

# Anti-inflammatory and Immunomodulatory Effects of Mullein Leaf Extract on Infectious Diseases: A Review

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Received: 7/4/2026

Accepted: 26/4/2026

Published: 15/6/2026

**Abstract**— There has been considerable interest in the use of medicinal plants as possible sources of therapeutic drugs against infectious diseases, especially because of growing concerns about antimicrobial resistance. *Verbascum thapsus* (mullein) is a well-known traditional medicinal plant known for its antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory activities. This review highlights recent scientific findings related to phytochemistry, anti-inflammatory properties, and immunomodulatory action of extracts obtained from mullein leaves with special focus on their possible application in the treatment of infectious diseases. Various experiments conducted on mullein extracts showed that they can regulate key inflammatory pathways such as NF-kappa B and MAPK signaling, inhibiting various pro-inflammatory cytokines including TNF-alpha, IL-1beta, and IL-6, and increasing anti-inflammatory cytokines like IL-10. Besides this, numerous studies carried out in vitro and in vivo have confirmed the antimicrobial potential of mullein against both Gram positive and Gram-negative bacteria, and its antioxidant action in decreasing oxidative stress. Based on this information, it can be concluded that this species of *Verbascum thapsus* is an excellent candidate for the development of a natural remedy to combat infectious diseases. Moreover, it also has the potential for use in veterinary medicine to increase immunity and manage infections in animals. Additional studies are necessary to determine its safety, dosage, and effectiveness in treatment.

**Keywords** — *Verbascum thapsus*, mullein, immunomodulation, anti-inflammatory, medicinal plants, and infectious diseases.

## INTRODUCTION

Infectious diseases have remained one of the major causes of morbidity and mortality across the world, especially with the increasing prevalence of antimicrobial resistance (1). Synthetic antimicrobial agents have remained popular, despite their efficacy

being hampered by resistance, side effects, and availability (2). This has led to increasing interest in natural agents, especially medicinal plants, which have shown promise as alternative or complementary agents. Medicinal plants have remained a rich source of bioactive agents, such as flavonoids, phenolic acids, iridoids, and glycosides, which have shown a variety of pharmacological activities, such as antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory effects (3). These agents have shown the ability to modulate immune responses, cytokine production, and oxidative stress, thus providing support to the body's natural defenses (4).

Inflammation is one of the key body responses to infection, though too much inflammation is detrimental (5). Thus, inflammation needs to be regulated while immune responses are still effective. Immunomodulation, which is the regulation of immune responses, is one of the emerging therapies for treating infections, especially those caused by pathogens (6). Natural compounds have shown promise, especially their ability to modulate multiple targets while being non-toxic (7). *Verbascum thapsus*, or mullein, is a plant used traditionally to treat respiratory infections, cough, bronchitis, and skin infections (8). Its use in folk medicine is quite extensive; thus, its pharmacological effects have been studied (8). Recent studies have shown that *Verbascum thapsus* leaf extracts have antibacterial, antiviral, and antioxidant effects, especially due to their chemical content, such as flavonoids, saponins, and phenolics (9). Mediators like TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, as well as important signaling pathways like NF- $\kappa$ B (10). The immunomodulatory effects of the plant are believed to be mediated by the enhancement of the function of the immune cells, as well as the regulation of cytokines, including the production of more IL-10 (11). In addition, the use of mullein plant extracts was observed in experimental studies to be effective in the

inhibition of the growth of microbes while promoting the immune response in the host (12).

From the above-mentioned studies, the mullein leaf plant extract was observed to be effective in the management of infectious diseases, including inflammation, because of the regulation of the immune response in the host (13). However, more studies are still required in the future regarding the use of the plant in the management of infectious diseases. The application of medicinal plants in veterinary medicine is becoming increasingly popular in recent times (14). Various diseases, particularly infections, continue to pose significant problems in both livestock and pet animals. Furthermore, the high consumption of antibiotics in animals has led to the development of antibiotic resistance (15). Hence, the search for plant-based natural products has become more common in recent years, where bioactivity can be used to modulate the immune system and fight infections in veterinary practice (16). For instance, the phytochemical composition of *Verbascum thapsus* includes components that can boost the immune system and reduce inflammatory responses to combat infections in animals (17). This review highlights recent experimental evidence on the anti-inflammatory and immunomodulatory mechanisms of *Verbascum thapsus* and discusses its potential applications in both human and veterinary medicine. The aim of the review is to assess the anti-inflammatory and immunomodulatory effects of the mullein plant leaf, including its potential use in the management of infectious diseases.

### **Phytochemical Composition of Mullein Leaves**

The therapeutic activity of *Verbascum thapsus* (mullein) is mainly due to its wide variety of phytochemicals (11). The leaves of this medicinal herb contain various bioactive compounds like flavonoids, phenolic acids, iridoid glycosides, saponins, and tannins (11). These compounds have been reported to possess various biological activities like antioxidants, anti-inflammatory, antimicrobial, and immunomodulatory activities (18). Flavonoids are the most abundant bioactive compounds in mullein leaves (18). These compounds are responsible for detoxifying reactive oxygen species (ROS) and reducing oxidative stress that is associated with infection and inflammation (19). These compounds also regulate immune responses and inhibit inflammatory responses (13). Phenolic compounds make up another group of phytochemicals in mullein. Phenolic compounds make significant contributions to the body's antioxidant defense system. They achieve this by protecting the body from lipid peroxidation. Phenolic acids also have an impact on the body's inflammatory response. They achieve this by inhibiting pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 (20) (Table1).

