mushroom or Judas's ear, is distinguished by its ear-like jelly form and brownish. An *auricula-judge* fruit body consists of a high content of protein, carbohydrates, and minerals like phosphorous, calcium, iron, and potassium. Due to the biological effects that their derived chemicals have on health, *Auricularia* species are the subject of much research (Elkhateeb *et al.*, 2018). The fruit bodies of *A. auricula-judge* grow on wood and are frequently consumed and used as anti-inflammatory, anti-diabetic, anti-hypertensive, immunomodulatory, anti-cancer, and

anti-microbial drugs in many Asian countries (Figure 3). *A. auricula-judge* has been commercialized in industry and is an encouraging source for new chemical compounds such as oleic acid, polyketides, terpenoid classes and pyran derivatives with various biological functions (Elkhateeb, *et al.*, 2020; Thomas *et al.*, 2020). *Tremella* is a genus of fungi belonging to Division; Basidiomycota, Class; Tremellomycetes, Order; Tremellales, Family; Tremellaceae. Basidiocarps are gelatinous and described as jelly fungi (Figure 3). *Tremella* species grow mainly on wood rotting. Some species of *Tremella* parasitize the fruiting bodies of their hosts (fungal hosts) and are sometimes attached to the host's hyphae, and others to wood mycelium. *Tremella* species occur worldwide as a group. Currently, more than 100 species of *Tremella* are identified worldwide. *Tremella fuciformis* and *Tremella aurantia* are cultivated commercially for food and medicinal purposes (Abou Zaid *et al.*, 2017). Exopolysaccharides from *T. fuciformis* may be beneficial for the fight against type 1 diabetes mellitus. When the blood glucose level is higher than exo-polysaccharides from *T. fuciformis* the lowering effect is not fast and the function is not satisfactory (Bach *et al.*, 2015). Kiho *et al.* 2001 reported that, continuous oral administration of a solution of acidic polysaccharide (TAP) (0.5 g/l) and TAP-H solution (degradation products of TAP) (1.5 g/l) reduced plasma glucose levels in diabetes and that demonstrated by using KK-A^y mice (non-insulin-dependent diabetes - NIDDM) (Kim *et al.*, 2010). TAP-H and TAP safely reduced total cholesterol, insulin, and triglyceride levels in the mice's blood. While the cholesterol content of all groups was lower than the control, fecal excretion of TAP-H TAP resulted in a considerable rise in total bile acid. In addition, TAP-H and TAP significantly reduced the plasma lipo peroxide level. A study shows that TAP-H and TAP have an anti-diabetic effect in a diabetes model mouse (Kiho *et al.*, 2001).

Other mushrooms (*Morchella*, *Cordyceps*)

Ascomycetes inhabit a wide range of ecological niches, perform vital ecosystem roles, particularly in carbon cycling and serve as symbiotic partners with several tree species. Most ascomycetes are usually associated with plants as pathogens or decomposers. For their usage as a source of food and therapeutic bioactive substances, ascomycetes mushrooms are well-known like *Morchella*. *Morchella* is one of the most economically beneficial and edible wild mushrooms (Figure 4). It has several common names, such as gucci, morel, common morel, yellow morel, sponge

morel, morel mushroom, true morel, and so on. *Morchella* has nutritional and medicinal value due to its unique bioactive compounds, such as fibers, vitamins, polysaccharides, proteins, and trace elements (Abou Zaid *et al.*, 2017; Chowdhury and Paul, 2020). *Morchella conica* is an edible mushroom that exhibits anti-diabetic properties. It was discovered that the pancreatic and liver's PTP1B protein indicators change when the controlled hyperglycaemic index changes. Involved in lowering increased blood glucose levels associated with diabetes, *M. conica* is a potential source of treatment for diabetes mellitus, which is further studied with oral hypoglycaemic therapy (Begum *et al.*, 2021).

