REVIEW ARTICLE

# Pharmacological Potential of *Inonotus Obliquus:* An Integrative Review of Antitumour, Immunomodulatory and Anti-Inflammatory Effects

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## Abstract

*Inonotus obliquus* (Chaga mushroom), long used in traditional medicine, has recently gained substantial scientific attention due to its diverse pharmacological activities. While numerous preclinical studies exist, the lack of a comprehensive understanding of its molecular mechanisms continues to hinder clinical translation. This review summarises current evidence on the antitumour, immunomodulatory, anti-inflammatory and antioxidant effects of *I obliquus*, with emphasis on the underlying cellular pathways. The pharmacological activity of Chaga is mediated by a complex array of bioactive compounds that collectively induce apoptosis and cell-cycle arrest in cancer cells, modulate the complement system, suppress pro-inflammatory mediators in macrophages and enhance antioxidant defence mechanisms. These effects result from multifactorial and often synergistic interactions with key signalling cascades, including nuclear factor-kappa B (NF-kB), mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways. Although experimental data are promising, the translation of *I obliquus* from a traditional remedy into standardised therapeutic formulations is constrained by chemical variability and a lack of robust clinical validation. Continued multidisciplinary research is essential to elucidate its pharmacological potential and to position Chaga as a valuable source of novel therapeutic agents in modern medicine.

**Key words:** Chaga mushroom; *Inonotus obliquus*; Antitumour effects; Anti-inflammatory agents; Phytochemicals; Biological products; Pharmacology.

## Introduction

The pervasive and growing incidence of chronic and oncological diseases constitutes a significant global health crisis. Epidemiological data from 2022 reveal approximately 20 million new cancer diagnoses and 9.7 million cancer-related fatalities worldwide, with projections for 2025 estimating over 2 million new cases and more than 600,000 deaths in the United States alone.[1, 2] Beyond the realm of oncology, chronic inflammatory conditions represent a substantial contributor to global mortality, accounting for roughly three-fifths of all deaths, encompassing ailments like cerebrovascular accidents, cardiac pathologies and metabolic disorders, for example, diabetes.[3–5] Concurrently, the global prevalence of autoimmune diseases is experiencing an upward trend, with an approximate annual increase of 19.1 %.[6]

Although established therapeutic strategies: chemotherapy, surgical interventions, radiation therapy and targeted pharmacotherapy, form the core of contemporary medical practice of anti-cancer therapy, their utility is frequently circumscribed by dose-dependent adverse effects, considerable inter-individual response heterogeneity and the pervasive challenge of developing therapeutic resistance.[7] These persistent limitations underscore an urgent imperative to investigate novel biologically active compounds, particularly those originating from natural sources, which often exhibit diverse pharmacological profiles coupled with potentially superior safety margins.

Within the vast array of natural products, *Inonotus obliquus (Ach ex Pers) Pilát, Hymenochaetaceae*, widely recognised as the Chaga mushroom, has emerged as a subject of considerable scientific inquiry. Its historical veneration in traditional medicinal practices across Eastern Europe and Asia, attributed to a spectrum of perceived health benefits.[8, 9] It is now being systematically validated by contemporary research that seeks to unravel the intricate molecular mechanisms underpinning its diverse biological actions.[10] Chaga is notably rich in a variety of potent bioactive constituents: polysaccharides, triterpenoids, polyphenols and melanin, which collectively confer its well-documented antioxidant, anti-inflammatory, immunomodulatory and antineoplastic properties.[11, 12] Recent investigations underscore its therapeutic promise; for instance, Chaga extracts have exhibited cytotoxic effects against breast cancer cells and impeded oral cancer cell proliferation by disrupting the cell cycle.[13, 14] Furthermore, specific triterpenoid compounds isolated from Chaga have demonstrated direct cytotoxicity towards various cancer cell lines, suggesting their potential as synergistic agents in conjunction with conventional cancer therapies.[15] The anti-inflammatory capabilities of *I obliquus* are also a focal point of ongoing research, with studies exploring its capacity to modulate immune responses and attenuate inflammatory cascades.[16]

