Biological Properties, Health Benefits and Semisynthetic Derivatives of Edible *Astraeus* Mushrooms (*Diplocystidiaceae*): A Comprehensive Review

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Edible Astraeus mushrooms are known for their nutritional and culinary benefits and potential therapeutic properties. However, more investigation and discussion are still needed to understand their mechanisms of action regarding observed biological activities and thorough chemical analysis of bioactive compounds. This review provides a comprehensive summary and discussion of the bioactive properties and mode of action of Astraeus extracts and their isolated compounds. It covers their reported antioxidant, anti-inflammatory, antidiabetic, anticancer, anti-tuberculosis, antimalarial, antiviral and antileishmanial activities, as well as their potential benefits on metabolic and cardiovascular health and immune function. The review highlights the significance of the biological potential of isolated compounds, such as sugar alcohols, polysaccharides, steroids, and lanostane triterpenoids. Moreover, the review identifies under-researched areas, such as the chemical analysis of Astraeus species, which holds immense research potential. Ultimately, the review aims to inspire further research on the nutraceuticals or therapeutics of these mushrooms.

1. Introduction

Extensive literature unequivocally demonstrates the therapeutic benefits of non-poisonous mushrooms as functional food and medicine. Mushrooms are widely known for their nutritional and culinary value. They are as important as plant and animal-derived products for human health and nutrition.[1] They have been used worldwide as sources of food.[2] Edible mushrooms are low in calories and fat but high in proteins,[3] carbohydrates, vitamins, minerals, amino acids, and dietary fibre.[4]

Mushrooms have also been traditionally used as medicine in some countries and, therefore, have immeasurable potential to be used as a regular therapeutic food.[2] Indeed, mushrooms are rich in bioactive compounds with antiviral,[5] antibacterial,[6] antifungal,[7] antiparasitic, antioxidant, anti-inflammatory,[8] anticancer,[9] anti-HIV,[10] antidiabetic,[11] neuroprotective,[12] immunomodulatory,[13,14] and anticoagulant properties.[15,16] Medicinal mushrooms have been actively investigated using modern research methods for their potential to treat human diseases, such as cancers, diabetes, hyperglycaemia, hyperlipidaemia, cardiovascular disease, metabolic disorders and neurodegenerative disorders.[17,18] Since the start of the COVID-19 pandemic, there has been a surge in investigation into the therapeutic potential of bioactive compounds in mushrooms to treat SARS-CoV-2 Infection (pathogen for COVID-19).[19,20]

1.1. *Astraeus* Species

Despite being used for medicine and food in many parts of the world, there has been limited research on the biological activities and phytochemicals of Astraeus species.[21–24]

Astraeus species, especially *A. hygrometricus*, *A. odoratus* and *A. asiaticus*, are rare and difficult to access, which makes them highly sought after and expensive. They are wild and only available during a short harvest season, particularly during the rainy season. In addition, due to uncontrolled picking and habitat loss, many of these mushrooms are being overexploited, leading to a decline in their populations.[25] This is particularly true for *A. Asiaticus* and *A. odoratus*, which grow in areas with *Dipterocarp* trees. It is important to note that other *Astraeus* mushrooms also have ectomycorrhizal relationships with several host tree species, such as *Acacia*, *Alnus, Cedrus, Castanea, Eucalyptus Pinus*, *Pseudotsuga*, and *Quercus*. Currently, there are no methods for cultivating these mushrooms, which may explain why there have been limited studies on their bioactive compounds.[26]

1.2. Taxonomy

Initially, Astraeus species were misidentified as *Geastrum* earthstars due to their similar appearance. Despite the resemblance, however, they are not closely related.[27] The genus *Astraeus* is

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currently classified within the *Diplocystidiaceae* family under the order of *Boletales* (Table 1).[28]

Table 2 lists twelve species of *Astareus* as documented in the literature. These species include *A. asiaticus*, *A. hygrometricus* (Pers.), *A. koreanus*, *A. morganii*, *A. odoratus*, *A. pteridis* (Shear), *A. sirindhorniae*, *A. smithii*, *A. telleriae*, and *A. thailandicus* Petchart.[23,27,29–32]

Table 1. Taxonomy of *Astraeus* species.

Domain	*Eukaryota*
Kingdom	*Fungi*
Division	*Basidiomycota*
Class	*Agaricomycetes*
Order	*Boletales*
Family	*Diplocystidiaceae*
Genus	*Astraeus*

1.3. Historical Overview of Discovery and Identification of *Astraeus* Species

Early studies by Zeller et al. (1948)[33] and Kirk et al. (2001)[34] suggested that the genus Astraeus comprised only two species: *A. hygrometricus* and *A. pteridis*. Initially, *A. hygrometricus* was thought to be a single species. However, a study by Fangfuk et al. (2010)[35] revealed that a Japanese species, previously classified as *A. hygrometricus* var. *koreanus*, was genetically distinct from *A. hygrometricus*. A later study by Phosri et al. (2013) confirmed that *A. hygrometricus*, as previously defined, is not a single species but consists of several distinct species. *A. hygrometricus*, or the hygroscopic earthstar, begins to resemble a puffball when young. However, as it matures, the outer layer of its fruit body tissue splits open in a star-like pattern, giving it the shape of an earthstar. This ectomycorrhizal species commonly grows alongside various trees (Table 2), especially in sandy soils. The genus is widespread in temperate and tropical regions worldwide,[27] including Africa, Asia, Australia, Europe, North America,[29] and South America.[23]

Other species, detailed in Table 2, have been identified using both morphological characteristics and molecular techniques (Phosri et al. 2004, 2007; Fangfuk et al. 2010). One notable example is the discovery of *Astraeus odoratus*, a distinct mushroom species, by Phosri in 2004.[30] This discovery marked a significant addition to mycology. Initially found in the Thai highlands, this rare species thrives in sandy or laterite-rich soil in dry lowland dipterocarp forests. Its presence was reported in various Southeast Asian countries by Phosri in 2007,[27] and recent findings have also identified it in the forests of Jharkhand, India.[32]

Astraeus asiaticus was identified as a distinct species from *A. hygrometricus* by Phosri et al. (2007)[27] It is mainly found in Asia, particularly in the northern and northeastern regions of Thailand, during the rainy season from May to August. Fresh basidiomes of *A. asiaticus* are often sold in domestic markets, along with *A. odoratus*. This species has also been found in Laos, Sri Lanka, and India, suggesting a wide geographical distribution.[27,36,37]

Astraeus pteridis (Shear) Zeller has been a source of confusion in the past; however, a molecular phylogenetic study conducted in 2013 by Phosri et al.[23] clarified that *A. pteridis* refers to the larger species of *Astraeus* found in the Pacific Northwest region of North America. *A. pteridis* has also been discovered in the Canary Islands, Madeira, and Argentina and may be widely distributed or have been translocated. *A. pteridis* forms ectomycorrhizal associations with several tree species, including *Pinus*, *Pseudotsuga*, *Alnus*, *Eucalyptus*, and *Castanea*.[27,38,39]

1.4. Morphology of *Astraeus*

Mushrooms of the *Astraeus* genus have an intricate peridium that is divided into three anatomical layers: exoperidium, endoperidium, and mesoperidium. The exoperidium opens up in the shape of a star, revealing a round spore sac. It is susceptible to moisture and will close to protect the spore sac when it is hot and dry, giving it the name of false or barometer earthstar.[27] The endoperidium encloses the fertile gleba mass in most species, while the mesoperidium connects to the inner exoperidium and outer endoperidium. The fertile gleba releases spores through a bellow mechanism.[24,37,45,46] Astraeus mush-

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Table 2. List of *Astraeus* species.

Species Name	Habitat	Distribution	Ref
A. asiaticus Phosri M.P. Martín & Watling	Found on sandy or lateritic soil in dry dipterocarp forests.	Thailand, India, Sri Lanka	[27,37]
A. hygrometricus (Pers.) Morgan	Found on sandy or lateritic soil in dry lowland forests associated with *Dipterocarp*, *Quercus baloot*, *Cedrus deodara*	Thailand, India, Afghanistan, North America, Mediterranean	[24,27,30,31,40,41]
A. hygrometricus var. koreanus	Found in dry to humid areas associated with pine trees	Japan	[35]
A. macedonicus Rusevska Karadelev Tellería & M.P. Martín, *sp. nov.*	Found on soil in deciduous forests.	Macedonia	[42]
A. morganii Phosri M.P. Martín & Watling	Found in sandy soil in fields and woods.	Colorado, USA	[23]
A. odoratus Phosri Watling M.P. Martín & Whalley	Found on sandy or lateritic soil in dry lowland dipterocarp forests.	Thailand, India	[24,30,31]
A. pteridis (Shear) Zeller	Found among conifer and eucalyptus trees on the forest floor, growing individually or in groups.	Portugal, Spain, USA, Mexico, New Zealand, Australia	[23,27,33,38]
A. ryoocheoninii Ryoo (A. koreana)	Found on sandy soil associated with *Pinus densiflora.*	South Korea and Japan	[43]
A. sirindhorniae Watling Phosri Sihan. A.W. Wilson & M.P.	Found partially buried in ultisols soil in dry deciduous forests associated with *Dipterocarpus tuberculatus* Roxb., *Shorea obtusa* Wall. and *Shorea siamensis* Miq.	North and Northeastern Thailand	[31,44]
A. smithii Watling M.P. Martín & Phosri	Found on soil surfaces, in the margins of woodland or open areas.	Michigan, USA	[23]
A. telleriae M.P. Martín Phosri & Watling	Found on soil, in open areas and margins of woodland of *Pinus* and *Quercus* trees.	Greece	[23]
A. thailandicus Petcharat	Found on the ground in a dry dipterocarp forest beneath the shade.	Thailand	[29]

rooms grow on the ground in a mutually beneficial relationship with trees and shrubs, known as ectomycorrhizal associations.

1.5. Nutritional Benefits of *Astraeus* Mushrooms

Astraeus mushrooms are known for their high nutritional value,[47] primarily due to their high protein and fibre content and low-fat content found in the basidiocarps of mushrooms.[21] Studies have been conducted to investigate the nutritional potential of three species of Astraeus mushrooms, namely *A. hygrometricus*, *A. asiaticus* and *A. odoratus*.[48–51] However, there is no reported data describing the nutritional properties of other *Astraeus* mushrooms. The research reveals that these mushrooms have high moisture content, with *A. hygrometricus*, *A. odoratus* and *A. asiaticus* mushrooms having 83.87%, 84.2%, and 82.4% moisture content, respectively.[50–52] This high moisture content significantly affected the levels of carbohydrates, soluble ions, proteins, fatty acids, and fibres. The incinerated residue ash content of the mushroom is directly proportional to its mineral content, as suggested by Sanmee et al. (2003).[48] The reported ash contents of *A. hygrometricus*, *A. odoratus*, and *A. asiaticus* were found to vary widely depending on the mushroom's part, maturity, and preparation. For example, the ash content of the young and major fruiting bodies of *A. hygrometricus* was 27.6% and 14.2%, respectively.[48] Interestingly, the ash content of uncooked (18.43%) and cooked *A. hygrometricus* fruiting bodies (15.52%) was very similar.[22] Meanwhile, the ash content of *A. odoratus* was found to be 0.98% and 18.43% based on the fresh and dry weight of their fruiting bodies, respectively.[51] Additionally, the ash content of the fruiting body of *A. asiaticus* (2.83%) was much lower than that of *A. hygrometricus* and *A. odoratus*.[52]

Digestible carbohydrates are those that can be easily digested. These include monosaccharides, disaccharides, and sugar alcohols such as arabitol, mannitol, and trehalose.[53] Non-digestible carbohydrates, especially polysaccharides, have prebiotic properties that benefit gut health and other health benefits, which will be discussed later. *Astraeus* mushrooms, including *A. hygrometricus* (35.4–64.3%), *A. asiaticus* (65.7%), and *A. odoratus* (20.6%), have high levels of both digestible and non-digestible carbohydrates.[22,47,48,51,52] Polysaccharides are vital components of mushroom cell walls, and they can be classified into two main groups: rigid fibrillars of chitin and abundant glucans, which include β-glucans with variable proportions of β-1,3 and β-1,6 linkages, as well as α-1,3-glucans.[54]

Recent findings have revealed that the fruiting body of *A. odoratus* contains a higher amount of crude protein (26.3%) than that of *A. hygrometricus* (14.7–16.8%) and *A. asiaticus* (17.8%). These three species of *Astraeus* contain to some extent equivalent amounts of protein as edible legumes (16.8–17.3%), which is higher than another edible mushroom Jelly Ear fungus (*Auricularia auricula-judae* (Bull.) Wettst., (10–16%).[55] *A. odoratus* fruiting body has higher fibre (35.4%) than that of *A. hygrometricus* (10.8–14.58%) and *A. asiaticus* (11.49%). These contents are lower than that of *Auricularia auricula-judae* (51–56%).[56] These mushrooms contain high fibre content, which benefits digestion, bowel health, and cardiovascular health.[57]

1.6. Aims

Among the different species of *Astraeus*, *A. hygrometricus* has been investigated the most for its biological properties of crude extracts and some isolated compounds. However, more investigations and discussions are still needed regarding the biological activities, phytochemical analysis, and mechanisms of action of extracts and active compounds from *Astraeus* species, including *A. hygrometricus*. This review aims to objectively cover the following topics to comprehensively explore the therapeutic potential of these edible mushrooms: (i) the biological activities of crude extracts and isolated compounds, (ii) identified compounds and (iii) the mechanism of actions of extracts and isolated compounds from various *Astraeus* species.

2. Chemistry of *Astraeus* Mushrooms

Only four species of *Astraeus* have been studied for their phytochemicals: *A. hygrometricus, A. odoratus, A. asiaticus, and A. pteridis*. Different compounds belonging to polysaccharide, terpenoid, and steroid families have been identified and isolated. The review attempts to provide a comprehensive list of the phytochemicals found in each of these *Astraeus* species.

2.1. Compounds Isolated from *A. hygrometricus*

Compounds that have been isolated from *A. hygrometricus* are listed in Figure 1. In early studies, Takaishi et al. (1987)[58] identified three lanostane-type triterpenes and two steroids: astrahygrone (**1**), astrahygrol (**2**), 3-epi-astrahygrol (**3**), ergosta-7,22-diene-3-ol (**6**) and ergosta-4,6,8-(14),22-tetraene-3-one (**8**) from the methanolic extract of *A. hygrometricus*. Hong-jun et al. (2007) reported the isolation of steryl ester (**7**) with an ergostane-type nucleus along with ergosterol (**9**) and ergosterol peroxide (**10**).[59]

Later work by Lai et al. (2012)[60] isolated another two lanostane-type triterpenes, astrakurkurone (**4**) and astrakurkurol (**5**). Furthermore, bioactive compounds such as β-carotene, lycopene and phytic acid (Supplementary Table S1) were identified by Pavithra et al. (2016).[36] The two research groups isolated and structurally determined polysaccharides from *A. hygrometricus*. Pramanik et al. (2000)[61] isolated a polysaccharide from a hot water extract of *A. hygrometricus*, which was structurally elucidated as →6)-β-*D*-galactopyranosyl-(1→6)-β-*D*-galactopyranosyl-[(2→1)-β-*D*-galacturonic acid]-(1→3)-α-*D*-glucopyranosyl-(1→ units (**11**). Chakraborty et al. 2004 conducted a structural analysis of a polysaccharide fraction (AQS–I) extracted from the hot aqueous extract of *A. hygrometricus*, and the structure was determined to be repeating units of (1→4)-α-*D*-glucopyranosyl-(I→6)-β-*D*-glucopyranosyl-(I→6) (**12**).[62] The second polysaccharide fraction (ASQ-II) was also isolated from