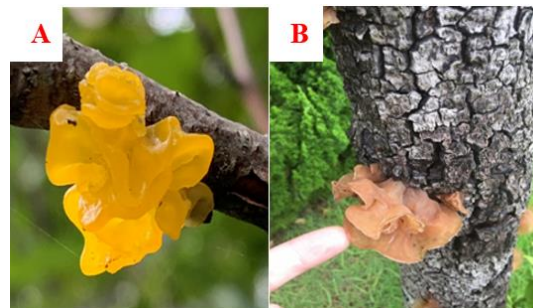


Figure 3. Medicinally important mushrooms. A. *Tremella mescentreca*; B. *A. auricula-judae* (Photographs were taken by Dr. S.C. Karunarathna and Dr. Waill Elkhateeb).

Elkhateeb *et al.* 2019 documented that, the polysaccharides of *Cordyceps sinensis* and *Cordyceps militaris* (insect pathogen mushrooms), represent the major existing compounds and exhibit anti-oxidant, anti-inflammatory, anti-microbial activities, anti-diabetic, and anti-cancer (Elkhateeb *et al.*, 2019). *Cordyceps sinensis* and *C. militaris* extracts are safe pharmacological agents with good anti-diabetic and anti-nephropathic properties and have significant potential as a new diabetes treatment method (Dong *et al.*, 2019). (Figure 4). By promoting glucose metabolism and significantly decreasing serum concentrations of triglycerides and total cholesterol, *C. militaris* extracts showed a significant decrease in blood glucose levels. Extracts of *C. militaris* exhibit anti-oxidative activity, as evidenced by normalized levels of glutathione peroxidase (GPx) and superoxide dismutase (SOD). The protective properties of *C. militaris* extracts against diabetic nephropathy were shown by their inhibitory effects on blood urea protein, uric acid, creatinine, and nitrogen (Zhang *et al.*, 2006; Paterson, 2008).



Figure 4. Medicinally important mushrooms. A. *Morchella*; B. *C. militaris* (Photographs were taken by Prof. T.C Wen).

Prospects of developing medicinal mushrooms for clinical trials in patients with diabetes

Currently, the enormous potential of mushrooms for treating diabetes has been studied. However, there are many unknowns and limitations in the application of fungal bioactive compounds in diabetic patients. Currently, most studies focus on polysaccharide-enriched fractions or crude mushroom extract. A relatively limited number of studies have also been conducted on several mushrooms used as medicines for type 2 diabetes patients. Therefore, further studies are needed to investigate the treatment of type 2 diabetes and the pure compounds and their therapeutic potential in diabetic patients by mushroom (Jovanović *et al.*, 2019).

Conclusion

Medicinal mushrooms represented by *Agaricus bisporus*, *Auricularia auricula-judge*, *Coprinus comatus*, *Cordyceps militaris*, *Cordyceps sinensis*, *Ganoderma applanatum*, *Ganoderma lucidum*, *Grifola frondosa*, *Inonotus obliquus*, *Laetiporus sulphureus*, *Lignosus rhinocerotis*, *Morchella conica*, *Phellinus baumii* and *Tremella fuciformis*. Since ancient times, have been touted as potential hypoglycaemic and anti-diabetic medicines and advised as a source of organic biologically active chemicals. Dietary fibers, proteins, Polysaccharides, and other bioactive compounds from separated edible mushrooms have been shown to lower blood sugar levels in both *vitro* and *vivo* models. Significant studies have been conducted to investigate the mechanisms of mushrooms' hypoglycaemic activities, and many triterpenes and polysaccharides have been extracted from them. However, it is important to identify and isolate

bioactive compounds with anti-diabetic potential from multiple mushroom species. Future investigations and research are required for bio prospect new medicinal and edible mushrooms for anti-diabetic efficacy and after that active biomolecules are isolated.