Despite the accumulating evidence substantiating the therapeutic promise of *I obliquus*, a holistic and integrated comprehension of the exact molecular mechanisms underpinning these observed effects continues to be an active frontier of scientific inquiry. The complex interplay among its diverse bioactive constituents and their specific interactions with cellular signalling pathways, immune system modulation and oxidative stress responses necessitates more profound elucidation. Furthermore, inherent challenges as compositional variability, the absence of stringent standardisation and cultivation protocols and the potential instability of metabolites within *I obliquus* extracts pose considerable impediments to their consistent reproducibility and subsequent pharmaceutical development.[17]

This review endeavours to systematically analyse and synthesise the contemporary scientific literature concerning the molecular mechanisms that govern the antitumour, immunomodulatory and anti-inflammatory properties of *Inonotus obliquus*. Aim of this study was to establish a scientific foundation that will guide future research, particularly in optimising the production, standardisation and clinical translation of *I obliquus*-derived compounds.

## Methods

A systematic literature search was conducted across *Scopus, Web of Science, PubMed, Google Scholar* and *eLibrary* to identify relevant studies. The search strategy employed a combination of keywords including: “Chaga mushroom”, “Inonotus obliquus”, “bioactivity”, “anticancer effects”, “immunomodulation” and “anti-inflammatory properties” – all within *Inonotus obliquus* theme (Figure 1).

Retrieved citations were managed using reference software for deduplication. Initial screening of titles and abstracts, followed by full-text review, identified studies relevant to the antitumour, immunomodulatory and anti-inflammatory actions of *I obliquus*. Inclusion criteria prioritised original research, systematic reviews and meta-analyses on English published between 2020 and 2025, focusing on molecular mechanisms. Exclusion criteria: non-peer-reviewed articles, conference abstracts without full papers and editorials; studies not directly related to the pharmacological mechanisms of *Inonotus obliquus*; articles published in languages other than English; duplicate publications. Data extraction concentrated on specific *I obliquus* compounds, experimental models, observed effects and proposed mechanisms of action.