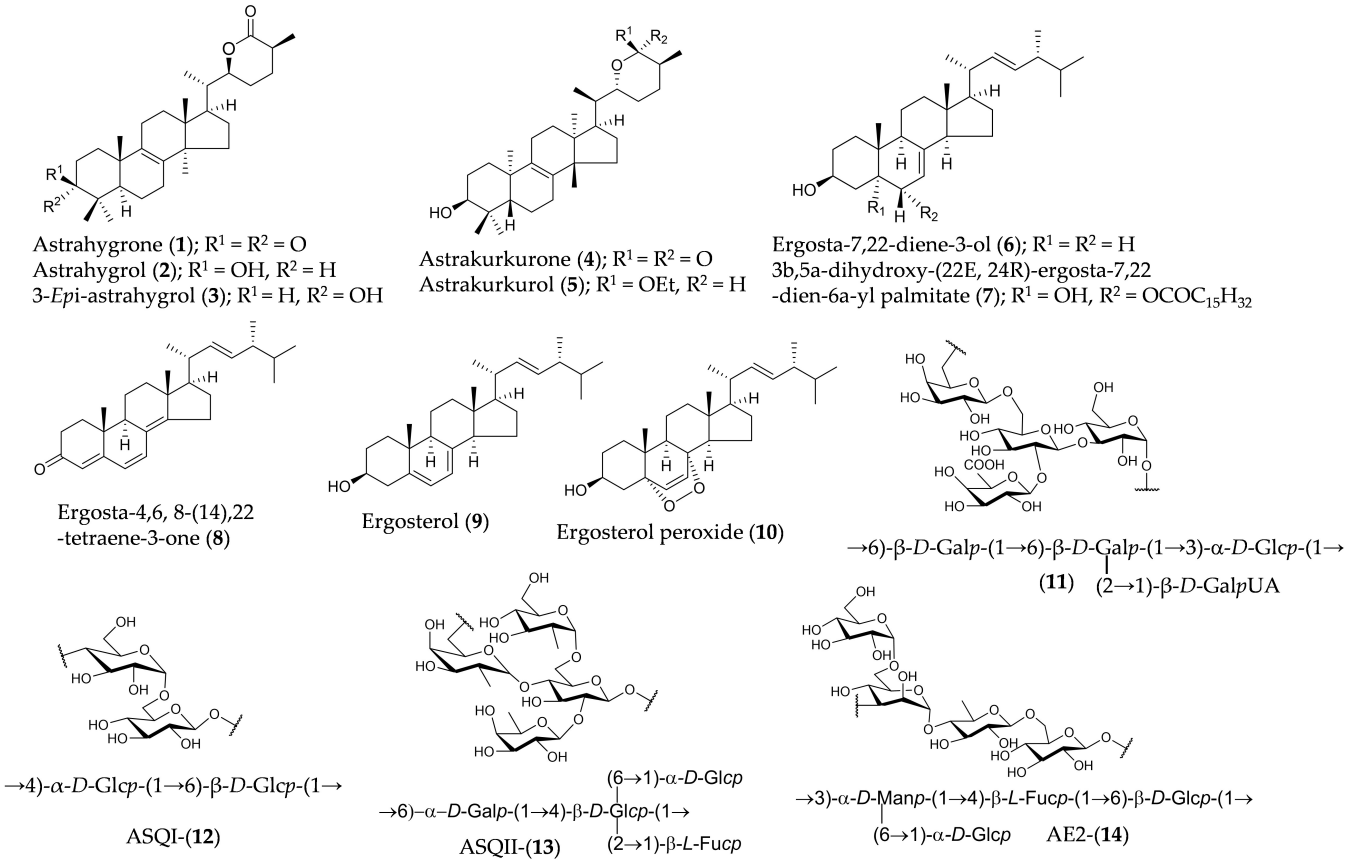


Figure 1. Compounds isolated from *A. hygrometricus*.[58–64]

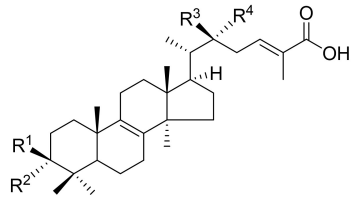
the same hot aqueous extract. The nuclear magnetic resonance (NMR) analysis identified ASQ-II as a heteroglycan with repeat units of α-(l→6)-*D*-galactopyranose, α-*D*-glucopyranosyl, β-*L*-fucose, and (l→2,4,6)-*D*-glucopyranose (**13**).[63] Additionally, the same group isolated another water-soluble polysaccharide (AE2) from an alkaline extract of *A. hygrometricus*. The polysaccharide (AE2) was determined to be repeating units of (1→3)-α-*D*-mannosyl, terminal α-*D*-glucosyl, (1→4)-linked β-*L*-fucosyl, and (1→6) linked β-*D*-glucosyl (**14**).[64]

Studies conducted to determine the nutritional composition of *A. hygrometricus* have revealed the presence of various substances such as sugars, sugar alcohols, organic acids, fatty acids, and amino acids. These findings are listed in Supplementary Table S1.[48,65–68] The sweet and meaty taste of *A. hygrometricus* is attributed to sugars, amino acids, and umami 5′-guanosine.[68]

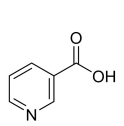
2.2. Phytochemicals Isolated from *A. odoratus*

Figure 2 lists phytochemicals isolated from *A. odoratus*. In the early work by Arpha et al. (2012),[69] astraodoric acids A–D (**15**–**18**) were isolated along with ergosterol (**9**) (Figure 1), artabotryol A (**36**) (also known as astraodorol), nicotinic acid (**21**), hypaphorine (**22**) and 5-hydroxyhypaphorine (**23**) from the extracts of *A. odoratus*. Isaka et al. (2016) analysed methanolic and hexane extracts of *A. odoratus*, which resulted in the isolation of 18 triterpenoids. These compounds include 12 newly discovered astraeusins A–L (**24**–**35**) and six known compounds, namely: astraodoric acids A (**15**), B (**16**), and D (**18**); artabotryols A (**36**) and B (**37**); and lanosterol (**38**).[70]

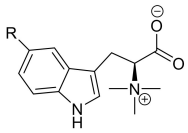
In 2017, Srisurichan et al.[71] were able to isolate three new compounds: astraodoric acid E (**19**), astraodoric acid F (**20**) and spiro-astraodoric acid (**39**). They also identified six known compounds: astraodoric acids A–D (**15**–**18**), hypaphorine (**22**)



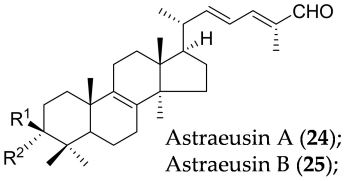
Astraodoric acid A (**15**); $R^1 = R^2 = O$, $R^3 = OAc$, $R^4 = H$
Astraodoric acid B (**16**); $R^1 = R^2 = O$, $R^3 = OH$, $R^4 = H$
Astraodoric acid C (**17**); $R^1 = H$, $R^2 = OH$, $R^3 = H$, $R^4 = OH$
Astraodoric acid D (**18**); $R^1 = H$, $R^2 = OH$, $R^3 = OAc$, $R^4 = H$
Astraodoric acid E (**19**); $R^1 = H$, $R^2 = OH$, $R^3 = OH$, $R^4 = H$
Astraodoric acid F (**20**); $R^1 = OH$, $R^2 = H$, $R^3 = OAc$, $R^4 = H$



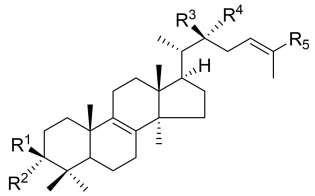
Nicotinic acid (**21**)



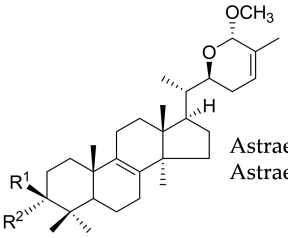
(+)-Hypaphorine (**22**); R = H
5-Hydroxyhypaphorine (**23**); R = OH



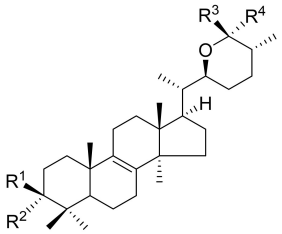
Astraeusin A (**24**); $R^1 = R^2 = O$
Astraeusin B (**25**); $R^1 = OH$, $R^2 = H$
Astraeusin C (**26**); $R^1 = H$, $R^2 = OH$



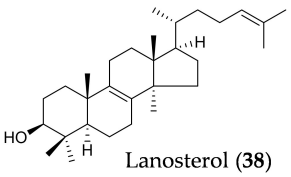
Astraeusin D (**27**); $R^1 = R^2 = O$, $R^3 = OH$, $R^4 = H$, $R^5 = CH_2OH$
Astraeusin E (**28**); $R^1 = OH$, $R^2 = H$, $R^3 = OH$, $R^4 = H$, $R^5 = CH_2OH$
Astraeusin F (**29**); $R^1 = H$, $R^2 = OH$, $R^3 = OH$, $R^4 = H$, $R^5 = CH_2OH$
Astraeusin G (**30**); $R^1 = OH$, $R^2 = H$, $R^3 = OAc$, $R^4 = H$, $R^5 = COOH$
Astraeusin H (**31**); $R^1 = H$, $R^2 = OAc$, $R^3 = OH$, $R^4 = H$, $R^5 = COOH$



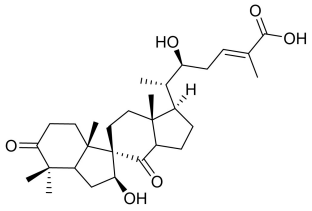
Astraeusin I (**32**); $R^1 = R^2 = O$
Astraeusin J (**33**); $R^1 = H$, $R^2 = OH$



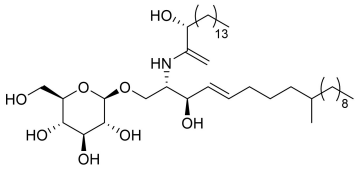
Astraeusin K (**34**); $R^1 = R^2 = O$, $R^3 = OH$, $R^4 = H$, or $R^3 = H$, $R^4 = OH$
Astraeusin L (**35**); $R^1 = H$, $R^2 = OH$, $R^3 = OH$, $R^4 = H$, or $R^3 = H$, $R^4 = OH$
Astraodorol (**36**) or Artabotryol A (**36**); $R^1 = H$, $R^2 = OH$, $R^3 = R^4 = O$
Artobotryol B (**37**); $R^2 = H$, $R^2 = OH$, $R^3 = OH$ (racemate), R4 = H (racemate)



Lanosterol (**38**)



Spiro-astraodoric acid (**39**)



Glucosylceramide (**40**)

Figure 2. Compounds isolated from *A. odoratus*.[69–71]

and glucosylceramide (**40**). Analysis of *A. odoratus*' proximate compositions revealed the presence of β-glucans and sugar alcohols like mannitol and inositol.[47,72]

2.3. Phytochemical Isolated from *A. asiaticus*

Figure 3 provides a list of various compounds that have been extracted from *A. asiaticus*. In 2015, Pinjuk et al.[73] discovered two new lanostane triterpenoids named astrasiaone (**41**) and astrasiate (**46**) from the extracts of *A. asiaticus* collected in Thailand. They also identified six known compounds, namely ergosterol (**9**), hypaphorine (**22**), artabotryol A–B (**36**–**37**) (Figures 1 and 2), artabotryol C1 (**42**) and 6-dehydrocerevisterol (**47**) (Figure 3). Isaka et al. 2017[74] later isolated 24 lanostane triterpenoids from *A. asiaticus*. Among these, seven were novel lanostane triterpenoids, namely 26-epi-astrasiaone (**43**), 26-epi-artabotryol C1 (**44**), astraeusin Q (**45**) and astraeusins M–P (**48**–**51**), and while the remaining seventeen were previously known compounds. These are astraodoric acids A–D (**15**–**18**), astraeusins A–C (**24**–**26**), astraeusin H (**31**), astraeusin K (**34**), artabotryol A–B (**36**–**37**), lanosterol (**38**), astrasiaone (**41**), artabotryol C1 (**42**), astrasiate (**47**), epi-inotodiol (**52**) and artabotryol D (**53**), which can be found in Figure 2 and 3, respectively.

Pandey et al. (2022)[46] analysed the proximate compositions of *A. asiaticus* and revealed the presence of phenolics, flavonoids, and ascorbic acid. These compounds contribute to the antioxidant properties of the mushroom. Currently, no research is available on the presence of polysaccharides in *A. asiaticus*.

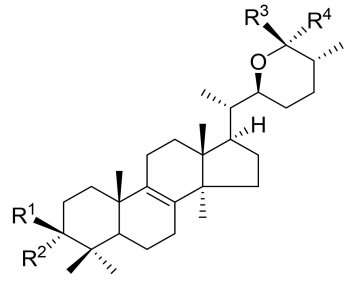
2.4. Phytochemical Isolated from *A. pteridis*

Stanikunaite et al. (2008)[75] is the only group that has conducted a chemical investigation of *A. pteridis* collected in Oregon, North America. This investigation has led to the isolation and identification of three novel triterpenoids: astrapteridone (**54**), astrapteridiol (**55**) and 3-epi-astrapteridiol (**56**), as shown in Figure 4. Additionally, known compounds previously isolated from other Asatraeus mushrooms were also found, namely astrahygrone (**1**), 3-epi-astrahygrol (**3**), hypaphorine (**22**) and lanosterol (**38**), as shown in Figures 1 and 2. Aside from the efforts of Stanikunaite et al. (2008),[75] the phytochemical analysis of *A. pteridis* remains underinvestigated.

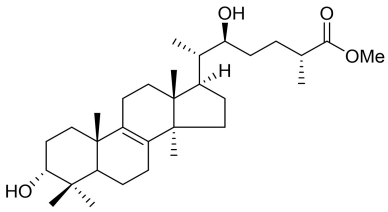
3. Biological Properties of *Astraeus*

3.1. Astraeus Hygrometricus

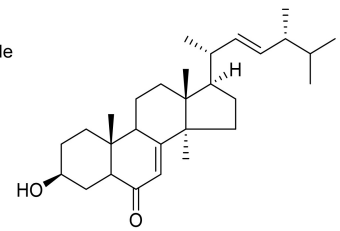
The crude extracts of *A. hygrometricus* are the most studied compared to those of *A. odoratus*, *A. asiaticus*, and *A. pteridis*. *A. hygrometricus* crude extracts are known to contain bioactive compounds, including heteroglycans, glucans, triterpenoids, polyphenols, fatty acids and other chemical substances.[21,76]



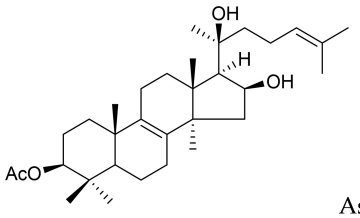
Astrasiaone (**41**); $R^1 = R^2 = O$, $R^3 = H$, $R^4 = OCH_3$
Artabotryol C1 (**42**); $R^1 = H$, $R^2 = OH$, $R^3 = H$, $R^4 = OCH_3$
26-epi-astrasiaone (**43**); $R^1 = R^2 = O$, $R^3 = OCH_3$, $R^4 = H$
26-epi-artabotryol C1 (**44**); $R^1 = H$, $R^2 = OH$, $R^3 = OCH_3$, $R^4 = H$
Astraeusin Q (**45**); $R^1 = H$, $R^2 = OAc$, $R^3 = R^4 = O$



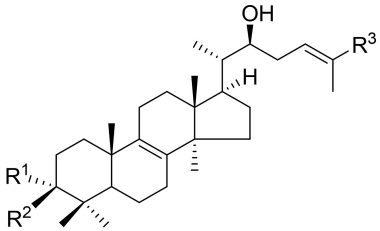
Astrasiate (**46**)



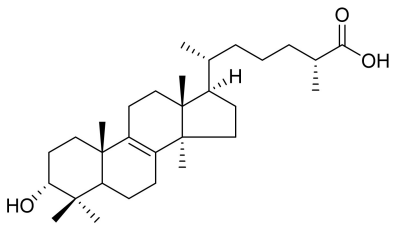
6-Dehydrocerevisterol (**47**)



Astraeusin M (**48**)

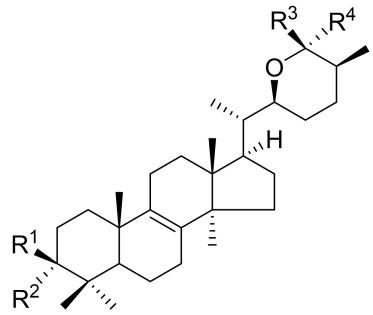


Astraeusin N (**49**); $R^1 = OH$, $R^2 = H$, $R^3 = Me$
Astraeusin O (**50**); $R^1 = OH$, $R^2 = H$, $R^3 = COOH$
Astraeusin P (**51**); $R^1 = OH$, $R^2 = H$, $R^3 = CHO$
Epi-inotodiol (**52**); $R^1 = H$, $R^2 = OH$, $R^3 = Me$



Artabotryol D (**53**)

Figure 3. Compounds isolated from *A. asiaticus*.[73,74]



Astrapteridone (**54**); $R^1 = R^2 = O$, $R^3 = H$, $R^4 = OH$
Astrapteridiol (**55**); $R^1 = OH$, $R^2 = H$, $R^3 = H$, $R^4 = OH$
3-epi-astrapteridol (**56**); $R^1 = H$, $R^2 = OH$, $R^3 = H$, $R^4 = OH$

Figure 4. Compounds isolated from *A. pteridis*.[75]

Several recent studies have been conducted on the biological activities of *A. hygrometricus* extracts, which are summarised in Tables 3 and 4. The discussed studies demonstrate that the extracts offer a variety of health benefits. Figure 5 outlines the potential mechanisms of bioactive compounds from *Astraeus* species that contribute to these benefits, which are further elaborated in the following sections.