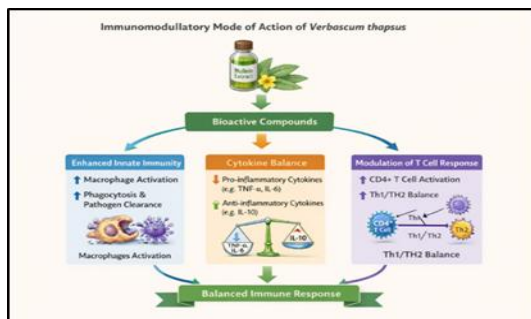
Iridoid glycosides, which include aucubin and catalpol, have also been isolated in mullein leaves. Iridoid glycosides have significant anti-inflammatory properties. They also have protective roles in the body. They achieve this by protecting body tissues from microbial infections and oxidative stress (21). Saponins make up another group of phytochemicals in mullein. Saponins have significant immunomodulatory properties. Saponins achieve this by stimulating macrophages in the body. Saponins also stimulate immune cell signaling pathways (22). (Table 1).

**Table 1.** Major Phytochemical Compounds in *Verbascum thapsus* and Their Biological Activities

no	Phytochemical Compound	Chemical Class	Biological Activity	Mechanism of Action	References
1	Quercetin	Flavonoid	Antioxidant, anti-inflammatory	Inhibits ROS and NF- $\kappa$ B activation	(19)
2	Kaempferol	Flavonoid	Immunomodulatory	Reduces inflammatory cytokines	(20)
3	Chlorogenic acid	Phenolic acid	Antioxidant	Prevents lipid peroxidation	(21)
4	Aucubin	Iridoid glycoside	Anti-inflammatory	Suppresses inflammatory mediators	(21)
5	Catalpol	Iridoid glycoside	Tissue protective	Regulates immune signaling	(21)
6	Saponins	Glycosides	Immunostimulatory	Enhances macrophage activity	(22)

### Anti-inflammatory Pathways of *Verbascum Thapsus*

The mechanism by which leaf extract of *Verbascum thapsus* exhibits its anti-inflammatory properties includes several cellular pathways that control immune response and inflammation. One of the key pathways in which this anti-inflammatory action occurs is through the modulation of nuclear factor kappa B (NF- $\kappa$ B) (8) (Figure1). When there are infections or inflammations, NF- $\kappa$ B will be activated and moved to the nucleus to stimulate the synthesis of pro-inflammatory cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 (23). The bioactive substances present in mullein can modulate NF- $\kappa$ B activity and reduce the expression of these pro-inflammatory cytokines. Besides the inhibition of NF- $\kappa$ B transcriptional activity, mullein also affects another important signaling pathway – the mitogen-activated protein kinases (MAPK) pathway (24). The downregulation of MAPK signaling leads to decreased synthesis of various pro-inflammatory mediators and enzymes such as cyclooxygenase-2 (COX-2) (25) (Figure 1). In turn, the presence of antioxidant molecules in mullein acts as an additional factor contributing to the anti-inflammatory activity of the extract due to their ability to neutralize oxidative stress (26) (Figure 1). Moreover, specific components of the plant, namely saponins and iridoid glycosides, stimulate the synthesis of anti-inflammatory cytokines, especially interleukin-10 (IL-10), thus limiting inflammation processes at the cellular level (27). All the abovementioned data confirm the involvement of multiple targets in the mechanisms of the anti-inflammatory activity of *Verbascum thapsus* (28).



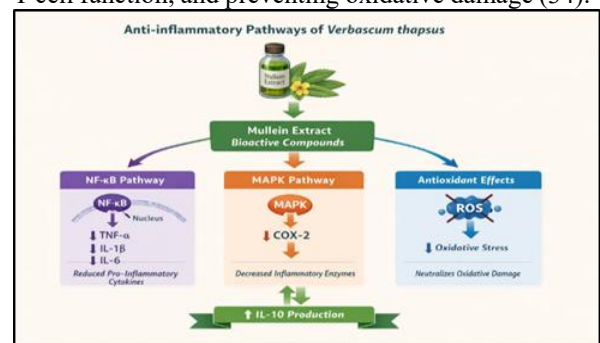
**Figure 1.** Anti-inflammatory Pathways of *Verbascum Thapsus*

### Immunomodulatory Mode of Action of *Verbascum thapsus*

The immunomodulatory properties of *Verbascum thapsus* (mullein) extract are based on their regulation of both innate and acquired immunity via various cellular and molecular pathways. Bioactive molecules like flavonoids, saponins, and iridoid glycosides act as

key mediators involved in the modulation of immune cells (29). They facilitate enhanced activation of macrophages and boost phagocytosis and pathogen clearance (30) (Figure2). Furthermore, mullein extract has been found to modulate cytokine synthesis through regulation of pro- and anti-inflammatory responses. Mullein extract decreases pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 while increasing the production of anti-inflammatory cytokines, mainly IL-10 (31) (Figure2).