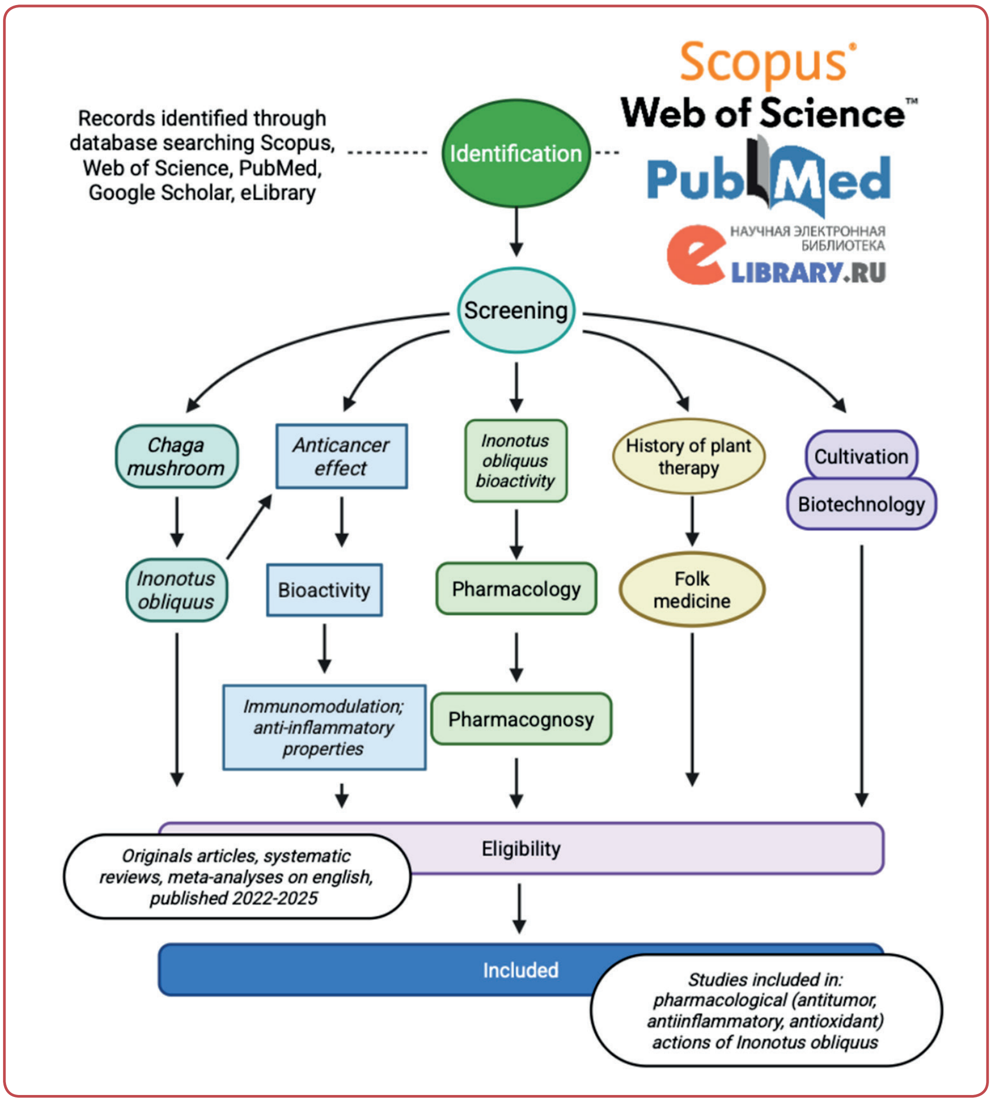


*Figure 1: Schematic representation of the systematic literature search*

## Chemical composition as the basis of pharmacological activity

The pharmacological efficacy of *Inonotus obliquus* is intrinsically linked to its diverse and complex phytochemical composition. The sterile conk of this fungus serves as a rich reservoir of biologically active compounds, encompassing a distinctive chromogenic polyphenol-carbon complex, various pigments, resins, an array of triterpenoids (including inotodiols), polysaccharides, sterols and organic acids.[18, 19] Furthermore, its mineral content, which can constitute up to 12.3 % of its dry mass, includes essential elements such as aluminium (Al), iron (Fe), silicon (Si), potassium (K), manganese (Mn), zinc (Zn) and sodium (Na).[20] This intricate blend of constituents collectively underpins the broad spectrum of therapeutic effects attributed to *I obliquus* (Table 1).

*Table 1: Main groups of biologically active compounds and pharmacological profiles of the Inonotus obliquus*

| Bioactive compounds | Pharmacological activity | References |
|---|---|---|
| Polysaccharides | Antitumour, anti-inflammatory, antiviral, antioxidant, immunomodulatory, hypoglycaemic, hypolipidaemic, hepatoprotective and others | 21 – 24 |

| | | |
|---|---|---|
| **Polyphenols** | Antioxidant | 25 |
| **Triterpenoids** | Antitumour, anti-inflammatory, antiviral and antioxidant | 26 – 28 |
| **Melanin** | Antioxidant, anti-inflammatory, antiviral, hypolipidemic and immunomodulatory | 29, 30 |

## Triterpenoids

Triterpenoids, including lanostane-type compounds (ie trametenolic acid, inotodiol and obliquol), represent another critical class of bioactive compounds, typically found in concentrations ranging from 0.3 – 0.6 %.[31] These compounds have potent cytotoxic effects against various cancer cell lines, positioning them as promising candidates for adjunctive cancer therapies.[15] For instance, research by Yeo et al demonstrated that ergosterol peroxide – a prominent triterpenoid found in Chaga, exhibits significant anticancer activity by suppressing the β-catenin pathway, thereby impeding oral cancer cell progression.[13] Further investigations by Wang et al indicate that Chaga triterpenoids can effectively inhibit dihydrofolate reductase and synergistically enhance the efficacy of conventional breast cancer treatments.[32] Beyond their antineoplastic actions, the anti-inflammatory and immunomodulatory attributes of these triterpenoids are well-documented. Studie by Shen et al have revealed their capacity to modulate macrophage polarisation and influence the expression of inflammatory mediators, highlighting their multifaceted therapeutic potential.[33]