3.1.1. Antioxidant Properties

A study by Biswa et al. (2010)[77] found that the ethanolic extract of *A. hygrometricus* showed significant *in vitro* scavenging activities against superoxide anion and hydroxyl radical with *half-maximal inhibitory concentration* (IC_{50}) values of 357.95 and 81.2 μg/mL, respectively. Ascorbic acid (IC_{50} = 65 μg/mL) was used as the positive control for the superoxide radical scavenging activity assay, while catechin (IC_{50} = 840 μg/ml) was used as the positive control for the hydroxyl radical scavenging activity assay. The extract also inhibited the lipid peroxidation with an IC_{50} of 87.96 μg/ml, compared to the control, catechin (IC_{50} = 455 μg/ml). Mandal et al. (2015)[78] conducted a study to examine the antioxidant properties of the aqueous extract of *A. hygrometricus*. Using ascorbic acid as a standard (with the same concentration used for the sample), they investigated the effect of this extract on scavenging 2,2-Diphenyl-1-picrylhydrazyl (DPPH), superoxide, and hydrogen peroxide radicals. The results showed that the IC_{50} values of *A. hygrometricus* on DPPH, superoxide and hydrogen peroxide radical scavenging were 200 μg/mL, 250 μg/mL, and 200 μg/mL, respectively. The IC_{50} values of the ascorbic acid standard for DPPH, superoxide, and hydrogen peroxide radical scavenging were approximately 75 μg/mL, 175 μg/mL, and 250 μg/mL, respectively. The researchers suggested that the high antioxidant activity of the aqueous extract of this mushroom could be attributed to its potent anti-inflammatory activity.

Badshah et al. 2015[79] reported that the methanolic crude extract of *A. hygrometricus* showed a high phenolic content and antioxidant activity. They found that the extract had an IC_{50} value of 9.3 μg/ml for DPPH radical scavenging activity compared to the ascorbic acid standard with IC_{50} = 7.5 μg/mL. In addition, The researchers conducted a toxicity test on the extract using the brine shrimp lethality test. They found that

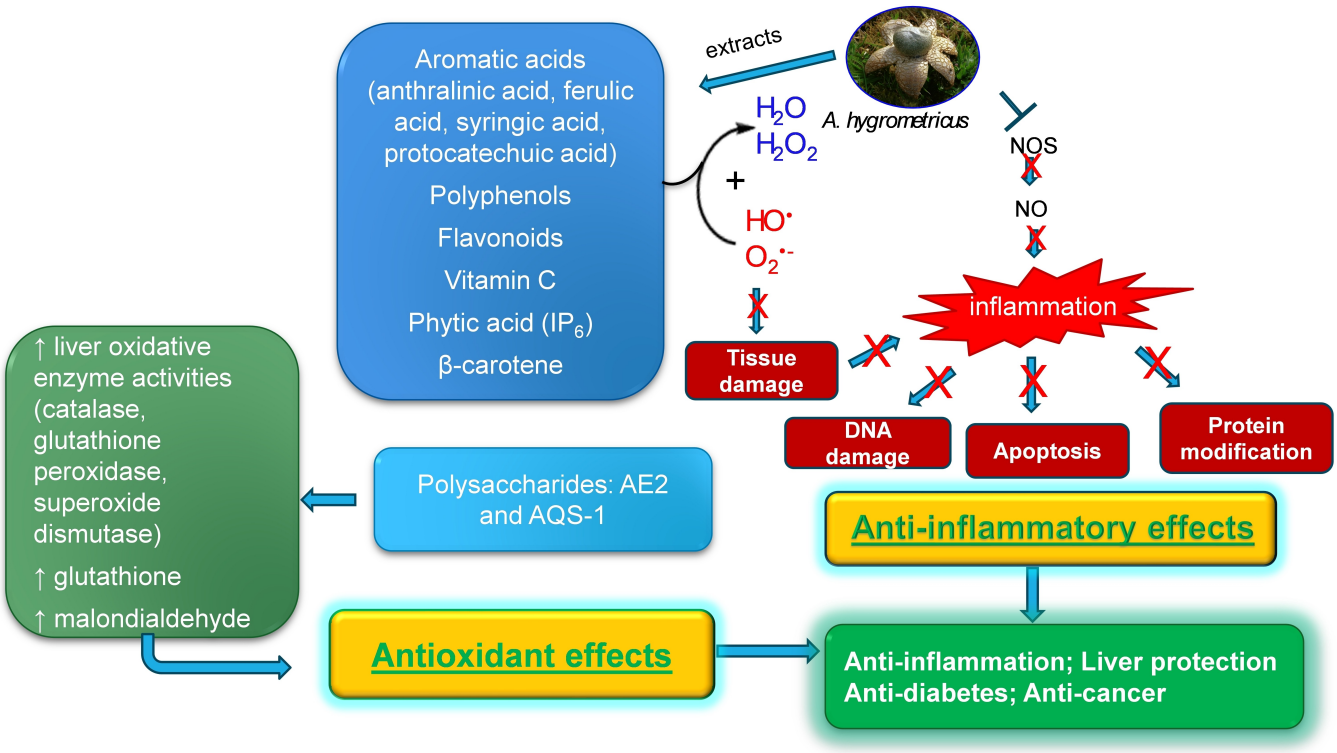


Figure 5. An overall summary of possible mechanisms of bioactive compounds from *Astraeus* species related to antioxidation and anti-inflammation effects.

Table 3. Antioxidant, anti-inflammatory, hepatoprotective, cardioprotective and immunomodulatory activities of *A. hygrometricus* extracts and compounds.

Bioactivity	Crude extract or Bioactive compound [a]	Experimental model	Finding/Active dose	Ref.
Antioxidant	Ethanolic extract	*In vitro* superoxide anion ($O2^{\bullet}-$), hydroxyl radical ($HO\cdot$) scavenging and lipid peroxidation inhibition assays	Scavenging activities against $O2^{\bullet}-$, $HO^{\bullet}$, and lipid peroxidation; IC50 values are 357.95, 81.2, and 87.96 μg/mL, respectively.	[86]
Antioxidant	Aqueous extract	*In vitro* DPPH, $O2^{\bullet}-$ and $HO^{\bullet}$ scavenging assays	Scavenging activities against DPPH, $O2^{\bullet}-$, and $HO^{\bullet}$; IC_{50} values are 200, 250, and 200 μg/ml, respectively.	[78]
Antioxidant	Methanolic extract	*In vitro* DPPH scavenging assay	Scavenging activity against DPPH; $IC_{50} = 9.3$ μg/mL	[79]
Anti-inflammatory	Ethanolic extract	*In vivo animal models:* carrageenan, dextran, or formalin-induced paw edema in three mice models	Extract reduced paw edema in three different models: (i) 69% and 68% reductions in the carrageenan-induced mode, (ii) 40% and 38% in the dextran-induced model after 3 and 5 hours of treatment with 125 mg/kg BW of extract, (iii) 50% and 56% reduction after 5 and 6 days of treatment with 125 mg/kg BW of extract.	[86]
Anti-inflammatory	Aqueous extract	*In vivo animal model:* carrageenan, induced paw edema mice model	Extract reduced paw edema by 49.91 % after 4 h of treatment with 600 mg/kg BW of extract	[78]
Hepatoprotective	Ethanolic extract	*In vivo* animal model of carbon tetrachloride (CCl_4) induced chronic hepatotoxicity	The extract reduced hepatoxic serum markers GPT, GOT, bilirubin, and ALP by 56.72%, 54.82%, 35%, and 30.88%, respectively, back to normal levels; histopathological examination showed normal liver tissue in animals treated with 150 mg/kg BW.	[88]
Cardioprotective	Ethanolic extract	*In vitro* platelet aggregation assay	The extract inhibited platelet aggregation by app. 70% at 10 mg/mL.	[94]
Antidiabetic: increased glucose uptake	Ethanolic extract	*In vivo* alloxan-induced diabetic mice	The extract decreased blood glucose levels by 36% and 49% in acute (24 h) and subacute (28 days) alloxan-induced diabetic mice treated with 500 mg/kg BW of extract, respectively.	[100]
Immunomodulatory: activation of splenocytes	Glucan fraction AQS–I (**12**)	*In vitro cell-based* (MTT) assay using spleen cells	Extract increased spleen cell viability by 33% compared to the vehicle control when treated with AQS–I (12) at 1 ng/mL.	[62]
Immunomodulatory: elevation of NO production, cytokines and improving phagocytic activity	Polysaccharide fraction AE2 (**14**)	*In vivo* animal model: Macrophages isolated from mice 24 h after treatments	At 10 and 20 mg/kg BW, the extract increased (i) NO concentrations (32 μM and 27 μM), respectively, compared to the control group (NO concentration 10.5 μM). (ii) levels of interleukin-1 (IL-1) at 1.6 and 1.4 TPI (thymocyte proliferation index), compared to the control group (IL-1 level = 1) (iii) increased surface expression of major histocompatibility complex (MHC) Class II and enhanced uptake of latex beads by macrophages	[128]
Immunomodulatory: elevation of NO production	Polysaccharide fraction AE2 (**14**)	*In vitro* cell-based: RAW 264.7 cells	Maximum NO production (65 μM) at a concentration of 100 mg/ml of AE2-(**14**), compared to the control group (NO production 10 μM).	[129]

[a] Refer to Figure 1 for more information on bioactive compounds. Abbreviations: $O2^{\bullet}-$, superoxide anion; $HO\cdot$, hydroxyl radical, DPPH, 2,2-Diphenyl-1-picrylhydrazyl, GPT, glutamate pyruvate transaminase; GOT, glutamate oxaloacetate transaminase; ALP, alkaline phosphatase.

the LC_{50} value was 19.0 μg/mL, which is lower than the LC_{50} value of the reference drug ampicillin trihydrate, which is 16 μg/mL. These values indicate that the methanolic extract of *A. hygrometricus* is relatively safe.

In 2010, Singh et al.[80] conducted a high-performance liquid chromatography (HPLC) analysis of extracts from *A. hygrometricus*. The study revealed the presence of several aromatic acids present in concentrations of μg per g of crude extract (μg/g). These acids included anthralinic acid (7.21 μg/g), ferulic acid (4.54 μg/g), syringic acid (4.37 μg/g), and protocatechuic acid (3.62 μg/g), which are known to possess potent antioxidant properties, as shown in Figure 5.[81–84] In 2021, Pal et al. determined the total phenol and flavonoid contents of the mushroom, which were found to be 3.427 mg gallic acid equivalents (GAE) and 74 mg quercetin equivalents (QE) per g of mushroom dry weight (DW), respectively. Pal et al. (2021)[66] analysed the ethyl acetate and methanolic extracts of *A. hygrometricus* using GC-MS. They found that the methanolic extract contained a richer variety of compounds (53 compounds) than the ethyl acetate extract. The compounds identified include aromatic compounds, polycyclic compounds, heterocyclic compounds, vitamins, fatty acids, and sugars. The

Table 4. Anticancer and Leishmanicidal activities of *A. hygrometricus* extracts and compounds.

Bioactivity	Crude extract or Bioactive compound[a]	Experimental model	Finding/Active dose	Ref.
Anticancer	Protein fraction	*In vitro cell-base:* B16-F0, HT-29, HeLa cells, DL, and sarcoma-180 in MTT assay	Cell growth inhibition against B16-F0, HT-29, HeLa cells, DL, and sarcoma-180 with IC_{50} values were 88.29, 57.8, 11, 10, and 10 μg/mL, respectively. At 11 μg/mL (IC_{50}), the cell cycle of HeLa cells was arrested at the G_0/G_1 and G_2/M phases when incubated for 48 h.	[132]
Anticancer	Methanolic and ethyl acetate extracts	*In vitro cell-based:* Jurkat cells, using MTT assay.	Cell growth inhibition against Jurkat cells with IC_{50} values of 22.7 and 68.9 μg/mL for methanolic and ethyl acetate extracts, respectively.	[66]
Anticancer	Methanolic and ethyl acetate extracts	In vitro cell-based: MOLT-4, Reh, NALM6, HepG2, A549, MCF-7, using MTT assay.	Cell growth inhibition against MOLT-4, with an IC_{50} = 7.25 g/mL (methanolic extract) and 16.10 g/mL (ethyl acetate extract).	[133]
Anticancer	Ethanolic extract	*in vivo animal model*, Ehrlich's ascites carcinoma (EAC) cells in the peritoneal cavity of mice	At a 150 mg/kg BW dose, the number of tumour cells decreased from 450×10^6 to 55×10^6 on the 21st day of administration.	[135]
Anticancer	astrakurkurone (**4**)	*In vitro cell-based:* Hep3B and HepG2 cells, using WST-1 assay	Cell growth inhibition against Hep3B and HepG2 cells with IC_{50} values of 58.8 μM and 122 μM, respectively.	[146]
Anticancer	Astrakurkurol (**5**)	In vitro cell-based: Hep3B, using WST-1 assay	Cell growth inhibition against Hep3B with IC_{50} = 22.6 μM	[136]
Anticancer	Alkaline extract (AE2)	*in vivo* animal model: mice with DL-bearing tumours	At doses of 10 or 20 mg/kg BW of AE2 extract, the survival times were extended to 27 and 29 days, respectively; the control group survival time was 23 days	[137]
Leishmanicidal	Terpenoid fraction (AHFa) and polysaccharide fraction (AHFb)	*In vitro*: anti-proliferative against *L. donovani* (MHOM/IN/83/AG83) promastigotes and intracellular amastigotes.	AHFa inhibited the growth of *L. donovani* promastigotes by inducing apoptosis with an IC_{50} = 550 μg/mL; AHFb inhibited amastigotes in macrophages with an IC_{50} = 90.9 μg/mL at 48 h.	[141]
Leishmanicidal	Astrakurkurone (**4**)	*In vitro*: anti-proliferative against *L. donovani* virulent strain AG83	Inhibiting the growth of *L. donovani* promastigotes by 90% at 10 μg/mL	[60]
Leishmanicidal	Astrakurkurone (**4**)	*In vitro*: anti-proliferative against *L. donovani* (MHOM/IN/83/AG83) promastigotes and intracellular amastigotes, using MTT assay.	Astrakurkurone (**4**) was effective against both *L. donovani* promastigotes and intracellular amastigotes, with an IC_{50} of 32.5 μg/mL and 2.5 μg/mL, respectively.	[142]

[a] Refer to Figure 1 for more information on bioactive compounds. Abbreviations: B16-F0, mouse melanoma; HT-29, colon cancer, DL, Dalton's lymphoma; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MOLT-4, T-cell acute lymphoblastic leukemic; Reh, B-cell acute lymphoblastic leukemic; NALM6, B-cell acute lymphoblastic leukemic; HepG2, human hepatocellular carcinoma; A549, human lung carcinoma; MCF-7, human breast cancer; WST-1, water-soluble tetrazolium salt.

phenolic compounds found in the extracts are also consistent with earlier HPLC analysis conducted by Singh.[80]

Kettawan et al. (2011)[85] reported DPPH antioxidant scavenging activities of raw and cooked *A. hygrometricus.* They found that the cooked mushrooms had reduced activity compared to the raw ones due to the loss of polyphenols. The concentration of polyphenols decreased from 110.2 GAE mg/100 g in raw mushrooms to 85 GEA mg/100 g in boiled mushrooms. In later studies, Pavithra et al.[22,36] also confirmed the loss of total antioxidant activity in cooked mushrooms, up to one-third less than that in the raw ones. The study further revealed a substantial loss of a few other natural antioxidants, such as flavonoids, vitamin C, phytic acid (IP6), and β-carotene reduced in cooked *A. hygrometricus* due to heating. To preserve the nutritional value of mushrooms and restore some antioxidant activity, consuming both cooked mushrooms and their broth is advisable.

3.1.2. Anti-Inflammatory Properties

A study conducted by Biswas et al. in 2010[86] found that the ethanolic extract of *A. hygrometricus* has potent anti-inflammatory properties against carrageenan, dextran, or formalin-induced paw edema in three mice models by inhibiting nitric oxide synthase (NOS) activity to reduce nitric oxide (NO) production which regulates inflammatory responses and resulting DNA damage, protein modification and apoptosis (Figure 5).[87] Animals in each model were divided into three groups (I, II and III). Animals in each group (I, II, and III) were given different injections 1 hour before chemical-induced inflammation. Group I received a vehicle control injection (0.2% DMSO in 2% gum acacia), Group II received A. hygrometric ethanolic extract (125 mg/kg BW), and Group III received the reference drug diclofenac (10 mg/kg BW), all by intraperitoneal injection. The paw thickness of the mice in each group was measured just before the chemical-induced inflammation. In the carrageenan-induced model, 20 μl solutions of 1% carrageenan in saline were injected into the right hind paw of all animals. Similarly, in

the dextran and formalin-induced models, the animals were injected with dextran solutions (20 μl, 1% in saline) and formalin solutions (20 μl, 2% in saline), respectively.