References

- Abou Zaid, O.A., Sonbaty, S.E., and Neama, M.A. (2017). Anti-diabetic activity of *Agaricus bisporus*: A biochemical and pathological study. *Int. J. Pharm. Sci.*, 7(2):1,740-1,745.
- Ajith, T.A. and Janardhanan, K.K. (2021). Antidiabetic properties of medicinal mushrooms with special reference to *Phellinus* species: A review. *The Natural Products Journal*, 11(2):120-126. DOI: 10.2174/2210315510666200124124540.
- Bach, E.E., Costa, S.G., Oliveira, H.A., Junior, J.S., da Silva, K.M., de Marco, R.M., and Wadt, N.S. (2015). Use of polysaccharide extracted from *Tremella fuciformis* berk for control diabetes induced in rats. *Emirates Journal of Food and Agriculture*, 27(7):585-591. DOI: <https://doi.org/10.9755/ejfa.2015>.
- Badalyan, S.M., Barkhudaryan, A., and Rapior, S. (2019). Recent progress in research on the pharmacological potential of mushrooms and prospects for their clinical application. In: *Medicinal Mushrooms*. Agrawal, D., and Dhanasekaran, M. (Eds). Springer, Singapore, 1-70. DOI: 10.1007/978-981-13-6382-5_1.
- Begum, N., Nasir, A., Parveen, Z., Muhammad, T., Ahmed, A., Farman, S., and Batiha, G.E. (2021). Evaluation of the hypoglycemic activity of *Morchella conica* by targeting protein tyrosine phosphatase 1B. *Front. Pharmacol.*, 12:1,148. DOI: 10.3389/fphar.2021.661803.
- Cao, H., Qin, D., Guo, H., Cui, X., Wang, S., Wu, Y., Zheng, W., Zhong, X., Wang, H., Yu, J., Zhang, H., and Han, C. (2020). The shaggy ink cap medicinal mushroom, *Coprinus comatus* (Agaricomycetes), a versatile functional species: A review. *International journal of medicinal mushrooms*, 22(3):245-255. DOI: 10.1615/IntJMedMushrooms.2020033988.
- Chen, H., Lu, X., Qu, Z., Wang, Z. and Zhang, L. (2010). Glycosidase inhibitory activity and antioxidant properties of a polysaccharide from the mushroom *Inonotus obliquus*. *Journal of Food Biochemistry*, 34:178-191. DOI: 10.1111/j.1745-4514.2009.00322.x
- Chowdhury, P., and Paul, S. (2020). The potential role of mushrooms in the prevention and treatment of diabetes: A review. *Journal of Biologically Active Products from Nature*, 10(5):429-454. DOI: 10.1080/22311866.2020.1831958.
- Daba, G., and Elkhateeb, W.A. (2020). The endless nutritional and pharmaceutical benefits of the Himalayan gold, *Cordyceps*; Current knowledge and prospective potentials. *Asian J. Nat, Prod, Biochem*, 18(2):1-8. DOI: 10.13057/biofar/180204.
- Daba, G.M., Elkhateeb, W., ELDien, A.N., Fadl, E., Elhagrasi, A., Fayad, W., and Wen, T.C. (2020). Therapeutic potentials of n-hexane extracts of the three medicinal mushrooms regarding their anti-colon cancer, antioxidant, and hypocholesterolaemia capabilities. *Biodiversitas*, 21(6):1-10. DOI: 10.13057/biodiv/d210615.
- De Silva, D.D., Rapior, S., Hyde, K.D., and Bahkali, A.H. (2012). Medicinal mushrooms in prevention and control of diabetes mellitus. *Fungal Diversity*, 56(1):1-29. DOI: 10.1007/s13225-012-0187-4.