## Polysaccharides

Polysaccharides, predominantly β-glucans, are a cornerstone of *I obliquus* bioactivity, typically comprising 6 – 8 % of its mass.[34] These macromolecules are recognised for their potent immunomodulatory and antineoplastic properties. Recent investigations highlight that specific water-soluble polysaccharides, like AcF1 and AcF3, derived from Chaga, can effectively activate macrophages, thereby initiating crucial antitumour responses and demonstrating significant potential in cancer immunotherapy.[35] Moreover, *I obliquus* polysaccharides (IOPs) have been shown to mitigate inflammatory processes by substantially reducing nitric oxide (NO) production and downregulating the expression of pro-inflammatory cytokines in cellular models.[36] Their immunomodulatory actions extend to modulating splenic lymphocyte activity through the nuclear factor-kappa B (NF-kB) and mitogen-activated protein kinases (MAPKs) signalling pathways, underscoring their complex interaction with the host immune system.[37]

## Other bioactive compounds

Beyond the well-characterised polysaccharides and triterpenoids, *I obliquus* is a rich source of numerous other pharmacologically active molecules (Figure 2). The distinctive melanin complex, responsible for the mushroom's characteristic dark pigmentation, has been shown to possess

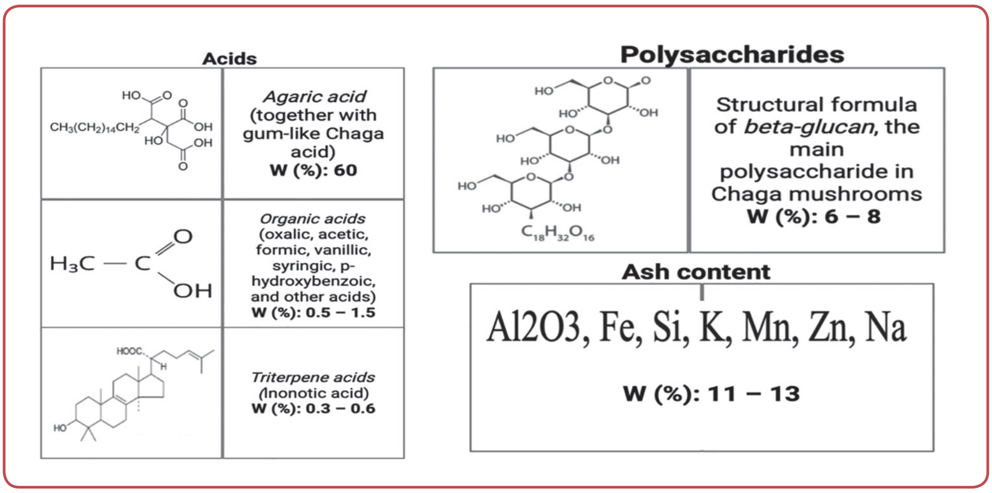


*Figure 2: Molecular structures of the principal bioactive compounds of Inonotus obliquus and their relative mass proportions*

substantial antioxidant, anti-inflammatory and immunomodulatory properties.[38] Furthermore, the fungus contains a diverse array of organic acids: oxalic, acetic, vanillic and *p*-hydroxybenzoic acids and other, which collectively contribute to its overall bioactivity. Notably, agaricic acid is present in significant proportions, approximately 60 %.[28] Emerging research, such as that by Hao et al and Fordjour et al, has also brought attention to a distinct class of styrylpyrone pigments. While their role is still under extensive investigation, there is a growing hypothesis that their biological activity may be comparable to that of plant flavonoids, suggesting another layer of therapeutic potential within *I obliquus*.[36, 39] This broad and varied chemical arsenal collectively contributes to the wide spectrum of therapeutic effects observed in *Inonotus obliquus*.

# Pharmacological action of *Inonotus obliquus*

## Signalling pathways modulation for antitumour activity

The antitumour potential of *Inonotus obliquus* metabolites has been extensively investigated, revealing a multifaceted action that extends beyond mere cytotoxicity to intricate modulation of cellular signalling pathways. Extracts and isolated compounds from *I obliquus* have demonstrated significant efficacy against a diverse range of malignancies: breast adenocarcinoma, colorectal carcinoma, lymphoma, leukaemia and lung adenocarcinoma.[16, 21]