The ethanolic extract from *A. hygrometricus* at a dosage of 125 mg/kg BW showed significant anti-inflammatory effects in three different models. In the carrageenan-induced model, the extract reduced paw edema by 69% and 68% after 3 and 5 hours of treatment, respectively, compared to reductions of 76% and 74% with the reference drug diclofenac (10 mg/kg BW). In the dextran-induced model, paw edema was reduced by 40% and 38% after 3 and 5 hours of treatment, respectively, compared to reductions of 67% and 59% with the reference drug. In the formalin-induced chronic inflammatory model, the extract reduced paw edema by 50% and 56% after 5 and 6 days of treatment, respectively, compared to reductions of 68% and 73% with the reference drug. The extract's phenols and flavonoid contents enhance its ability to prevent inflammation in laboratory animal models, as suggested by the authors.[86]

A similar study by Mandal et al. (2015)[78] used aqueous extracts of *A. hygrometricus* to test its anti-inflammatory properties on carrageenan-induced paw edema in rats, which was linked to its strong antioxidant effects. The study revealed that the extract displayed significant anti-inflammatory activity at doses of 200, 400, and 600 mg/kg BW compared to the control group. It also showed that the extract exhibited a similar efficacy to the standard drug sodium diclofenac (1 mg/kg). The highest inhibition activity, with a mean percentage of 49.91%, was seen at 600 mg/kg BW after 4 hours of administration. The anti-inflammatory activity observed in the extract could be attributed to the presence of polyphenols and flavonoids in this mushroom,[36,79,80,85] which was also suggested by Biswa et al. 2010.[86]

It needs to be noted that none of the studies investigated the exact pathway mediating the anti-inflammatory effects of *A. hygrometricus* or its extracts apart from the antioxidant effects, which needs to be followed up in future studies.

3.1.3. Hepatoprotective Properties

In a study by Biswas et al. in 2011,[88] the ethanolic extract of *A. hygrometricus* demonstrated hepatoprotective properties in an animal model of carbon tetrachloride (CCl_4) induced chronic hepatotoxicity. Chronic exposure to CCl_4 resulted in an increase in serum markers indicating liver injury, such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT), bilirubin, and alkaline phosphatase (ALP) activities. When a 150 mg/kg BW extract was administered, it reduced the serum markers GPT, GOT, bilirubin, and ALP by 56.72%, 54.82%, 35%, and 30.88%, respectively, compared to the reference drug silymarine at the same dosage (150 mg/kg BW). The histopathological examinations of the liver sections from animals treated with only CCl_4 showed severe necrosis, fatty infiltration, fibrosis, and lymphocyte infiltration in the hepatocytes. However, the chronic hepatotoxic effects were reported to be moderate to low in the livers of animals treated with the extract and silymarin. In these liver tissues, relatively normal lobular patterns were observed, resembling normal liver tissue. Moreover, the extract also brought these serum biomarkers back to normal levels and boosted the liver antioxidant enzymes. These results indicate that the antioxidants present in the extract can prevent the chain reaction caused by CCl_4 intoxication by scavenging the intermediate free radicals, as discussed in the previous section.[88]

Oxidative stress significantly contributes to the development of liver injuries. Reactive immune cells like Kupffer cells (liver resident macrophages) in response to stimuli, cytochrome p450, and mitochondrial oxidative phosphorylation during ATP synthesis in liver cells are the primary sources of reactive oxygen species (ROS).[89,90] As oxidative stress and inflammation play a key role in the pathogenesis of liver diseases, extracts with anti-inflammatory and antioxidative properties hold promise for effectively safeguarding liver health.[91]

Although the hepatoprotective properties of other mushrooms (e.g. Ascomycota and Basidiomycota) and their extracts have been studied, the understanding of the active molecules is limited,[92] which is even more scanty for *A. hygrometricus*. In addition, in the study of *Ganoderma lucidum*, several mechanisms have been suggested, such as antioxidant activities, enzyme modulation, immunomodulation, antifibrosis, and inhibiting NO production.[92] However, it is unclear which signalling pathway is the target of *A. hygrometricus* during its liver protective action, which has not been comprehensively investigated in previous studies. Nevertheless, as previously discussed, the extracts of *A. hygrometricus* are rich in flavonoids, phenolic compounds, β-carotene, vitamin C, and phytic acid (IP_6).[22,36,66,79,80,85] These compounds possess potent antioxidant and anti-inflammatory properties, which, we speculate, help protect cells against oxidative stress-associated inflammatory response and liver cell injuries by reducing the production of free radicals and singlet oxygen (Figure 5). This, in turn, helps protect and prevent liver disorders induced by hepatotoxins and hepatitis virus.[92]

3.1.4. Cardioprotective Properties

Platelet attachment participates in the development of coronary artery atherosclerosis and plays a key role in blood clot formation during atherosclerotic plaque rupture, contributing to myocardial infarction due to coronary thrombosis. Natural products that can reduce platelet aggregation would contribute to their cardiovascular protection effects.[93] Bishwa et al. (2011)[94] demonstrated the potential benefits of using the ethanolic extract of *A. hygrometricus* as a cardio-protector. At a 10 mg/mL concentration, the ethanolic extract of *A. hygrometricus* inhibited platelet aggregation by approximately 70% compared to the control adenosine diphosphate (ADP) (ADP's $IC_{50} = 4.5$ μM). According to the authors, the extract inhibited platelet aggregation through two pathways. The first pathway inhibited prostaglandin synthesis, and the second pathway stimulated NO synthesis. The extract, at a concentration of 10 mg/mL, inhibited prostaglandin synthesis after a 30 minute

incubation, as indicated by the malondialdehyde level. When washed platelets were exposed to the extract in the absence of ADP, there was an increase in the synthesis of NO, which peaked after 30 minutes of incubation.

The ethanolic extracts would also decrease the incidence of cardiac hypertrophy and provide beneficial effects in various cardiovascular conditions.[93,94] The treatment with the extract of *A. hygrometricus* resulted in decreased expression of hypertrophy markers in cardiomyocytes, including atrial natriuretic factor (ANF) and β-myosin heavy chain (β-MHC), as well as proto-oncogenes such as *c-fos, c-myc, and c-jun*.[95] The study observed a reduction in hypertrophic changes in cardiomyocytes compared to the treatment with angiotensin II (AngII). AngII induces myocardial hypertrophy by constricting kidney blood vessels, increasing blood pressure, and causing heart muscle cells to enlarge. This also induces the expression of hypertrophy-associated genes, including ANF and β-MHC, and proto-oncogenes *c-fos*, *c-myc*, and *c-jun* in myocardial cells.[95] These findings suggest that using *A. hygrometricus* extract could be a potential novel therapy for treating cardiomyocyte hypertrophy.

Polyphenols have also been extensively researched for their protective effects against cardiovascular diseases, such as atherosclerosis, myocardial ischemia, stroke, and hypertension. One such polyphenol is gallic acid, which has been found to have anti-atherosclerotic activity due to its ability to inhibit platelet aggregation.[96] Additionally, polyphenols have been known to protect against AngII-induced hypertension in rats by reducing endothelial dysfunction, inhibiting NADPH oxidase nox1 and p22phox subunits and NADPH-dependent ROS production, and promoting NO production that relaxes aorta.[97] Hence, the presence of polyphenols in the extract may contribute to its cardioprotective effects.[79,80]

Pal et al. (2021)[66] conducted a GC-MS analysis on the methanol extract of *A. hygrometricus* collected from West Bengal, India. The study revealed that approximately 45% (without an internal standard) of the total volatile compounds present in the extract were fatty acids. Further quantitative analysis by Kakumyan et al. (2009)[67] identified oleic (7,052 μg/g), linoleic (4,146 μg/g), palmitic (1,639 μg/g) and stearic (C18, 108 μg/g) acids as the major fatty acids present in the extract, with oleic acid being the most abundant (7,052 μg/g) (Supplementary Table S1). Fatty acids, particularly linolenic acid (omega-3), linoleic acid (omega-6), and oleic acid (omega-9), are key active substances that protect our hearts. They can regulate lipid homeostasis, prevent the oxidation of cell membrane lipids, and help reduce blood cholesterol levels. They also help maintain normal lipid and protein metabolism and enhance liver detoxification function.[98] Possible mechanisms through which these compounds provide cardioprotection are illustrated in Figure 6. Since our body cannot produce these fatty acids independently, we must acquire them through diet. As such, consuming foods rich in monounsaturated fatty acids is believed to have several health benefits, including lowering the level of low-density lipoprotein (LDL) cholesterol in the body and reducing the risk of coronary heart disease.[99]

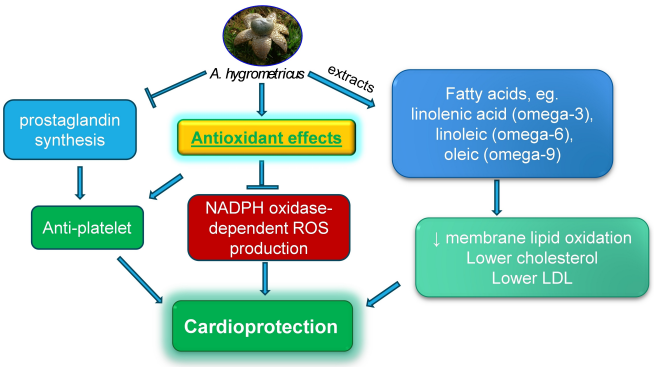


Figure 6. Possible mechanisms by which bioactive compounds from *A. hygrometricus* provide cardioprotection.

3.1.5. Antidiabetic Properties

The research carried out by Bishwa et al. (2013)[100] revealed the significant hypoglycemic effects of an ethanolic extract from *A. hygrometricus* in alloxan-induced diabetic mice. The orally administered ethanolic extract at a dose of 500 mg/kg BW decreased blood glucose levels by 36% and 49% in acute (24 h) and subacute (28 days) studies, compared to the standard drug glyburide (10 mg/kg BW) used in the control group. This dose enhanced glucose tolerance, indicating improved peripheral glucose uptake during oral glucose tolerance in the diabetic mice. However, the working mechanism was not investigated in this study.

Several bioactive compounds present in the extracts of *A. hygrometricus* may contribute to its antidiabetic properties. Polysaccharides, for instance, are known to affect insulin production by reducing NO and inducible NO synthase (iNOS) production, protecting β cells against inflammatory cytokines and promoting β cell proliferation to reduce blood glucose levels (Figure 5).[101] In animals, these polysaccharides can also significantly reduce glucose, serum cholesterol, triglycerides, and ketone levels by regulating PPAR-γ transcription and exerting potent antioxidative activities. Studies conducted by Ganeshpurkar et al. (2014)[102] and Nyam et al. (2017)[103] found that polysaccharides could improve hyperglycemia and hypercholesterolemia, along with other complications of type 2 diabetes (T2D) mellitus. A study by Oh et al. (2010) found that extracellular *Agaricus blazei* Murill contains β-glucans and glycoproteins, which can significantly reduce blood glucose levels. This is due to increased plasma insulin levels, the expression of glucose transporter (GLUT)-4 in fat tissues, and antioxidative capacity.[104] The presence of polysaccharides (**11**–**14**) (Figure 1) in *A. hygrometricus* may contribute to its antidiabetic properties.[61–64]

Phenolic compounds and flavonoids are known to have significant antidiabetic effects by inhibiting the activity of aldose reductase enzymes,[105] such as α-glucosidase and α-amylase.[106] Ferulic acid,[107] syringic acid,[83] and protocatechuic acid[108] are some of the phenolic acids that have been reported by Singh et al. (2010)[80] in the extract of *A. hygrometricus*. For example, Phenolic acids are not only excellent antioxidants but

also have antidiabetic properties. For example, Alegbe et al. (2019) found that protocatechuic acid, when administered at a dosage of 38.57 mg/kg, had a hypoglycemic effect in rats with alloxan monohydrate-induced diabetes that was comparable to the effect of metformin at a dosage of 200 mg/kg BW.[109] This effect is achieved by inhibiting α-amylase and α-glucosidase, and reducing lipid peroxidation. Protocatechuic acid has been shown to improve the translocation of GLUT-4 and glucose uptake by activating the insulin signalling pathway in human visceral adipocytes. A possible mechanism involves increasing glucose uptake by stimulating the tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and initiating subsequent events, such as the interaction of phosphoinositide-3-kinase (PI3 K) with IRS-1 and the phosphorylation of Akt. In addition, protocatechuic acid was also able to activate p-adenosine-monophosphate-activated protein kinase (p-AMPK) levels in human visceral adipocytes.[110,111] These findings suggest that phenolic compounds in the extract of *m* could exert anti-diabetic effects via similar mechanisms.

Analysis of soluble sugars of *A. hygrometricus* extract was carried out by Sanmee et al. (2003) and Yoshida et al. (1986),[48,65] using HPLC identified four major sugar alcohols: mannitol (6.52 mg/g DW), glycerol (0.12 mg/g DW), myo-inositol (inositol, 0.14 mg/g DW) and meso-erythritol (0.02 mg/g DW) (Supplementary Table S1). Sugar alcohols, such as mannitol, myo-inositol, and erythritol, give *A. hygrometricus* its sweet taste and also contribute to its antidiabetic effects due to incomplete absorption in the small intestine and partial metabolism by the human body, which provides less energy compared with sugar.[112,113]

Mannitol is safe for consumption by diabetic individuals. It has the potential to be a treatment for hyperglycemia.[114,115] It can inhibit α-glucosidase and α-amylase, decrease glucose absorption in the small intestine of diabetic rats and increase glucose uptake in muscle. Mannitol could thus effectively regulate postprandial blood glucose levels.[116]

Myo-inositol and IP6 are beneficial in treating insulin resistance through several actions, including producing secondary messengers for insulin signalling.[113,117] They can stimulate insulin secretion by β cells by regulating Ca^{2+} mobilisation and reducing insulin resistance in diabetic rats.[118] Studies have found that they can also improve lipid profile by increasing HDL-cholesterol levels to prevent vascular damage in type 2 diabetes.[119,120] Therefore, supplementing the diet with myo-inositol and IP6 derived from *A. hygrometricus* may be beneficial in preventing diabetic complications.[118]

Erythritol is a commonly used commercial calorie-free sweetener that does not affect blood glucose or insulin levels (GI = 0 and insulinemic index = 2).[121,122] Studies suggest it can help manage hyperglycemia in diabetic and non-diabetic individuals due to its antioxidant properties.[112,123] A study on diabetic rats showed that erythritol can reduce blood glucose levels and decrease creatinine, lipid peroxidation, and 5-hydroxymethylfurfural.[122] Erythritol delays gastric emptying, reduces glucose absorption, and increases muscle glucose uptake. It stimulates the release of gut hormones cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1), which promote satiation, reduce gastric emptying, and modulate glucose homeostasis.[124] Erythritol can improve insulin secretion and muscle glucose by promoting GLUT-4 and insulin receptor substrate-1 (IRS-1) mRNA expression, particularly in diabetic animals.[125] However, a recent study published in Nature Medicine also showed that erythritol could significantly increase platelet aggregation, resulting in an increased risk of myocardial infarction and stroke in users. Larger scale etiological studies are needed to understand the risk among different age and racial populations.[126]

3.1.6. Immunomodulatory Properties

Chakraborty et al. (2004)[62] found that a glucan fraction AQS–I (**12**) (Figure 1) fractionated from the water-soluble extract of the fruit bodies of *A. hygrometricus* can strongly activate splenocytes at a dose of 10 ng/mL. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method results indicated a 33% increase in spleen cell viability compared to the vehicle control when treated with AQS–I (12) at 1 ng/mL. Splenocytes are immune cells in the spleen, including T cells, B cells, and macrophages. They play a crucial role in promoting the immune response in living systems.

Mallick et al. (2009)[127] first conducted a study on the macrophage-stimulating polysaccharides found in the alkaline extract of *A. hygrometricus*. They used ion exchange purification to isolate a specific polysaccharide fraction AE2-(**14**) (Figure 1), which was suggested to bind to the cell surface and then be taken up, potentially through phagocytosis. When macrophages isolated from Swiss albino mice were treated with extract AE2-(**14**), they exhibited increased nitric oxide (NO) production in a dose-dependent manner, with the highest NO production (33.7 μM per $2x10^5$ macrophages) observed at a dose of 100 μg/mL of AE2-(**14**). Similarly, the production of cytokines, including tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1), was enhanced, with a maximum production of these cytokines observed at a dose of 100 μg/mL of AE2-(**14**). Compared to the control group, the phagocytosis capacity by the AE2-treated macrophages was more than doubled. Additionally, there was a greater surface localisation of lipid rafts after treatment, which may facilitate membrane trafficking and impact cellular function.