- Ding, Z., Lu, Y., Lu, Z., Lv, F., Wang, Y., Bie, X., and Zhang, K. (2010). Hypoglycaemic effect of comatic, an antidiabetic substance separated from *Coprinus comatus* broth, on alloxan-induced-diabetic rats. *Food Chemistry*, 121(1):39-43. DOI: 10.1016/j.foodchem.2009.12.001.
- Dong, Y., Jing, T., Meng, Q., Liu, C., Hu, S., Ma, Y., and Teng, L. (2014). Studies on the antidiabetic activities of *Cordyceps militaris* extract in diet-streptozotocin-induced diabetic Sprague-Dawley rats. *Biomed. Res. Int.*, 1-10. DOI: 10.1155/2014/160980.
- Dotan, N., Wasser, S.P., and Mahajna, J. (2011). The culinary-medicinal mushroom *Coprinus comatus* as a natural antiandrogenic modulator. *Integr. Cancer Ther.*, 10(2):148-159. DOI: 10.1177/1534735410383169.
- Du, B. and Xu, B. (2014). An insight into anti-diabetic effects of mushrooms. In: *Mushrooms: Cultivation, antioxidant properties and health benefits*. Pesti, G. (Eds.). New York: Nova Science Publishers, 141-155.
- Ekowati, N., Yuniati, N., Hernayanti, H., and Ratnaningtyas, N. (2018). Antidiabetic potentials of button mushroom (*Agaricus bisporus*) on alloxan-induced diabetic rats. *Biosaintifika*, 10(3):655-662. DOI: 10.15294/biosaintifika.v10i3.17126.
- Elkhateeb, W., Thomas, P., Elnahas, M., and Daba, G. (2021a). Hypogeous and epigeous mushrooms in human health. In: *Advances in Macrofungi*. Sridhar, K.R., and Deshmukh, S.K. (Eds.). CRC Press, Boca Raton, 7-19. DOI: 10.1201/9781003191278-2.
- Elkhateeb, W.A. (2020). What medicinal mushroom can do. *Chem. Res. J.*, 5(1):106-118.
- Elkhateeb, W.A., and Daba, G.M. (2021a). Highlights on the golden mushroom *Cantharellus cibarius* and unique shaggy ink cap mushroom *Coprinus comatus* and smoky bracket mushroom *Bjerkandera adusta* ecology and biological activities. *J. Mycol. Mycological Sci.*, 4(2):1-8. DOI: 10.23880/oajmms-16000143.
- Elkhateeb, W.A., and Daba, G.M. (2021b). Mycotherapy of the good and the tasty medicinal mushrooms *Lentinus*, *Pleurotus*, and *Tremella*. *J. Pharmaceutics and Pharmacology Research*, 4(3):1-6. DOI: 10.31579/2693-7247/029.
- Elkhateeb, W.A., Daba, G.M., El-Dein, A.N., Sheir, D.H., Fayad, W., Shaheen, M.N., and Wen, T.C. (2020). Insights into the in-vitro hypocholesterolaemia, antioxidant, antitovavirus, and anticolon cancer activities of the methanolic extracts of a Japanese lichen, *Candelariella vitellina*, and a Japanese mushroom, *Ganoderma applanatum*. *Egypt. Pharm. J.*, 19(1):67. DOI: 10.4103/epj.epj_56_19.
- Elkhateeb, W.A., Daba, G.M., Thomas, P.W., and Wen, T.C. (2019). Medicinal mushrooms as a new source of natural therapeutic bioactive compounds. *Egypt. Pharm. J.*, 18(2):88-101. DOI: 10.4103/epj.epj_17_19.
- Elkhateeb, W.A., El Ghwas, D.E., Gundoju, N.R., Somasekhar, T., Akram, M., and Daba, G.M. (2021b). Chicken of the woods *Laetiporus Sulphureus* and *Schizophyllum commune* treasure of medicinal mushrooms. *J. Microbiol. Biotechnol.*, 6(3):1-7. DOI: 10.23880/oajmb-16000201.
- Elkhateeb, W.A., El-Hagrassi, A.M., Fayad, W., El-Manawaty, M.A., Zaghlol, G.M., Daba, G.M., and Ahmed, E.F. (2018). Cytotoxicity and hypoglycemic effect of the Japanese jelly mushroom *Auricularia auricula-judae*. *Chemistry Research Journal*, 3:123-133.