One prominent mechanism involves the induction

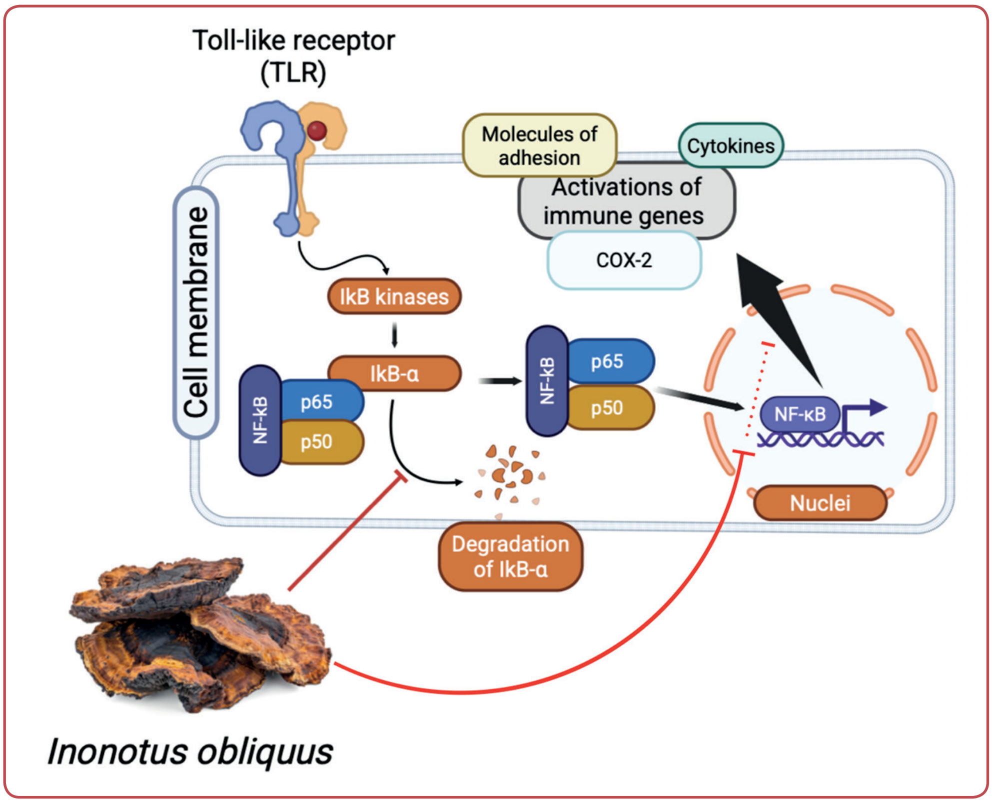


*Figure 3: Schematic representation of the potential modulatory effect of Inonotus obliquus (Chaga mushroom) on the NF-kB signalling pathway. The figure illustrates the hypothesised mechanism by which I obliquus bioactive compounds inhibit the activation of the NF-kB pathway via suppression of IkB-α degradation and IkB kinase activity, leading to reduced nuclear translocation of NF-kB (p65/p50) and subsequent downregulation of pro-inflammatory cytokines and adhesion molecules.*

*TLR – Toll-like receptor; NF-kB – nuclear factor kappa-B; IkB-α – inhibitor of nuclear factor kappa-B-alpha; COX-2 – cyclooxygenase-2; red arrows indicate points of application (inhibition);*

of apoptosis (a programmed cell death pathway crucial for eliminating cancerous cells. Aqueous extracts of *I obliquus* (AEIO) shown to exert cytotoxic effects on human cervical cancer (HeLa-S3) cells, with continuous administration in *in vivo* models leading to substantial tumour reduction and decreased metastatic node formation.[40, 41] Furthermore, specific polysaccharides, as α-linked fucoglucamannan endo-polysaccharide (EPIO) isolated from AEIO, have exhibited potent tumour suppressive effects, significantly inhibiting carcinoma growth and enhancing survival rates in murine models of melanoma.[42, 43]

The modulation of the cell cycle is another critical aspect of *I obliquus* antitumour activity. Methanolic and ethanolic extracts (MEIO and EEIO, respectively) were observed to effectively inhibit the proliferation of human colorectal cancer HT-29 cells by arresting the cell cycle at the G1-phase.[44] This arrest is mediated through the suppression of key cell cycle regulatory proteins, including cyclin-dependent kinases (CDK2, CDK4) and cyclin D1, while simultaneously upregulating cyclin-dependent kinase inhibitors like p21 and p27, ultimately leading to apoptotic cell death.[14, 45, 46]