Mallick et al. (2010)[128] conducted a study on the immunomodulatory properties of AE2-(**14**) using a mouse model. The research findings indicated that treatment with AE2-(**14**) at doses of 10 and 20 mg/kg BW resulted in increased production of NO. The NO concentrations were measured at 32 μM and 27 μM, respectively, compared to the control group treated with phosphate-buffered saline (PBS), where the NO production was measured at 10.5 μM. Additionally, at the same dosages, AE2-(**14**) also led to higher levels of interleukin-1 (IL-1) at 1.6 and 1.4 TPI (thymocyte proliferation index), in comparison to the PBS-treated group (IL-1 level = 1 TPI). The study also observed improved phagocytic activity in macrophages from AE2-(**14**)-treated mice, with increased surface expression of major histocompatibility complex (MHC) Class II and enhanced

uptake of latex beads by macrophages. Moreover, AE2-(**14**) administration bolstered the activation of natural killer cells type 1 (NK-1) and the proliferation of splenocytes. Notably, the cytokine level in the helper T (Th1) cells culture supernatant was also increased, indicative of heightened immune response. Furthermore, analysis of serum cytokine levels suggested a bias towards a Th1-type immune response. Th1 cells play a crucial role in host defence against intracellular pathogens as they activate macrophages and neutrophils. Mallick et al. (2011) further investigated how AE2 affects macrophage activities using RAW 264.7 cells.[129] AE2-treated RAW264.7 cells treated with AE2-(**14**) at varying concentrations (ranging from 1–200 μg/mL) showed an increase in NO production in a dose-dependent manner. The maximum NO production (65 μM) was observed at a concentration of 100 mg/ml of AE2-(**14**), compared to the control group treated with PBS, where the NO production was approximately 10 μM. The increase in NO production in RAW264.7 cells was attributed to the up-regulation of inducible NO synthase (iNOS) mRNA expression induced by AE2-(**14**). The cellular phosphorylation of IκB kinase (Ikk) was also increased in RAW 264.7 cells, resulting in the nuclear factor (NF-κB) translocation to the nucleus. This confirmed that AE2 activates macrophages via the NF-κB pathway. As mentioned earlier, AE2-(**14**) (Figure 1) may play a key role in the immunomodulatory property of AE2.[64]

Mushroom polysaccharides are primarily composed of β-glucan polymers and are well-known for their therapeutic and nutritional benefits. Literature has highlighted their therapeutic properties, including antioxidant, immunomodulatory, anti-cancer, and anti-inflammatory effects. The immunomodulatory and anti-inflammatory properties of mushroom polysaccharides have been extensively researched, making them highly valuable in both nutraceutical and pharmaceutical applications. However, an in-depth understanding of their working mechanisms still requires further investigation.[130,131]

3.1.7. Anticancer Properties

Cancer cell lines are commonly used for the initial screening of potential anti-cancer effects and active compounds. A study conducted by Maiti et al. in 2008 suggested antiproliferative properties of the bioactive protein fraction, which can induce apoptosis in several cancer cell lines, including mouse melanoma (B16-F0), colon cancer (HT-29), HeLa cells, Dalton's lymphoma (DL), and sarcoma-180. In the MTT assay, it was found that the protein fraction of *A. hygrometricus* inhibited the cell growth of the mentioned cell lines. The IC_{50} values for inhibition were 88.29, 57.8, 11, 10, and 10 μg/mL, respectively, compared with PBS control. The protein extract was shown to arrest the cell cycle of HeLa cells at the G_0/G_1 and G_2/M phases when incubated for 48 hours at a concentration of 11 μg/mL (IC_{50}).[132]

A recent study by Pal et al. (2021)[66] investigated the potential effect of the methanol and ethyl acetate extracts of *A. hygrometricus* on suppressing leukemia using the Jurkat (T-cell acute lymphoblastic leukemia) cells. The methanolic extract exhibited significant anticancer activity against the cell line, with an IC_{50} value of 22.7 μg/mL. In contrast, the ethyl acetate extract showed weaker anti-leukemic effects, with an IC_{50} of 68.9 μg/mL. Notably, both extracts had very little effect on healthy human peripheral blood mononuclear cells (PBMCs) at the highest test concentration (100 μg/ml), indicating their specificity towards Jurkat cells. The same group[133] further investigated the potential anticancer activity of ethyl acetate and methanolic extracts of *A. hygrometricus* against various cancer cell lines, including MOLT-4 (T-cell acute lymphoblastic leukemic), Reh (B-cell acute lymphoblastic leukemic), NALM6 (B-cell acute lymphoblastic leukemic), HepG2 (human hepatocellular carcinoma), A549 (human lung carcinoma) and MCF-7 (human breast cancer), as well as two non-cancerous cell lines, BEAS-2B (human non-tumorigenic lung epithelial) and PBMCs, using MTT method. The results confirmed that the extracts had minimal toxicity against normal cells (PBMCs and BEAS-2B), as seen in the initial study.[66] The IC_{50} values for PBMCs and BEAS-2B were 555.77 and 702.44 μg/mL, respectively, for the ethyl acetate extract. For the methanol extract, the IC_{50} values were 925.39 and 465.45 μg/mL against PBMCs and BEAS-2B, respectively. The methanolic extract was found to be the most effective against MOLT-4, with an IC_{50} value of 7.25 g/mL. This extract was safe for non-cancer cells, with safety index (SI) values of 64.20 and 127.67 against BEAS-2B and PBMC, respectively. The ethyl acetate extract was moderately effective in suppressing the proliferation of MOLT-4 ($IC_{50} = 16.10$ g/mL) with SI values of 43.63 and 34.52 against BEAS-2B and PBMC, respectively, compared to the methanolic extract. These findings suggest that the methanolic extract of *A. hygrometricus* is the most effective and safe extract against MOLT-4 among other tested cancerous cell lines. The methanolic extract selectively induced apoptosis in MOLT-4 cells and halted cell cycle progression at the G_0/G_1 stage through sequential events, including reducing the antiapoptotic Bcl-2 protein, increasing the proapoptotic protein (Bax), and activating the caspase-9 and caspase-3 cascade. In MOLT-4 cells, the methanolic extract also impaired mitochondrial membrane potential and increased the production of ROS. This suggests that the methanolic extract can effectively induce apoptosis in MOLT-4 cells through the disruption of the function of the powerhouse mitochondria.

The research conducted by Dasgupta et al. (2019)[134] suggests that the presence of astrakurkurone (**4**), as shown in Figure 1, in *A. hygrometricus* extract,[60] could be responsible for the anticancer activities in the studies by Biswas et al. (2012)[135] and Pal et al. (2021, 2024).[66,133]

In a study conducted by Dasgupta et al. (2019),[134] the WST-1 assay was used to measure in vitro cytotoxicity. It was found that astrakurkurone (**4**) caused cell death at median lethal dose (LD_{50}) values of 58.8 μM and 122 μM for Hep3B (human liver adenocarcinoma) and HepG2 cells, respectively. In contrast, astrakurkurone (4) showed no toxicity in the normal liver cell (Chang liver) line, even at the highest dose of 250 μM. The anticancer drug doxorubicin was used as a positive control and had LD_{50} values of 4 μM and 9 μM for Hep3B and HepG2, respectively. Astrakurkurone (**4**) also reduced the migration of these cancer cells at IC_{50} concentrations of 29 μM for Hep3B and 61 μM for Hep G2. The mechanism of action of astrakurkur-

one (**4**) was suggested to be via inducing cell apoptosis, disrupting mitochondrial membrane potential, and upregulating the expression of Bcl-2 family proteins, such as Bax, along with downstream effector caspases 3 and 9. The molecular docking study also predicted that the drug interacts directly with the antiapoptotic proteins Bcl-2 and Bcl-xL.[134]

Nandi et al. (2019)[136] studied the anticancer properties of astrakurkurol (**5**) (Figure 1) using Hep3B cells, as well as normal cells (PBMC and Chang cells), in the WST-1 cell proliferation assay. The results showed that astrakurkurol (**5**) inhibited cell growth in a dose-dependent manner, with an IC_{50} value of 22.6 μM, compared to the reference drug doxorubicin (IC_{50} = 0.3 μM). However, when astrakurkurol (**5**) was administered at a concentration of approximately 30 μM, the percentage of cell viability of Chang and PBMC cells was higher than 90%. These results suggest that astrakurkurol (**5**) selectively targeted Hep3B cells over normal cells.

Astrakurkurol (**5**) also inhibited the migration and invasion ability of Hep3B cells by down-regulating the tumour metastasis-related protein MMP2, even at a low dose of 3.34 μM which is lower than the effective dose for apoptosis at 10.3 μM. Astrakurkurol (**5**) induced apoptosis reflected by increased DNA fragmentation, chromatin condensation, nuclear shrinkage, membrane blebbing, and cell cycle arrest in Sub-G_1, G_0/G_1, S, and G_2/M phases. This action was medicated by stimulating death receptor-associated proteins (Fas), which activate downstream caspase-8 and tBid, followed by ROS production, leading to mitochondrial dysfunction and apoptosis, as well as the inhibition of the Akt and NF-κB pathways.

An *in vivo* study by Mallick et al. (2010),[137] treatment with AE2 led to a significant reduction in tumour growth, increased survival rates in mice, and reversed the immunosuppression caused by the tumours. In mice with DL-bearing tumours that were given AE2 at doses of 10 or 20 mg/kg BW, the survival times were extended to 27 and 29 days, respectively, compared to a median survival time of 23 days for the control group. AE2 also induced apoptosis in DL cells, which is consistent with the tumour reduction effects in mice. The same research group investigated the underlying mechanism of immune modulation using a murine macrophage cell line (RAW 264.7).[129] It showed that AE2 modulates the immune response of macrophages through the MAPK (mitogen-activated protein kinase) signal transduction pathway. The group also discovered and isolated polysaccharides from the AE2 containing a water-soluble AE2-(**14**),[64] as shown in Figure 1. Mushroom polysaccharides are well-known to exert anticancer activity by inhibiting cancer cell growth, improving immune function and acting as adjuvant chemotherapy against various cancer cells. The proposed mechanisms include increasing mitochondrial-mediated apoptosis, the expression of anti-cancer genes (e.g. p53, Bax, miR-3131, miR-3687, miR-1207–5p, has-miR-1285), and suppressing cancer-promoting factors (e.g. Bcl-2, cyclin D1/CDK4, cyclin E/CDK2, AKT, miR-27a), as well as regulating the classical signalling pathway elements for inflammatory responses, such as Toll-like receptor (TLR)4, NF-kB, IkB, and p38 MAPK pathway.[130]

According to a study conducted by Biswas in (2012),[135] an ethanolic extract with a high concentration of phenolic compounds (80 mg pyrocatechol equivalents/100 g fresh weight) and flavonoids (40 mg quercetin equivalents/100 fresh weight) was found to strongly inhibit cancer growth by causing cell cycle deregulation and apoptosis in Ehrlich's ascites carcinoma (EAC) cells implanted in the peritoneal cavity of Swiss albino mice. The study demonstrated that the extract reduced the number of tumour cells in mice in a dose-dependent manner. Specifically, when given at a dose of 150 mg/kg BW, the number of tumour cells decreased from 450×10^6 to 55×10^6 on the 21st day after EAC cell administration. There was an increase in the number of cells in the sub-G_0/G_1 population, indicating cancer cell apoptosis. The study also found an increase in the expression of the proapoptotic protein p53 (Tumor suppressor protein that protects from DNA damage) in the carcinoma cells. Proapoptotic gene *Bax* was upregulated during p53-mediated apoptosis, while the anti-apoptotic protein Bcl-2 (B-cell lymphoma-2) was downregulated, resulting in a decrease in the Bcl2/Bax ratio. It was suggested that the apoptogenic action of the extract might be due to its high amount of flavonoids and phenolic compounds, which have been suggested to possess such biological effects.[77]

Yadav et al. (2022)[138] conducted an *in silico* study to investigate the anticancer activity and mode of action of compounds extracted from *A. hygrometricus*. They found that two compounds, astrakurkurone (**4**) and ergosta-4,6,8-(14)-22-tetraene-3-one (**8**), showed potential anticancer activities against two cell lines of renal carcinoma, RCC4 and VMRC-RCZ. The IC_{50} values of Astrakurkurone (**4**) against RCC4 and VMRC-RCZ cells were predicted to be 0.636 μmol and 0.63 μmol, respectively. Similarly, ergosta-4,6,8-(14)-22-tetraene-3-one (**8**) (Figure 1) showed predicted IC_{50} values of 0.631 and 0.626 μmol against RCC4 and VMRC-RCZ cell lines, respectively. Both compounds have satisfactory profiles of absorption, distribution, metabolism, and excretion based on the criteria for drug-likeness, drug safety, and bioavailability.

The above findings suggest that key compounds such as astrakurkurone (**4**), astrakurkurol (**5**), ergosta-4,6,8-(14)-22-tetraene-3-one (**8**), and polysaccharides AE2-(**14**) (Figure 1) could be responsible for the anticancer activities found in the crude extracts of *A. hygrometricus*.

3.1.8. Leishmanicidal Properties

Visceral leishmaniasis is a tropical disease caused by *Leishmania donovani* and *Leishmania infantum* parasites. The disease is prevalent in East Africa, Asia, South America, and the Mediterranean Basin. However, the available treatments are limited to a few outdated and poorly tolerated drugs that have multiple adverse effects, low oral bioavailability, and a high potential for developing resistance.[139,140]

In 2012, Lai et al. reported promising activity of astrakurkurone (**4**), derived from *A. hygrometricus*, by inhibiting the growth of *L. donovani* promastigotes by 90% at 10 μg/mL on the sixth day of culture. However, astrakurkurol (**5**) showed no such activity. The positive control, miltefosine, inhibited the growth

of *L. donovani* promastigotes by around 49% at 10 μg/mL on the sixth day of culture.[60]

Mallick et al. (2014)[141] investigated the effects of terpenoid fraction (AHFa) and water-soluble polysaccharide fraction (AHFb) of *A. hygrometricus* against *L. donovani*. They found that AHFa can inhibit the growth of *L. donovani* promastigotes by inducing apoptosis with an IC_{50} of 550 μg/mL. On the other hand, AHFb was found to inhibit intracellular amastigotes in macrophages, with an IC_{50} of 90.9 μg/mL, by increasing the levels of NO and the pro-inflammatory cytokine IL-12. The authors hypothesised that AHFb's polysaccharides, such as the isolated polysaccharides (**11**–**14**), as shown in Figure 1, may have activated macrophages and promoted their scavenge ability against amastigotes through immunomodulation.[61–64] The group further investigated the effectiveness of astrakurkurone (**4**) and AHFa in eliminating *L. donovani* promastigotes.[142] They discovered that the compound selectively produced ROS, leading to mitochondrial dysfunction and depletion of glutathione, which ultimately inhibited the proliferation of the promastigotes. Astrakurkurone (**4**) was effective against both promastigotes and intracellular amastigotes, with an IC_{50} of 32.5 μg/mL and 2.5 μg/mL, respectively, compared to the standard antileishmanial drug sodium antimony gluconate (IC_{50} = 360 μg/mL). A selectivity index (SI) of 100 (LC_{50} splenocytes/IC_{50} amastigotes) was observed for astrakurkurone (**4**).

Mallick et al. (2016)[143] investigated the mechanism of action of astrakurkurone (**4**) against *L. donovani*. They discovered that astrakurkurone (**4**) increased the expression of TLR9 in macrophages infected with *L. donovani*. This increase in TLR9 plays a crucial role in eliminating *L. donovani* amastigote. A synergistic effect was also observed when astrakurkurone (**4**) was combined with a TLR9 agonist (CpG). Furthermore, in silico evidence from a docking study between mouse TLR9 and astrakurkurone (**4**) supported these findings. Toll-like receptors (TLRs) are known to play a significant role in mediating immune responses to pathogen-derived ligands and connecting adaptive immunity with innate immunity. They are important regulators of inflammatory pathways in the gut.[144,145] It was also observed that astrakurkurone (**4**) could induce protective cytokines such as γ-interferon and IL-17, which helps reduce the parasite burden *in vivo*. Additionally, astrakurkurone (**4**) was nontoxic towards peripheral blood mononuclear cells from immunocompromised patients suffering from visceral leishmaniasis. The above findings suggest that astrakurkurone (**4**) is an antileishmanial compound that can enhance host immune efficiency and help parasite clearance *in vitro* and *in vivo* without causing toxicity.