- Friedman, M. (2016). Mushroom polysaccharides: chemistry and antiobesity, antidiabetic, anticancer, and antibiotic properties in cells, rodents, and humans. *Foods*, 5(4):80. DOI: 10.3390/foods5040080.
- Hsu, C.H., Liao, Y.L., Lin, S.C., Hwang, K.C., and Chou, P. (2007). The mushroom *Agaricus Blazei* Murill in combination with metformin and gliclazide improves insulin resistance in type 2 diabetes: a randomized, double-blinded, and placebo-controlled clinical trial. *J. Altern. Complement Med.*, 13(1):97-102. DOI: 10.1089/acm.2006.6054.
- Huang, Q., Chen, L., Teng, H., Song, H., Wu, X., and Xu, M. (2015). Phenolic compounds ameliorate the glucose uptake in HepG2 cells' insulin resistance via activating AMPK. *J. Funct. Foods*, 19:487-494. DOI: 10.1016/j.jff.2015.09.020.
- Husen, F., Hernayanti, H., Ekowati, N., Sukmawati, D., and Ratnaningtyas, N.I. (2021). Antidiabetic effects and antioxidant properties of the saggy ink cap medicinal mushroom, *Coprinus comatus* (Agaricomycetes), in streptozotocin-induced hyperglycemic rats. *Int. J. Med. Mushrooms*, 23(10):9-21. DOI: 10.1615/IntJMedMushrooms.2021040020.
- Jang, J.S., Lee, J.S., Lee, J.H., Kwon, D.S., Lee, K.E., Lee, S.Y., and Hong E.K. (2010). Hispidin produced from *Phellinus linteus* protects pancreatic β -cells from damage by hydrogen peroxide. *Arch. Pharm. Res.*, 33:853-861. DOI: 10.1007/s12272-010-0607-5.
- Jeong, S., Jeong, Y., Yang, B., Islam, R., Koyyalamudi, S., Pang, G., and Song, C.H. (2010). White button mushroom (*Agaricus bisporus*) lowers blood glucose and cholesterol levels in diabetic and hypercholesterolemic rats. *Nutr. Res.*, 30(1):49-56. DOI: 10.1016/j.nutres.2009.12.003.
- Jovanović, J.A., Mihailović, M., Uskoković, A., Grdović, N., Dinić, S., and Vidaković, M. (2021). The effects of major mushroom bioactive compounds on mechanisms that control blood glucose level. *J. Fungi.*, 7(58):1-15. DOI: 10.3390/jof7010058.
- Jung, S.H., Lee, Y.S., Shim, S.H., and Lee, S. (2005). Inhibitory effects of *Ganoderma applanatum* on rat lens aldose reductase and sorbitol accumulation in streptozotocin-induced diabetic rat tissues. *Phytother. Res.*, 19:477-480. DOI: 10.1002/ptr.1638.
- Kiho, T., Kochi, M., Usui, S., Hirano, K., Aizawa, K., and Inakuma, T. (2001). Antidiabetic effect of an acidic polysaccharide (TAP) from *Tremella aurantia* and its degradation product (TAP-H). *Biol. Pharm. Bull.*, 24(12):1,400-1,403. DOI: 10.1248/bpb.24.1400.
- Kim, H.M., Kang, J.S., Kim, J.Y., Park, S.K., Kim, H.S., Lee, Y.J., and Han, S.B. (2010). Evaluation of antidiabetic activity of polysaccharide isolated from *Phellinus linteus* in non-obese diabetic mouse. *Int. Immunopharmacol.*, 10(1):72-78. DOI: 10.1016/j.intimp.2009.09.024.
- Kou, L., Du, M., Liu, P., Zhang, B., Zhang, Y., Yang, P., and Wang, X. (2019). Anti-diabetic and anti-nephritic activities of *Grifola frondosa* mycelium polysaccharides in diet-streptozotocin-induced diabetic rats via modulation on oxidative stress. *Appl. Biochem. Biotechnol.*, 187(1):310-322. DOI: 10.1007/s12010-018-2803-6.
- Kubo, K., Aoki, H., and Nanba, H. (1994). Anti-diabetic activity present in the fruit body of *Grifola frondosa* (Maitake). *I. Biol Pharm. Bull.*, 17(8):1,106-1,110. DOI: 10.1248/bpb.17.1106.
- Ma, H.T., Hsieh, J.F., and Chen, S.T. (2015). Anti-diabetic effects of *Ganoderma lucidum*. *Phytochemistry*, 114:109-113. DOI: 10.1016/j.phytochem.2015.02.017.