Beyond direct cytotoxicity and cell cycle arrest, *I obliquus* metabolites influence various molecular signalling pathways implicated in cancer progression. Bioinformatic analyses have highlighted the role of core genes (*NFKB1, TNF, CD4, IL1B, IFNG, MMP9, MMP2, IL6* and *AKT1*), which are frequently upregulated in colorectal cancer tumour samples. High expression of IFNG, IL1B and MMP9 has been correlated with shorter survival times in colorectal cancer patients, suggesting these genes as potential prognostic biomarkers and therapeutic targets.[47–49] *I obliquus* phytochemicals may exert anticancer effects by modulating these pathways, thereby interfering with tumour growth, metastasis and immune evasion. For instance, triterpenoids and ergosterol derivatives found in Chaga are known to contribute to these effects by modulating pathways like NF-kB and AKT, which are central to cell survival, proliferation and inflammation in cancer (Figure 3).[15, 46]

## Immunomodulatory effects

The human immune system, a complex network encompassing both innate and adaptive arms, plays a pivotal role in host defence, pathogen clearance and the maintenance of immunological homeostasis. Dysregulation within this system is implicated in a wide array of pathological conditions, for example, autoimmune diseases, chronic inflammation and oncogenesis.[50, 51] Consequently, compounds capable of precisely modulating immune responses represent promising avenues for novel pharmacotherapeutic strategies. The immunomodulatory capacity of *Inonotus obliquus* is a subject of intense contemporary research, with recent studies elucidating its intricate interactions with various components of the immune system.

*Inonotus obliquus* demonstrated significant, yet often context-dependent, immunomodulatory properties. Shen et al highlighted the bilateral effects of Chaga extracts on tumour necrosis factor (TNF)-α and interleukin (IL)-1β levels in macrophages, suggesting a nuanced regulatory capacity that can either suppress or enhance immune responses depending on the cellular environment.[33] Further contemporary investigations, like those by Wang et al support the notion that *I obliquus* polysaccharides can modulate immune responses by inhibiting the TLR4 / NF-kB signalling pathway, thereby reducing the release of pro-inflammatory cytokines and contributing to immune balance.[25]

Specific fractions derived from *I obliquus* exhibit distinct modulatory actions. The melanin fraction, for example, has been shown to indirectly inhibit the complement-mediated cascade, suggesting a potential role in mitigating excessive or inappropriate complement activation that contributes to tissue damage in inflammatory and autoimmune conditions.[2] Conversely, certain triterpenoids (3β-hydroxy-8,24-diene-21-al and inotodiol) have exhibited potent activity in human complement protein fixation assays, leading to the activation of the complement cascade.[15] This dualistic effect underscores the sophisticated immunomodulatory potential of *I obliquus*, where specific bioactive components can either suppress or enhance immune responses depending on the context and the specific compound isolated.

Polysaccharides from *I obliquus* are particularly recognised for their immunostimulating activity. Wold et al demonstrated that fungal polysaccharides are potent activators of macrophages, triggering critical antitumour functions by engaging pattern recognition receptors (PRRs) on innate immune cells.[52] This activation leads to enhanced immune surveillance and pathogen clearance.

Similarly, Zhang et al explored the immunomodulatory effects of *I obliquus* polysaccharides (IOPs) on dendritic cells, observing an upregulation of co-stimulatory molecules and cytokine production, which are crucial for initiating adaptive immune responses.[53] The ability of IOPs to modulate splenic lymphocyte activity through NF-kB and MAPKs signalling pathways further emphasises their complex interaction with the host immune system, as reported by Sang et al.[37] These findings collectively underscore the significant promise of *I obliquus* polysaccharides as natural immunomodulators with potential applications in cancer immunotherapy and infectious disease management.