3.2. Astraeus Odoratus

The literature indicates that the biological properties of extracts of *A. odoratus* have been researched less than those of *A. hygrometricus*. *A. odoratus* extracts possess antioxidant and antidiabetic properties.[51,72,85,147,148] The nutritional composition of the mushroom has been studied, revealing potential health benefits.[47,72] Lanostane triterpenoids were commonly isolated from this genus, some with antimycobacterial (*M. tuberculosis*), antimalarial, and cytotoxic activities.[69,71,149,150] The biological activities of extracts and isolated compounds of *A. odoratus* are summarised in Table 5.

3.2.1. Antioxidant Properties

The antioxidant properties of *A. odoratus*, as investigated by Srikram et al. (2016), reveal its potential health benefits.[51] The team analysed the aqueous extract of the mushroom and showed significant total antioxidant capacity (TAC), total phenol content (TPC), and total flavonoid content (TFC). The TFC data, expressed as mg of catechin equivalents (CE) per 100 grams of dry weight (mg CE/100 g DW), and the TPC, expressed in terms of mg of gallic acid equivalents (GAE) per 100 grams of dry weight (mg GAE/100 g DW), were 205.26 mg CE/100 g DW and 266.44 mg GAE/100 g DW, respectively. The TAC, determined using the ferric reducing potential (FRAP) assay, was 7.61 mmol Trolox equivalents (TE) /100 g DW), a value comparable to that reported by Kettawan et al.[85] A comprehensive study conducted by Fong-in et al. (2023)[147] further confirmed the TAC, TPC, and TFC values of the aqueous extract from dry *A. odoratus*. The TPC and TFC values were 839.99 mg GAE/100 g DW and 269.97 mg CE/100 g DW, respectively. The TAC value was approximately 650 mg ascorbic acid equivalents (AAE)/100 g DW or 3.69 mmol AAE/100 g DW. Despite using different controls for determining TAC values, these findings unequivocally confirm the antioxidant potential of *A. odoratus*.

3.2.2. Antidiabetic Properties

Glucose uptake is a key process for reducing postprandial blood glucose levels, occurring primarily in muscle cells at a rate of 80%. Under physiological conditions, glucose uptake lowers glucose levels in the cultural medium. A study conducted by Rodphet et al. (2013)[151] investigated the antidiabetic properties of 95% ethanolic crude extract from *A. odoratus* and its five different fractions (H_2O, 25% MeOH, 50% MeOH, 75% MeOH, and 100% MeOH). The results showed that the 95% EtOH extract, aqueous (H_2O) fraction, and 75% MeOH fraction were effective against α-glucosidase, with IC_{50} values of 63.3, 98.9, and 23.4 μg/mL, respectively. In contrast, the IC_{50} of acarbose, an α-glucosidase inhibitor used for diabetes treatment, was 3.6 mg/mL. Furthermore, the study also investigated the glucose-lowering effect of the ethanolic extract and the five fractions in L6 myotubes (muscle cells). Results showed that at a concentration of 400 μg/mL, the 100% MeOH fraction and aqueous fraction improved glucose uptake by 42% and 22%, respectively, compared with the positive control, 500 nM insulin. On the other hand, the 95% EtOH extract was inactive at the same concentration.

The researchers from the same group conducted a further study to determine the effect of the hexane fraction of *A. odoratus* on glucose uptake in L6 myotubes.[148] It was fractionated from the 95% ethanolic crude extract, as their

Table 5. Bioactivities of extracts and isolated compounds of *A. Odoratus*.

Bioactivity	Crude extract or Bioactive compound[a]	Experimental model	Finding/Active dose	Ref.
Antioxidant	Aqueous extract	Using FRAP assay	TAC = 7.61 mmol TE per 100 g of the extract	[51]
Antioxidant	Aqueous extract	Using FRPA assays	TAC = 3.69 mmol AAE/100 g DW	[147]
Antidiabetic: inhibition of α-glucosidase	95% ethanolic extract, aq fraction, 75% methanol fraction	In vitro α-glucosidase enzyme inhibition assay	IC_{50} values of 63.3, 98.9, and 23.4 μg/mL for ethanolic extract, aq fraction and methanolic fraction, respectively.	[151]
inhibition of α-amylase and lipid-digesting enzyme	hexane and 80% ethanolic extracts	α-amylase and lipid-digesting enzyme	hexane extract inhibited α-amylase, with an IC_{50} = 17.4 mg/mL, lipid-digesting enzyme, with an IC_{50} = 591 mg/mL	[72]
Antidiabetic: Glucose uptake	Methanolic extract	cell-based assay using L6 myotubes (muscle cells)	400 μg/mL, the 100% MeOH fraction and aqueous fraction improved glucose uptake by 42% and 22%, respectively	[151]
Antidiabetic: Glucose uptake	Hexane fraction derived from 95% ethanolic crude extract	cell-based assay using L6 myotubes (muscle cells)	IC_{50} = 81 μg/mL with a plateau effect observed at 200 μg/mL	[148]
Anticancer	astraodoic acids A (15) and astraodoic acids B (16)	Cell-based: cell growth inhibition against KB and NCI–H187 cell lines, using REMA	astraodoic acids A (**15**) IC_{50} values of 34.69 μg/mL and 19.99 μg/mL against KB and NCI–H187 cell lines, respectively; astraodoic acids B (**16**), IC_{50} values of 18.57 μg/mL and 48.35 μg/mL, against KB and NCI–H187 cell lines, respectively;	[69]
Anticancer	Astraodoric acid A (**15**), astraeusin B (**25**), J (**33**), L (**35**), and artabotryol B (**37**)	Cell-based: cell growth inhibition against NCI–H187, MCF-7 and KB cell lines, using REMA	IC_{50} values ranged from 13–47 μg/mL for the five compounds across the three cell lines. artabotryol B (**37**), IC_{50} values of 16, 23 and 13 μg/mL against NCI–H187, MCF-7 and KB cell lines, respectively.	[70]
Anticancer	astraodoric acids A (**15**), C (**17**), D (**18**), and astraodoric acid E (**19**)	Cell-based: cell growth inhibition against BT474, Chago-K1, Hep-G2, KATOIII, MCF-7 and SW620), using	exhibited weak cytotoxicity against all cell lines, with IC_{50} values ranging from 20–50 μg/mL	[71]
Anti-TB	astraodoric acid A (**15**) and astraodoric acid B (**16**)	Cell growth inhibition against *Mycobacterium tuberculosis* H37Ra, using a GFP-based fluorescent detection assay.	astraodoric acid A (**15**), MIC = 50 μg/mL; astraodoric acid B (**16**), MIC = 25 μg/mL.	[69]
Antibacterial	astraodoric acid A (**15**), astraodoric acid D (**18**), and astraeusin H (**31**)	Cell growth inhibition *Bacillus cereus*, and *Enterococcus faecium, using* resazurin microplate assay	astraodoric acid A (**15**), astraodoric acid D (**18**) and astraeusin H (**31**), MICs = of 6.25, 12.5 and 25.0 μg/mL *against B. cereus*, respectively; astraodoric acid A (**15**), astraodoric acid B (**16**), and astraeusin H (**31**), MICs = 6.25, 25 and 12.5 μg/mL against *E. faecium*, respectively	[70]
Antimalarial	Synthetic derivatives **36a–g**[2]	Against *P. falciparum* (K1, multidrug resistant strain), using microculture radioisotope technique	Compounds **36a-g** with IC_{50} values of 4.85, 4.48, 4.16, 4.46, 3.45, 3.23, and 3.41 μg/mL, respectively.	[149]

[a] Refer to Figure 2 for more information on bioactive compounds. [2]Refer to Figure 7 for more information on compounds **36a–g**. Abbreviations: TAC, total antioxidant capacity; FRAP, ferric-reducing potential FRAP; TE, Trolox equivalents; AAE, ascorbic acid equivalents; KB, epidermoid carcinoma; NCI–H187, human small cell lung cancer; MCF-7, human breast cancer; REMA, resazurin microplate assay; GFP, green fluorescent protein.

preliminary results showed that the hexane fraction had a stronger glucose uptake ability than the parent 95% ethanolic extract. The study found that the hexane fraction increased glucose uptake dose-dependently with IC_{50} = 81 μg/mL, compared to insulin as the positive control (IC_{50} = 6.6 nM). The effect reached a plateau at 200 μg/mL. At a concentration of 100 μg/mL, the hexane fraction enhanced glucose uptake by increasing the synthesis of GLUT-1 and GLUT-4 and their activities through p38 mitogen-activated protein kinase (p38MAPK).

The composition of the hexane fraction was further analysed using thin-layer chromatography (TLC) and HPLC, which revealed a high content of ergosterol (**9**) (Figure 1) and the presence of other compounds, such as lanostane triterpenoids. The authors suggested ergosterol (**9**) as the main contributor to increased glucose uptake in L6 myotubes. According to the literature, ergosterol (**9**) is known to upregulate GLUT-4 expression and enhance GLUT-4 translocation by increasing the phosphorylation of protein kinase B (Akt) and protein kinase C.[152]

Arpha et al. (2012)[69] isolated three pure compounds (Figure 2) from the hexane extract of *A. odoratus*, which were identified as ergosterol (**9**) (0.029%), artabotryol A (**36**) (0.089%), and astraodoric acid A (**15**) (0.011%). Artabotryol A (**36**) and astraodoric acid A (**15**) have not yet been studied for their ability to enhance glucose uptake in cells. However, other related lanostane triterpenoids have shown potential for anti-

inflammatory effects related to diabetes by increasing NO production in macrophages, the ability to inhibit α-glucosidase and reduce glucose uptake in the small intestine, the enzyme protein tyrosine phosphatase 1B (PTP1B, an inhibitor of insulin signalling), as well as increase glucose update and inhibit gluconeogenesis in liver cells, as reported in studies by Zhang et al. (2020)[153] and Yang et al. (2022)[154] Therefore, further investigation into the antidiabetic properties of these compounds is encouraged, as it could provide additional support for the potential use of *A. odoratus* for blood glucose management.

In 2022, Wunjuntuk et al.[72] conducted a study to analyse the proximate composition of dietary fibre, β-glucan contents, and inhibitory activities of starch and lipid-digesting enzymes of *A. odoratus* cultivated in Thailand. They found that *A. odoratus* has the highest total dietary fibre, soluble fibre, and β-glucan content compared to other mushrooms, with values of 77.1 g/100 g DW, 72.3 g/100 g DW, and 24.9 g/100 g DW, respectively. The ability of the mushroom's hexane and 80% ethanolic extracts to inhibit α-amylase, α-glucosidase and porcine pancreas type 2 lipase was tested. The hexane extract inhibited α-amylase with an IC_{50} value of 17.4 mg/mL, compared to the positive control acarbose (IC_{50} = 0.01 mg/mL). However, the hexane extract did not exhibit any activity against α-glucosidase or porcine pancreas type 2 lipase at the highest test concentration of 1000 mg/mL. On the other hand, the 80% ethanolic extract did not exhibit any activity against the starch enzymes at the highest test concentration. However, it did show weak inhibition against the lipid-digesting enzyme, with an IC_{50} of 591 mg/mL, compared to the positive control orlistat (IC_{50} = 0.94 mg/ml). It is worth noting that the 80% ethanolic extract did not inhibit α-glucosidase, which was opposite to the findings of Rodphet et al. (2013),[151] who reported that their 95% ethanolic extract was active against the enzyme at an IC_{50} of 63.3 μg/mL.

In 2023, On-nom et al. conducted a study on *A. odoratus* to analyse its sugar alcohol content[47] and found that this mushroom contains a high amount of mannitol (62 mg/g DW) and a low amount of inositol (0.88 mg/g DW). As previously discussed, these sugar alcohols are useful in treating insulin-resistant diabetes through various mechanisms.[113,117,155] The researchers also found the glycaemic index (GI) of the mushroom to be low (GI = 27). This low GI is attributed to the β-glucan content discovered in this study (27.0 mg/g DW). A low GI rating (55 or below) for slowly absorbed carbohydrates has been recommended for the long-term management of blood glucose levels in people with T2D.[156] The carbohydrate matrix in *A. odoratus* plays a significant role in sugar hydrolysis. High β-glucan content can slow down sugar hydrolysis, meaning that *A. odoratus* provides sugar but with a low GI. Therefore, it is suitable for consumption by people with diabetes.[157,158]

3.2.3. Anticancer Properties

Arpha et al. (2012)[69] discovered the anticancer properties of astraodoic acids A (**15**) and B (**16**) using the cancer cell growth inhibition assay and a resazurin microplate assay (REMA). Compounds (**15**) and (**16**) are isolated lanostane triterpenes found in *A. odoratus*. Astraodoic acid A (**15**) showed weaker cytotoxicity against human epidermoid carcinoma (KB) than human small cell lung cancer (NCI–H187) cell lines, with IC_{50} values of 34.69 μg/mL and 18.57 μg/mL, respectively. On the other hand, astraodoic acid B (**16**) exhibited stronger cytotoxicity against KB than NCI–H187 cell lines, with IC_{50} values of 19.99 μg/mL and 48.35 μg/mL, respectively. These are compared to the positive control doxorubicin, which had IC_{50} values of 0.28, 0.067, and 0.058 μg/mL against KB and NCI–H187, respectively.

In 2016, Isaka et al.[70] explored the cytotoxicity of 18 lanostane triterpenoids from *A. odoratus* (Figure 2*)* and five compounds with weak activity against NCI–H187, MCF-7, and KB cell lines using the resazurin microplate assay. The following compounds showed varying levels of effectiveness against different cell lines. Astraodoric acid A (**15**), astraeusin B (**25**), J (**33**), L (**35**), and artabotryol B (**37**) displayed IC_{50} values ranging from 13–47 μg/mL. In contrast, the positive control doxorubicin had IC_{50} values of 0.079, 7.4, and 0.60 μg/mL against NCI–H187, MCF-7, and KB cell lines, respectively. On the other hand, astraodoric acids B (**16**) and D (**18**), astraeusin A (**24**), astraeusins C–I (**26**–**32**), astraeusin K (**34**) did not show activity against the three cell lines or non-cancerous VERO (African green monkey kidney fibroblasts) cells, even at the highest test concentration of 50 μg/mL. Out of the active compounds, artabotryol B (**37**) displayed slightly higher cytotoxicity in NCI–H187, MCF-7, and KB cell lines with IC_{50} values of 16, 23, and 13 μg/mL. However, it was also toxic (IC_{50} = 9 μg/mL) to VERO cells. Astraodoric acid A (**15**) displayed similar cytotoxicity against KB (IC_{50} = 35 μg/mL) as previously reported by Arpha et al. (2012).[69]

It is worth noting that even at the highest test concentration of 50 μg/mL, Arpha et al. (2012)[69] and Isaka et al. (2016)[70] reported that the compounds mentioned, except for astraeusin J (**33**) (with an IC_{50} of 25 μg/mL), were ineffective against MCF-7.

Srisurichan et al. (2017)[71] investigated the cytotoxicity of triterpenoids isolated from *A. odoratus* using an MTT assay. They tested nine different compounds against six human tumour cell lines (BT474, Chago-K1, Hep-G2, KATOIII, MCF-7 and SW620), as well as a human diploid lung fibroblast cell line (Wi-38). The results showed that astraodoric acid A (**15**), astraodoric acid C (**17**), astraodoric acid D (**18**), and astraodoric acid E (**19**) exhibited weak cytotoxicity against all cell lines, with IC_{50} values ranging from 20–50 μg/mL, where doxorubicin was used as a positive control with IC_{50} values ranging from 0.08–0.7 μg/mL.