- Niwa, A., Tajiri, T., and Higashino, H. (2011). *Ipomoea batatas* and *Agaricus blazei* ameliorate diabetic disorders with therapeutic antioxidant potential in streptozotocin-induced diabetic rats. *J. Clin. Biochem. Nutr.*, 48:194-202. DOI: 10.3164/jcbn.10-78.
- Nowakowski, P., Naliwajko, S.K., Markiewicz-Żukowska, R., Borawska, M.H., and Socha, K. (2020). The two faces of *Coprinus comatus*-Functional properties and potential hazards. *Phytother. Res.*, 34(11):2,932-2,944. DOI: 10.1002/ptr.6741.
- Nyam, K.L., Chow, C.F., Tan, C.S., and Ng, S.T. (2017). Antidiabetic properties of the tiger's milk medicinal mushroom, *Lignosus rhinocerotis* (Agaricomycetes), in streptozotocin-induced diabetic rats. *Int. J. Med. Mushrooms*, 19(7):607-617. DOI: 10.1615/IntJMedMushrooms.2017021186.
- Patel, Y., Naraian, R., and Singh, V.K. (2012). Medicinal properties of *Pleurotus* species (oyster mushroom): A review. *World J. Fungal & Plant Biol.*, 3(1):1-12. DOI: 10.5829/idosi.wjfpb.2012.3.1.303.
- Paterson, R.R. (2008). *Cordyceps*-A traditional Chinese medicine and another fungal therapeutic bio factory? *Phytochemistry*, 69(7):1,469-1,495. DOI: 10.1016/j.phytochem.2008.01.027.
- Patocka, J. (2019). Will the sulphur polypore (*Laetiporus sulphureus*) become a new functional food? *Global Journal of Medical and Clinical Case Reports*, 6(1):6-9.
- Peng, H., and Shahidi, F. (2020). Bioactive compounds and bioactive properties of chaga (*Inonotus obliquus*) mushroom: A review. *Journal of Food Bioactives*, 12:9-75. DOI: org/10.31665/JFB.2020.12245.
- Perera, P.K. and Li, Y. (2011). Mushrooms as a functional food mediator in preventing and ameliorating diabetes. *J. Funct. Food Health Dis.*, 1(4):161-171. DOI: 10.31989/ffhd.v1i4.133
- Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D., and Bitto, A. (2017). Oxidative stress: harms and benefits for human health. *Oxid. Med. Cell Longev.*, 2017:8416763. DOI: 10.1155/2017/8416763.
- Rašeta, M., Popović, M., Čapo, I., Stilić, N., Vukmirović, S., Milošević, B., and Karaman, M. (2020). Antidiabetic effect of two different *Ganoderma* species tested in alloxan diabetic rats. *Rsc. Advances*, 10(17):10,382-10,393. DOI: 10.1039/c9ra10158f.
- Ratnaningtyas, N.I., Hernayanti, H., Ekowati, N., and Husen, F. (2022). Ethanol extract of the mushroom *Coprinus comatus* exhibits antidiabetic and antioxidant activities in streptozotocin-induced diabetic rats. *Pharm. Biol.*, 60(1):1,126-1,136. DOI: 10.1080/13880209.2022.2074054.