## Anti-inflammatory activity

Chronic and dysregulated inflammation is a fundamental pathological process underlying numerous diseases like autoimmune disorders, metabolic syndromes and various chronic conditions.[54] Macrophages, as pivotal immune cells, play a central role in orchestrating inflammatory responses.[55] Upon activation by pro-inflammatory stimuli such as lipopolysaccharide (LPS) and interferon-gamma (IFNγ), macrophages adopt a pro-inflammatory phenotype, characterised by the release of potent inflammatory mediators, including cytokines (eg TNF-α, IL-8, IL-6, IL-12, IL-1β etc) and nitric oxide (NO).[56, 57] Excessive NO production, mediated by inducible nitric oxide synthase (iNOS), is a key contributor to chronic inflammation and the pathogenesis of many inflammatory disorders.[58] Consequently, compounds capable of inhibiting NO synthesis and modulating inflammatory cascades are of significant therapeutic interest.

Recent research by Alhallaf et al indicated that various Chaga extracts possess anti-inflammatory activity in LPS-stimulated RAW 264.7 cells, highlighting their potential to mitigate inflammatory responses.[36] The anti-inflammatory mechanisms of *I obliquus* are multifaceted, involving the modulation of various signalling molecules and pathways. For instance, certain melanin fractions and triterpenoids – 3β-hydroxy-8,24-diene-21-al and inotodiol, have been shown to attenuate the inflammatory response by reducing the production of NO.[15]

Beyond direct cytokine and NO modulation, *I obliquus* also influences other critical inflammatory pathways. Fu et al explored the anti-inflammatory and immunomodulatory properties of *I obliquus* polysaccharides in rheumatoid arthritis, suggesting their involvement in complex signalling networks.[59] Furthermore, Peng et al demonstrated that Chaga intervention significantly reduced the enrichment of NK T-cells and Treg in inflammatory signalling pathways in a model of folic acid-induced renal fibrosis, indicating a broader impact on immune cell subsets and their inflammatory contributions. The ability of *I obliquus* to downregulate pro-inflammatory M1 macrophages and upregulate anti-inflammatory M2 macrophages further underscores its capacity to rebalance immune responses towards a resolution of inflammation.[60] These findings collectively highlight the robust anti-inflammatory potential of *I obliquus* through its diverse chemical constituents and their intricate interactions with cellular signalling pathways.

## Antioxidant activity

Oxidative stress, characterised by an imbalance between the production of reactive oxygen species (ROS) and the capacity of biological systems to neutralise them, is a critical factor in the pathogenesis of numerous chronic diseases (for example, cardiovascular disorders and neurodegenerative conditions).[61] The antioxidant mechanisms of *I obliquus* are multifaceted, encompassing direct scavenging of free radicals, enhancement of endogenous antioxidant enzyme activities and chelation of metal ions.[62]

Key antioxidant compounds identified in *I obliquus* include polyphenols, triterpenoids and melanins. Hao et al highlighted that styrylpyrone polyphenols, abundant in Chaga, are potent electron-donating agents, enabling them to neutralise free radicals and interrupt chain reactions of lipid peroxidation.[39] This direct scavenging mechanism is crucial for mitigating cellular damage. Furthermore, triterpenoids, including lanostanoids, contribute to antioxidant defence by modulating cellular redox status and influencing signalling pathways involved in oxidative stress responses, as demonstrated by D'Elia et al.[63] Their work suggests that these compounds can activate cellular defence mechanisms against oxidative insults.

The melanin fraction of *I obliquus* also exhibits significant radical-scavenging activity, acting as a potent antioxidant by directly quenching various ROS.[64] This broad-spectrum activity underscores the protective potential of Chaga against oxidative damage.

## Conclusion

Presented literary review elucidates the profound pharmacological landscape of Chaga mushroom, affirming its status as a compelling natural reservoir of bioactive compounds. The intricate interplay of its diverse constituents – polysaccharides, triterpenoids, polyphenols and melanins, orchestrates a potential spectrum of therapeutic actions, notably potent antitumour, sophisticated immunomodulatory, anti-inflammatory and antioxidant effects.

While the accumulated evidences advocate for the therapeutic promise of *I obliquus*, its full clinical realisation remains contingent upon addressing several critical challenges. The inherent variability in its phytochemical profile, the absence of universally standardised extraction and formulation protocols and the imperative for rigorous clinical validation represent significant hurdles. Future research must transcend descriptive observations, moving towards a deeper, integrated understanding. This necessitates precise mechanistic elucidation of individual and synergistic compound actions using advanced omics technologies, coupled with expanded preclinical models that encompass a wider array of cellular and *in vivo*, *ex vivo* systems.

## Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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## Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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