3.2.4. Antibacterial Properties

Arpha et al. (2012)[69] researched the potential antibacterial properties of compounds from *A. odoratus* against *Mycobacterium tuberculosis* H37Ra. The study found that astraodoric acids A (**15**) and B (**16**) displayed weak activity against the bacterium with minimum inhibitory concentration (MIC) values of 50 and 25 μg/mL, respectively. The study also used isoniazid (MIC of

0.023–0.046 μg/mL), a positive control anti-tuberculosis drug, which showed significantly higher activity than astraodoric acids A (**15**) and B (**16**). Interestingly, other lanostane triterpenoids structurally similar to astraodoric acids were isolated from *Ganoderma sp.* BCC 16642. These compounds showed much higher activity against *M. tuberculosis* H37Ra with MICs in the 3.31–0.781 μg/mL range.[150]

In 2016, Isaka et al.[70] tested the effectiveness of their isolated compounds against Gram-positive bacteria, *Bacillus cereus*, and *Enterococcus faecium*. Astraodoric acid A (**15**), astraodoric acid D (**18**) and astraeusin H (**31**) showed weak activities against *B. cereus* with MIC values of 6.25, 12.5 and 25.0 μg/mL, respectively, while the positive control, vancomycin HCl, had a MIC of 1 μg/mL. Comparatively, astraodoric acid A (**15**), astraodoric acid B (**16**), and astraeusin H (**31**) showed weak activities against pathogenic *E. faecium* with MIC values of 6.25, 25 and 12.5 μg/mL, respectively, while the positive control, tetracycline HCl, had a MIC of 0.098 μg/mL. However, the mechanisms of antitubercular effects have been understudied in natural products, including *A. odoratus*. Future studies can consider investigating the effect of inhibiting the enzymes involved in bacterial metabolism, which are commonly observed in most anti-TB drugs.[69]

3.2.5. Antimalarial Properties

According to the guidelines of the World Health Organization (WHO), the various plant species reviewed are classified into four main categories based on their effectiveness against different strains of *Plasmodium falciparum*. These categories are highly active (IC_{50} < 5 μg/mL), promisingly active (IC_{50} 5–15 μg/mL), moderately active (IC_{50} 15–50 μg/mL) and inactive (IC_{50} > 50 μg/mL).[159] Later, Lemma et al. (2017)[160] comprehensively reviewed the data on *in vitro* antiplasmodial activities derived from 58 reports that covered 752 medicinal plants traditionally used for malaria treatment in Africa and Asia. The herbs were categorised based on their antiplasmodial activities as very good, good, moderate, or inactive, based on their IC_{50} values of < 0.1 μg/ml, 0.1–1 μg/mL, > 1–5 μg/mL, and > 5 μg/mL, respectively.

In 2014, Nasomjai et al.[149] conducted a study to investigate the antimalarial potential of astraodorol (**36**) and its ten synthetic derivatives. Astraodorol (**36**) is a major lanostane-type triterpene found in *A. odoratus*.[69] Using *P. falciparum* (K1, multidrug resistant strain), the results showed that astraodorol (**36**) had no antimalarial activity. However, some of its synthetic derivatives **36a**–**g** (Figure 7) exhibited antimalarial activity with IC_{50} values of 4.85, 4.48, 4.16, 4.46, 3.45, 3.23, and 3.41 μg/mL, respectively, with dihydroartemisinin (mefloquine) as a positive control (IC_{50} of 0.036 μg/mL). Only compound **36e** showed toxicity against VERO cell lines, with IC_{50} 26.48 μg/mL.

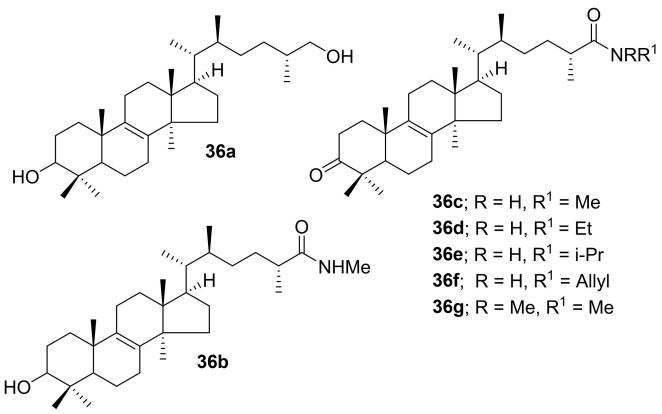


Figure 7. Synthetic derivatives of astraodorol (**36a–g**) were shown to have antimalarial activity.[149]

3.3. Astraeus Asiaticus

Several studies have highlighted various medicinal properties of *A. asiaticus*. Isaka et al. (2017)[74] and Pimjuk et al. (2015)[73] identified its anticancer properties. Isaka et al. (2017)[74] found it has antimalarial activity against *P. falciparum* K1. Phadannok et al. (2020)[148] discovered its antidiabetic properties, while Tassaneetritap et al. (2021)[161] discovered its antiviral activity against Herpes Simplex Virus type 2. Pandey et al. (2022)[46,52] also explored its antioxidant properties. Table 6 summarises the biological activities of extracts and isolated compounds of *A. asiaticus*.

3.3.1. Antioxidant Properties

Pandey et al.[52] conducted a study in 2022 to investigate the antioxidant properties of acetone and chloroform extracts of *A. asiaticus* using the DPPH assay. The IC_{50} values for the acetone and chloroform extracts were 40.63 and 58.38 μg/mL, respectively, compared to positive control butylated hydroxyanisole BHA (IC_{50} = 32.41 μg/mL). The study found that the acetone extract had a more potent antioxidant activity than the chloroform extract due to the presence of phenolics, flavonoids, and ascorbic acid. Specifically, the acetone extract had 15.84 mg GAE /g DW, 2.76 mg QE /g DW, and 1.70 mg AAE /g DW for phenolic, flavonoid, and ascorbic acid contents, respectively. On the other hand, the chloroform extract had 6.22 mg GAE /g DW, 1.26 mg QE /g DW, and 1.09 mg AAE /g DW for phenolic, flavonoid, and ascorbic acid, respectively.

The group further studied the antioxidant properties of hot water and hexane extracts of *A. asiaticus*.[46] They also re-investigated the antioxidant properties of the acetone extract. The hot water extract exhibited strong ROS scavenging activity with an IC_{50} value of 42.54 μg/mL, while the hexane extract showed less potent antioxidant activity with an IC_{50} value of 82.97 μg/mL, in comparison to the positive control BHA (IC_{50} = 32.41 μg/mL). Surprisingly, the acetone extract showed weaker activity (IC_{50} = 54.06 μg/mL) than a previous study.[52] The IC_{50} values were used to reflect the amount of phenolic, flavonoid,

Table 6. Bioactivities of extracts and isolated compounds of *A. Asiaticus.*

Bioactivity	Crude extract or Bioactive compound[a]	Experimental model	Finding/Active dose	Ref.
Antioxidant	acetone and chloroform extracts	*In vitro* DPPH scavenging assay	IC_{50} values were 40.63 and 58.38 μg/mL for the acetone and chloroform extracts, respectively	[52]
Antioxidant	hot water, hexane, and acetone extracts	*In vitro* DPPH scavenging assay	IC50 values were 42.54, 82.97 and 54.06 μg/mL. for hot water, hexane, and acetone extracts, respectively	[46]
Antidiabetic: glucose uptake	Hexane fraction	cell-based assay using L6 myotubes (muscle cells)	IC_{50} = 144 μg/mL required to decrease medium glucose to 50%.	[148]
Anticancer	Astrasiate (**46**) and artabotryol B (**37**)	cell-based: cell growth inhibition against KB and NCI–H187 and MCF-7 cell lines, using REMA	Astrasiate (**46**), IC_{50} values 46.49 and 36.94 μg/mL against KB and NCI–H187, respectively artabotryol B (**37**), IC_{50} values 38.78 and 19.54 μg/mL against KB and NCI–H187respectively	[73]
Anticancer	astraeusin M (**48**), astraeusin P (**51**) and *epi*-inotodiol (**52**)	cell-based: cell growth inhibition against NCI–H187, MCF-7, and KB, using REMA	epi-inotodiol (**52**), IC_{50} values of 30, 18, and 18 μg/mL against NCI–H187, MCF-7, and KB, respectively; astraeusin P (**51**), IC_{50} values of 49 and 34 μg/mL against NCI–H187 and KB, respectively; astraeusin M (**48**), IC_{50} = 25 μg/mL against NCI–H187	[74]
Antiviral: anti-Herpes Simplex Virus	Aqueous extract	*In vitro* against HSV-1, HSV-2 and HSV-2 ACV using VERO as host cells.	at 62.50 μg/mL, inhibited approximately 80% of the attachment of HSV-1 and HSV-2 to the tested VERO cells; at 125 μg/ml, inhibited approximately 50% of the attachment of HSV-2 ACV; at 500 μg/mL, 100% inhibition was observed for all three viruses; all three viruses were completely eradicated at 500 μg/mL dose	[161]
Antimalarial	astraeusin M (**48**)	Against *P. falciparum* (K1, multidrug resistant strain), using a microculture radioisotope technique	IC_{50} = 3.0 μg/mL	[74]

[a] Refer to Figure 3 for more information on bioactive compounds. Abbreviations: DPPH, 2,2-Diphenyl-1-picrylhydrazyl; KB, epidermoid carcinoma; NCI–H187, human small cell lung cancer; MCF-7, human breast cancer; REMA, resazurin microplate assay; HSV-1, Herpes Simplex Virus 1; HSV-2, Herpes Simplex Virus 2; HSV-2 ACV, Acyclovir-resistant Herpesvirus 2; VERO, African green monkey kidney fibroblasts.

and ascorbic acid contents in the extracts. For instance, the hot water extract contained 6.8 mg GAE/g DW, 2.03 mg QE/g DW, and 0.167 AAE/g DW for phenolic, flavonoid, and ascorbic acid, respectively. On the other hand, the hexane extract had much lower phenolic (2.16 mg GAE/g DW), flavonoid (1.01 mg QE/g DW), and ascorbic acid (0.11 mg AAE/g DW) contents. The acetone extract used in this study exhibited lower levels of phenolic (3.95 mg GAE/g DW), flavonoid (1.65 mg QE/g DW), and ascorbic acid (0.14 mg AAE/g DW) contents when compared to a previous study.[52] These reduced contents are consistent with the weaker activity observed in this study, with an IC_{50} value of 54.06 μg/mL.

3.3.2. Antidiabetic Properties

In a study conducted by Phadannok et al. (2020),[148] it was demonstrated that when the extract of *A. asiaticus* was added to L6 myotubes, the glucose level in the medium further decreased compared to the basal level, indicating enhanced glucose uptake activities by the extracts. The concentration of *A. asiaticus* required to decrease medium glucose to 50% (EC_{50}) was 144 μg/mL, compared to insulin, the positive control, which had an EC_{50} of 6.6 nM. The range of *A. asiaticus* required for glucose-lowering effect was 12.5–200 μg/mL, reaching approximately 70% at 200 μg/mL and plateauing at 400 μg/mL (80% response) after 50 hours of incubation. L6 cells remained viable at 400 μg/mL of *A. asiaticus*. Therefore, for further studies, *A. asiaticus* at 200 μg/mL and an incubation time of 50 hours were used to investigate the mechanism of action, which was driven by the increase in GLUT1 and GLUT-4 protein levels. It can be postulated that *A. asiaticus* activates GLUT-4 partially through p38MAPK, as well as PI-3 K, for synthesis and translocation to the cell membrane. Thus, *A. asiaticus* has a better insulin-mimetic effect than *A. odoratus*.

The hexane fraction *A. asiaticus* was analysed using TLC and HPLC, which showed that ergosterol (**9**) is the main active compound and the contributor to enhancing glucose uptake in L6 myotubes. Ergosterol (**9**) is known to enhance GLUT-4 translocation and upregulate GLUT-4 expression and the phosphorylation of Akt and protein kinase C.[152] The TLC and HPLC analysis also revealed the presence of other compounds, including lanostane triterpenoids. In 2015, Pimjuk et al. isolated artabotryol B (**37**) (0.024%) and artabotryol C1 (**42**) (0.05%) from the hexane extract of *A. asiaticus.* Isaka et al. 2017[74] isolated another three major compounds from the hexane fraction of *A. asiaticus*, namely astrasiaone (**41**) (0.22%), astraeusin M (**48**) (0.16%), and astraeusin A (**24**) (0.12%). Four minor compounds were also obtained, including 26-*epi*-astrasione (**43**) (0.09%), lanosterol (**38**) (0.03%), astrabotryol A (**36**) (0.02%), and astrabotyol B (**37**) (0.02%). Interestingly, the group also isolated ergosterol (**9**) as a major compound (0.32%) from the polar ethyl acetate fraction.

No literature indicates whether these isolated compounds from *A. asiaticus*, except for ergosterol (**9**), have been investigated for antidiabetic properties. However, recent works by Yang et al. (2022),[154] Zhang et al. (2020),[153] and Chen et al. (2019)[162] have revealed the antidiabetic effects of related lanostane tetracyclic triterpenoids present in mushrooms. These studies suggest that the isolated compounds from the hexane fractions of *A. asiaticus*[73,74] should be further investigated for their potential antidiabetic properties and working mechanisms. There is ample evidence to indicate the therapeutic benefits of sugar alcohols and polysaccharides.[101–103,113,117,130,131] Investigating the potential antidiabetic and other therapeutic properties of sugar alcohols and polysaccharides[47,62–64,66,67,72] in *A. asiaticus* would be worthwhile.

3.3.3. Anticancer Properties

Pimjuk et al. (2015)[73] screened eight compounds (**9**, **22**, **36**, **37**, **41**, **42**, **46**, and **47**) isolated from *A. asiaticus* against KB, NCI–H187, MCF-7 cancer cell lines, and normal VERO cells. Astrasiate (**46**) and artabotryol B (**37**) were slightly toxic against KB and NCI–H187, with IC_{50} values of 46.49 and 36.94 μg/mL and 38.78 and 19.54 μg/mL, respectively. The remaining compounds (**9**, **22**, **36**, **41**, **42**, and **47**) were inactive against the three cancer cell lines and VERO cells at the highest tested concentration of 50 μg/mL. Artabotryol B (**37**) was also toxic to VERO cells, with an IC_{50} of 17.95 μg/mL. It is noteworthy that there is a slight difference in the cytotoxicity level of artabotryol B (**37**) against the same cell lines compared to artabotryol B (**37**) (IC_{50} values of 13 and 16 μg/mL for KB and NCI–H187 cell line, respectively) isolated from *A. odoratus*.[70] This variation is primarily due to the purity of the test compounds.

Isaka et al. (2017)[74] screened thirteen compounds (**17**, **41**–**46**, and **48**–**53**) isolated from *A. asiaticus* against three cancer cell lines (NCI–H187, MCF-7, and KB) and VERO cells, the resazurin microplate assay. *Epi*-inotodiol (**52**) has weak cytotoxicity against NCI–H187, MCF-7, and KB with IC_{50} values of 30, 18 and 18 μg/mL, respectively. In contrast, astraeusin P (**51**) showed weaker cytotoxic activities against NCI–H187 and KB with IC_{50} values of 49 and 34 μg/mL. While astraeusin M (**48**) only showed activity against NCI–H187 with IC_{50} values of 25 μg/mL. Doxorubicin hydrochloride was used as a positive control against NCI–H187, MCF-7, and KB, with IC_{50} values of 0.079, 7.4, and 0.6 μg/mL, respectively. Astraeusin M (**48**), astraeusin P (**51**), and epi-inotodiol (**52**) were found to be also toxic to VERO cells, with IC_{50} values of 16.0, 9.9, and 17 μg/mL, respectively. The remaining tested compounds (**17**, **41**–**46**, **49**, **50**, and **53**) showed no cytotoxicity against all four cell lines at the highest test concentration of 50 μg/mL.

As discussed in a previous study by Isaka et al. 2016,[70] the artabotryol B (**37**) isolated from *A. odoratus* showed cytotoxic properties on various cell lines. The researchers found that artabotryol B (**37**) was active against KB and NCI–H187 cell lines but at lower IC_{50} values. Furthermore, artabotryol B (38) was toxic to VERO cells, with an IC_{50} of 9 μg/mL, twice as toxic as the findings of Pimjuk et al. (2015).[73] These results imply that artabotryol B (**37**) is more toxic to normal VERO cells than the tested cancerous cell lines.

3.3.4. Antiviral Properties

A recent patent application by Tassaneetritap et al. (2021)[161] reported on the antiviral properties of an aqueous extract of *A. asiaticus* against various types of Herpes Simplex Virus (HSV), including Herpes Simplex Virus 1 (HSV-1), Herpes Simplex Virus 2 (HSV-2), and Acyclovir-resistant Herpesvirus 2 (HSV-2 ACV). Acyclovir is a commonly used antiviral medication for treating symptoms caused by HSV-1 and HSV-2 viruses. The study highlighted the antiviral activity of *A. asiaticus* against *Enterovirus* 71 (EV–A71) and Coxsackie virus A16 (CAV16), which are responsible for hand, foot, and mouth disease (HFMD). The results showed that the aqueous extract of *A. asiaticus* can inhibit the attachment of HSV-1, HSV-2, and HSV-2 ACV to host cells (VERO cells). At a concentration of 62.50 μg/mL, the extract inhibited approximately 80% of the attachment of HSV-1 and HSV-2 to the tested VERO cells. This was in comparison to the positive control acyclovir, which had an IC_{10} value of 0.2 μg/mL. For HSV-2 ACV, 125 μg/ml of the extract was required to inhibit 50% of attachment, while 100% inhibition was observed for all three viruses at 500 μg/mL.[161] These findings suggest that the aqueous extract of *A. asiaticus* can prevent viruses from entering and infecting the host cells through attachment.