- Sękowski, K., Grudziąż-Sękowska, J., Pinkas, J., and Jankowski, M. (2022). Public knowledge and awareness of diabetes mellitus, its risk factors, complications, and prevention methods among adults in Poland-A 2022 nationwide cross-sectional survey. *Front. Public Health.*, 10:1029358. DOI: 10.3389/fpubh.2022.1029358.
- Sun, J. E., Ao, Z. H., Lu, Z.M., Xu, H.Y., Zhang, X.M., Dou, W.F., and Xu, Z.H. (2008). Antihyperglycemic and anti-lipid peroxidative effects of dry matter of culture broth of *Inonotus obliquus* in submerged culture on normal and alloxan-diabetes mice. *J. Ethnopharmacol.*, 118(1):7-13. DOI: 10.1016/j.jep.2008.02.030.
- Szychowski, K.A., Skóra, B., Pomianek, T., and Gmiński, J. (2021). *Inonotus obliquus* - from folk medicine to clinical use. *J. Tradit. Complement. Med.*, 11:293-302. DOI: 10.1016/j.jtcme.2020.08.003.
- Thomas, P.W., Elkhateeb, W.A., and Daba, G.M. (2020). Chaga (*Inonotus obliquus*): A medical marvel but a conservation dilemma. *Sydowia*, 72:123-130. DOI: 10.12905/0380.sydowia72-2020-0123.
- Wang, C., Chen, Z., Pan, Y., Gao, X., and Chen, H. (2017). Anti-diabetic effects of *Inonotus obliquus* polysaccharides-chromium (III) complex in type 2 diabetic mice and its sub-acute toxicity evaluation in normal mice. *Food Chem. Toxicol.*, 108:498-509. DOI: 10.1016/j.fct.2017.01.007.
- Wińska, K., Mączka, W., Gabryelska, K., and Grabarczyk, M. (2019). Mushrooms of the genus *Ganoderma* used to treat diabetes and insulin resistance. *Molecules*, 24(22):4,075. DOI: 10.3390/molecules24224075.
- Wu, S.J., Tung, Y.J., and Ng, L.T. (2020). Anti-diabetic effects of *Grifola frondosa* bioactive compound and its related molecular signalling pathways in palmitate-induced C2C12 cells. *J. Ethnopharmacol.*, 260:112962. DOI: 10.1016/j.jep.2020.112962.
- Wu, T., and Xu, B.B. (2015). Antidiabetic and antioxidant activities of eight medicinal mushroom species from China. *International Journal of Medicinal Mushrooms*, 17(2):1-10. DOI: 10.1615/IntJMedMushrooms.v17.i2.40.
- Xiao, C., Wu, Q.P., Cai, W., Tan, J.B., Yang, X.B., and Zhang, J.M. (2012). Hypoglycemic effects of *Ganoderma lucidum* polysaccharides in type 2 diabetic mice. *Arch. Pharm. Res.*, 35(10):1,793-801. DOI: 10.1007/s12272-012-1012-z.
- Yang, K., Zhang, S., Ying, Y., Li, Y., Cai, M., Guan, R., Sun, P. (2020). Cultivated fruit body of *Phellinus baumii*: A potentially sustainable antidiabetic resource. *ACS Omega*, 5(15):8596-8604. DOI: 10.1021/acsomega.9b04478.
- Zhang, G., Huang, Y., Bian, Y., Wong, J.H., Ng, T.B., and Wang, H. (2006). Hypoglycemic activity of the fungi *Cordyceps militaris*, *Cordyceps sinensis*, *Tricholoma mongolicum*, and *Omphalia lapidescens* in streptozotocin-induced diabetic rats. *Appl. Microbiol. Biotechnol.*, 72(6):1,152-1,156. DOI: 10.1007/s00253-006-0411-9.