Moreover, the study found that the aqueous extract of *A. asiaticus* can eliminate approximately 70% of HSV-1, HSV-2, and HSV-2 ACV at a concentration of 62.50 μg/mL. All three viruses were completely eradicated at a 500 μg/mL concentration. This indicates that the extract can effectively eliminate these enveloped viruses and prevent potential infections caused by them. At 125 μg/mL, the extract can completely block the entrance of HSV-1, HSV-2, and HSV-2 ACV into the host cells. At 500 μg/mL, the extract from *A. asiaticus* completely inhibited HSV-1 replication. For HSV-2 and HSV-2 ACV, the extract inhibited ~65% of viral replication at the same concentration.

The authors also showed that the aqueous extract of *A. asiaticus* can be co-administered with acyclovir to effectively inhibit the replication of HSV-1 and HSV-2 viruses at lower concentrations. The study found that a combination of 300 μg/mL (IC_{65}) of *A. asiaticus* and 0.2 μg/mL of acyclovir (IC_{10}) can synergistically inhibit 82.5% of HVS-1 replication. In comparison, 500 μg/mL (IC_{65}) of *A. asiaticus* combined with 0.2 μg/mL of acyclovir (IC_{10}) can completely inhibit HVS-2 replication. Additionally, the study found that a combination of 300 μg/mL (IC_{20}) of *A. asiaticus* and 12.5 μg/mL of Acyclovir (IC_{10}) can synergistically inhibit 72% of HSV-2 ACV replication. They observed that HSV-1 and HSV-2 can develop resistance to acyclovir without the aqueous extract of *A. asiaticus*. They also showed that the aqueous extract of *A. asiaticus* can completely inhibit viral replication of EV–A71 and CAV16 (100%) at 400 μg/ml. Furthermore, the aqueous extract of A. asiaticus had no detectable toxicity effect on the Vero cell line, even at a dosage as high as 2000 μg/ml.

As mentioned above, the aqueous extracts of *A. hygrometricus* and *A. odoratus* a rich source of bioactive polysaccharides.[47,62–64,72] Similarly, potential bioactive polysaccharides, waiting to be discovered, may be responsible for the reported antiviral activities of the active aqueous extract of *A. asiaticus.*

3.3.5. Antimalarial Properties

Isaka et al. (2017)[74] tested their isolated compounds against *P. falciparum* K1, a multi-drug-resistant strain of malaria. Only astraeusin M (**48**) showed antimalarial activity, with an IC_{50} value of 3.0 μg/mL, while the other compounds showed no activity at the highest test concentration of 10 μg/mL. Based on the World Health Organization (WHO) guidelines,[159] astraeusin M (**48**) would be considered highly active ($IC_{50} < 5$ μg/mL). However, according to the categories developed by Lemma et al. 2017,[160] astraeusin M (**48**) would only be considered moderately active. The positive control, dihydroartemisinin (Mefloquine), displayed an IC_{50} of 0.79 ng/mL against *P. falciparum* K1. Astraeusin M (**48**) was toxic to VERO cells at an IC_{50} of 16 μg/mL, with a safety index of 5.3. Furthermore, the antimalarial activity of astraeusin M (**48**) is comparable to that of astraodorol synthetic derivative **36a–g** (Figure 7).[149] However, the working mechanism is yet to be determined in future studies.

3.4. Astraeus Pteridis

There is no evidence to suggest that *A. pteridis* has been used as traditional medicine or as food. In comparison to the three previously discussed *Astraeus* species, *A. pteridis* has been the least studied in terms of its biological properties. Table 7 summarises the biological activities of extracts and isolated compounds of *A. pteridis.*

3.4.1. Anti-Tuberculosis

In 2007, a study by Stanikunaite et al.[163] investigated the crude extract of *A. pteridis* collected in Oregon, North America, for its antimicrobial, antimalarial, antioxidant, anti-inflammatory, anti-tuberculosis and anticancer properties. The 95% and 70% ethanolic extracts were inactive in all assays except for the anti-tuberculosis assay. The study found that the 95% ethanolic extract is active against *M. tuberculosis* H37Rv (ATCC 27294) with an IC_{50} of less than 20 μg/mL. The 70% ethanolic extract is moderately active with an IC_{50} value of 20–50 μg/mL.

The team conducted a follow-up investigation on an active 95% ethanolic extract[75] by evaluating isolated compounds for their activity against *M. tuberculosis* H37Rv. They found that astrahygrone (**1**), 3-epi-astrahygrol (**3**) (Figure 1) and 3-epi-astrapteridiol (**56**) (Figure 4) exhibited moderate activity, with MIC values of 64.0, 58.0 and 34.0 μg/mL, respectively, compared to positive control rifampin with MIC ranges of 0.06–0.125 μg/mL. These results are comparable to the anti-tuberculosis activity of astraodoric acids A (**15**) and B (**16**) [(MIC) values of 50 and 25 μg/mL, respectively] reported by Arpha et al. (2012).[69] However, hypaphorine (**22**), astrapteridone (**54**) and astrapteridiol (**55**) showed no activity (MIC of > 64 μg/mL). Furthermore, none of the isolated compounds exhibited cytotoxicity to VERO cells up to 100 μg/mL.

Astrahygrone (**1**) and 3-epi-astrahygrol (**3**) are compounds that were also found in *A. hygrometricus*.[58] Nasomjai et al. (2014) tested the antimalarial activity of synthetic astrahygrone (**1**) against *P. falciparum* (K1, multidrug-resistant strain) and its cytotoxicity activity against KB, MCF-7, and NCI–H187 cell lines. They also tested its toxicity against VERO cells.[149] However, astrahygrone (**1**) was inactive in all assays at a concentration of 50 μg/mL. Apart from its anti-tuberculosis activity, no other biological activities have been reported for 3-epi-astrahygrol (**3**).

Since the research conducted by Stanikunaite et al. (2007),[163] no additional studies have been reported on the biological properties of *A. pteridis.* It is important to note that despite the bioactive properties of *A. hygrometricus*, *A. odoratus*, and *A. asiaticus*, *A. pteridis* is a species that has been under-researched. This could be because *A. pteridis* has not been used as food or medicine for local communities.

3.5. Safety and Toxicity of *Astraeus mushrooms*

It is important to note that consuming wild mushrooms, including *Astraeus* mushrooms, carries potential risks. This underscores the crucial role of public safety and awareness in

Table 7. Bioactivities of extracts and isolated compounds of *A. pteridis.*

Bioactivity	Crude extract or Bioactive compound[a]	Experimental model	Finding/Active dose	Ref.
Anti-TB	95% ethanolic extract and 70% ethanolic	*In vitro* assay against *M. tuberculosis* H37Rv (ATCC27294) using micro-plate Alamar Blue assay.	95% ethanolic extract is active against *M. tuberculosis* H37Rv (ATCC 27294) with an IC_{50} of less than 20 μg/mL; 70% ethanolic extract is moderately active with an IC_{50} value of 20–50 μg/mL	[163]
Anti-TB	astrahygrone (**1**), 3-epi-astrahygrol (**3**), and 3-epi-astrapteridiol (**56**)	*In vitro* assay against *M. tuberculosis* H37Rv (ATCC27294) using micro-plate Alamar Blue assay.	astrahygrone (**1**), 3-epi-astrahygrol (**3**) and 3-epi-astrapteridiol (**56**) are active against *M. tuberculosis* H37Rv (ATCC 27294), with MIC values of 64.0, 58.0 and 34.0 μg/mL, respectively	[75]

[a] Refer to Figures 3 and 4 for more information on bioactive compounds.

managing their gathering and consumption. An edible mushroom is defined as one that is safe and suitable for consumption. There is ample evidence that *A. hygrometricus, A. odoratus*, and *A. asiaticus* have been sold and consumed as food in many parts of Asia.[26,27,36,37,48,68]

A revised evidence-based classification system for categorising mushroom edibility has been established with greater clarity by Li et al.[164] The system classifies mushrooms based on 2,786 taxa and 9,783 case reports into four categories: E1 for edible and confirmed, E2 for edible with conditions, E3 for edible uncertainty, and P for poisonous. *A. hygrometricus* has been classified as E2, indicating that it can be consumed after being cooked or prepared in a way that makes it safe to eat.

Sing et al. (2020)[68] conducted a study investigating the proximate nutritional composition and taste-imparting components in *A. hygrometricus* mushrooms growing wild in India. The analysis revealed that trace elements such as copper (Cu) and zinc (Zn), as well as toxic elements[165] like arsenic (As), mercury (Hg), cadmium (Cd), chromium (Cr), nickel (Ni) and lead (Pb), were not found in *A. hygrometricus*. The authors suggested that *A. hygrometricus* is safe and can provide health benefits attributed to minerals.

The safety of extracts and isolated compounds of *A. hygrometricus* is discussed in the following. Badshah et al. (2015)[79] conducted a toxicity test on the methanolic extract of *A. hygrometricus* using the brine shrimp lethality test. They found that the LC_{50} value was 19.0 μg/mL, lower than the LC_{50} value of the reference drug ampicillin trihydrate, which is 16 μg/mL. These values indicate that the methanolic extract of *A. hygrometricus* is relatively safe. Pal et al. (2021, 2024)[66,133] demonstrated that the extracts from *A. hygrometricus* are non-toxic to healthy human PBMC cells. The methanol and ethyl acetate extracts had minimal effect on cell growth, even at the highest test concentration (100 μg/mL). The authors concluded that the extracts are safe for PBMC cells.

Mallick et al. (2009, 2010)[127,128] demonstrated that polysaccharide AE2-(**14**) isolated from *A. hygrometricus* showed no sign of hepatotoxicity and spleen toxicity in AE2 (20 mg/kg)-treated mice. These findings suggest that polysaccharide AE2-(**14**) is safe for use. Astrakurkurone (**4**) and astrakurkurol (**5**) are the two major terpenoids isolated from *A. hygrometricus*. Mallick et al. (2016)[143] estimated the LC_{50} value of astrakurkurone (**4**) against murine splenocytes at a high dose of 250 μg/ml (531.1 μM). Dasgupta et al. (2019)[134] further showed that astrakurkurone (**4**) had no toxicity in the normal liver cell (Chang liver) line, even at the highest dose of 250 μM. Nandi et al. (2019)[136] demonstrated that when astrakurkurol (**5**) was administered at a concentration of approximately 30 μM, the cell viability of Chang liver and PBMC cells was higher than 90%.

The safety or toxicity of *A. odoratus*, *A. asiaticus*, or *A. pteridis* can be determined by their edibility in local communities over the years through traditional knowledge. Unlike *A. hygrometricus*, there is a lack of systematic classification of their edibility. Analytical data on trace and toxic elements are unavailable for *A. odoratus*, *A. asiaticus*, or *A. pteridis*, making it difficult to conclude the potential health risks of consuming these mushrooms. However, their safety or toxicity may be assessed based on the existing biological data on extracts and isolated compounds.

Phadannok et al. (2020)[148] discovered that the hexane fractions of *A. odoratus* and *A. asiaticus* are non-toxic to normal L6 myotubes (muscle cells). They observed increased cell viability (> 120%) when treated with extracts of *A. odoratus* and *A. asiaticus* at 200 and 400 ug/mL concentrations, respectively, using the MTT assay. Additionally, in the study by Tassaneetritap et al. (2021),[161] it was shown that the aqueous extract of *A. asiaticus* had no detectable toxic effects on the Vero cell line, even at a dosage as high as 2000 μg/mL.

The majority of compounds isolated from *A. odoratus* showed little to no toxicity towards VERO cells, even at the highest test concentration of 50 μg/mL. However, artabotryol B (**37**) was toxic to VERO cells, with an IC_{50} value of 9 μg/mL.[70] Similarly, most of the compounds from *A. asiaticus* showed minimal to no toxicity to normal VERO cells at 50 μg/mL.[73,74] However, specific compounds such as artabotryol B (**37**), astraeusin M (**48**), astraeusin P (**51**), and epi-inotodiol (**52**) were found to be toxic to VERO cells with IC_{50} values of 17.95, 16.0, 9.9, and 17 μg/mL, respectively.

In the case of *A. pteridis*, its isolated compounds were non-toxic against VERO cells at 50 μg/mL. Notably, the compounds found in *A. odoratus*, *A. asiaticus*, and *A. pteridis* are present in very low concentrations. For example, the concentrations of artabotryol B (**37**) are around 0.03%[70] and 0.024%[73] in *A. odoratus* and *A. asiaticus*, respectively.

These findings have highlighted the potential non-toxic nature of these *Asatraeus* species. However, concerns such as safety and awareness in their gathering and consumption should be carefully considered since there are always potential risks in consuming wild mushrooms.

4. Conclusions

The nutritional composition of *A. hygrometricus*, *A. odoratus*, and *A. asiaticus* suggests that these mushrooms are rich sources of minerals, proteins, both digestible and non-digestible carbohydrates, unsaturated fatty acids, and amino acids. Therefore, they have the potential to be classified as functional foods that offer significant health benefits. However, more research is needed to determine the nutritional profile of *A. pteridis* and realise its potential health benefits. Unfortunately, these mushrooms are not readily available to the general public due to their scarcity, emphasising the need for further research into their sustainable cultivation. Such cultivation could bring about substantial social, commercial, and environmental benefits. Additionally, growing these mushrooms commercially would help reduce the environmental impact by decreasing the need for wild harvesting.

This review presents a comprehensive discussion of the bioactive properties and possible mode of action of *Astraeus spp* extracts and isolated compounds, including antioxidant, anti-inflammatory, antidiabetic, anticancer, anti-tuberculosis, antimalarial, antiviral, and antileishmanial activities. Addition-

ally, the review explores the potential benefits of these compounds for metabolic and cardiovascular health as well as immune function. It further highlights the significance of the biological potential of isolated bioactive compounds such as sugar alcohols, polysaccharides, steroids and lanostane triterpenoids. It emphasises the need for further research into the phytochemistry of *Astraeus* mushrooms, which has not been explored thoroughly. It also highlights the nontoxic nature of mushroom extracts in *in vitro* studies, considering their long history of safe consumption as food. These findings are particularly significant in the context of drug safety and effectiveness, suggesting that these mushrooms could hold promise for nutraceutical or therapeutic applications. However, further research is needed to ensure their efficacy and safety, particularly in terms of drug stability, formulation, and metabolism.

List of Abbreviations

AAE	Ascorbic acid equivalent
ADP	adenosine diphosphate
Akt	Serine/threonine kinase or serine/threonine kinase (PKB)
AMPK	Adenosine-monophosphate-activated protein kinase
ANF	Atrial natriuretic factor
AngII	Angiotensin II
Bax	Proapoptotic protein
BW	body weight
CAV16	Coxsackie virus A16
CCK	Cholecystokinin
CE	Catechin equivalents
DMSO	Dimethyl sulfoxide
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EC_{50}	Half-maximal effective concentration
EV–A71	Enterovirus 71
FAs	Fatty acids
FRAP	ferric reducing potential
GAE	gallic acid equivalents
GI	glycaemic index
GLP-1	Glucagon-like peptide-1
GLUT-1	Glucose transporter type-1
GLUT-4	Glucose transporter type-4
HDL	High-density lipoprotein
HFMD	hand, foot and mouth disease
HSV	Herpes simplex virus
HSV-2ACV	Acyclovir-resistant HSV-2 strain
IC_{50}	Half-maximal inhibitory concentration
Ikk	IκB kinase
IL-1	Interleukin-1
IRS-1	Insulin receptor substrate-1
LC_{50}	Half-maximal lethal concentration
LDL	Low-density lipoprotein
MAPK	Mitogen-activated protein kinase
β-MHC	β-myosin heavy chain
MIC	Minimum inhibition concentration
NADH	Nicotinamide adenine dinucleotide H
NF-kB	Nuclear factor kappa B
NMR	Nuclear magnetic resonance
PBMCs	Peripheral blood mononuclear cells
PGE2	Prostaglandin E2
PI3k	phosphatidylinositol 3-kinase
QE	quercetin equivalents
ROS	Reactive oxygen species
SI	Safety index
TAC	Total antioxidant capacity
T2D	Type 2 diabetes
TE	Trolox equivalent
TFC	Total flavonoid content
TLC	Thin-layer chromatography
TLR9	Toll-like receptor-9
VERO	African green monkey kidney fibroblasts

Author Contributions

Alison Ung: Conceptualisation, methodology, validation, formal analysis, data curation, writing-original draft preparation, reviewing and editing. Hui Chen: formal analysis, reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interests

The author declares no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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