Moreover, the extract influences the process of T-cell differentiation and activation, especially CD4+ T helper cells, which are crucial in facilitating immune responses (31). The phytochemicals in mullein can be said to modulate the Th1/Th2 balance, thus avoiding overreaction of the immune system and chronic inflammation (32). Additionally, the anti-oxidative nature of mullein plays an indirect role in its immunomodulatory effects due to its ability to decrease oxidative stress that interferes with the functions of immune cells (Figure 2). In scavenging free radicals, the extract ensures the efficiency of the immune response (33). These results, taken together, indicate that *Verbascum thapsus* acts via a multifaceted mechanism of action by stimulating innate immune cells, regulating cytokine network activity, modulating T cell function, and preventing oxidative damage (34).



**Figure 2.** Immunomodulatory Mode of Action of *Verbascum thapsus*

### Potential Role of *Verbascum thapsus* in Infectious Diseases

*Verbascum thapsus*, commonly known as mullein, is a medicinal plant that has been used in the treatment of various infectious diseases, including those of the respiratory tract, such as bronchitis, cough, tuberculosis, and asthma, for several centuries (8). The leaves of the plant are used in the preparation of various medicinal formulations, including teas, extracts, and syrups, due to their soothing, antimicrobial, and anti-inflammatory effects (35). Recent pharmacological studies on the plant have confirmed some of the medicinal uses of the plant by showing that it possesses significant antimicrobial,

antioxidant, and immunomodulatory effects (36). The immune system is an essential component of the body that recognizes infectious agents and eliminates them from the body. Sometimes, an imbalance in the immune system can result in excessive inflammation, which can cause tissue damage (37). Thus, an ideal drug should possess the capacity to control infectious agents as well as inflammation (37). Mullein appears to possess such effects by modulating various immune pathways that are associated with inflammation. flavonoids, phenolic acids, and iridoid glycosides, which have been known to inhibit pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and interleukin-6 (IL-6), which are responsible for inflammation in both bacterial and viral infections (27). The suppression of inflammation may be beneficial in protecting the body from further damage and in helping the body recover from infection (27). Additionally, mullein extracts have been known to have antimicrobial properties against various pathogenic microorganisms, including both Gram-positive and Gram-negative bacteria. Phenolic compounds and flavonoids present in mullein have been known to interfere with microbial cell membranes, inhibit microbial enzyme production, and interfere with microbial replication. The antimicrobial properties of mullein make it more beneficial as a natural remedy for microbial infections (26).

Mullein is especially useful in respiratory infections, as it possesses expectorant and anti-inflammatory properties. It has been shown that this plant relieves respiratory inflammation, soothes irritated mucus membranes, and helps to expel mucus from the respiratory system (8). This may help to increase respiratory efficiency and help to expel pathogens from the respiratory system (8). Another way that mullein helps to control infections involves the antioxidant properties of this plant. In any infection, the immune cells of the host produce free radicals as a defense mechanism (38). Although free radicals are useful for eliminating pathogens, they may also damage host tissues and increase the level of inflammation. The antioxidant compounds found in the leaves of the mullein plant help to neutralize these free radicals and protect host tissues from damage (39).

In addition, it has also been found to affect immune cells, which are activated through an improvement in macrophage activation and cytokine production (27). This is an important aspect of immune system balance, which is achieved through the promotion of immune responses without causing inflammation (40). This is particularly important in cases of chronic infections and inflammation (40). Therefore, considering the antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory effects of *Verbascum thapsus*, it is

possible to suggest that this medicinal plant can be used as an alternative therapeutic option in the management of infectious diseases. However, further research is required to completely understand its mechanisms of action, optimal therapeutic doses, and its safety and efficacy in humans (17).

#### **Experimental Evidence of *Verbascum thapsus***

Recently conducted experiments have brought out several interesting scientific facts about the medicinal actions of *Verbascum thapsus* (41). Mullein extracts have been proved in various vitro and vivo experiments to have good antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory properties (42). This is primarily due to the presence of several bioactive phytochemical compounds present in mullein (42). These include flavonoids, phenolic acids, iridoid glycosides, and saponins. All these phytochemicals act upon specific cellular mechanisms related to immune system function and inflammation responses (8). The in vitro experiment has shown that the extracts obtained from mullein leaves have good inhibitory potential against some pathogenic microbes (9). The extracts have been seen to exert growth suppression on Gram positive and negative bacteria like *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (13). The antimicrobial action of these extracts is mainly because of their ability to disrupt microbial cell membrane structure, inhibit microbial enzymes and interfere with bacterial metabolic processes. Moreover, it has been found that these extracts also have good antioxidant properties, where they scavenge ROS to prevent oxidation (43).

Moreover, the efficacy of *Verbascum thapsus* as a therapeutic agent has been demonstrated through in vivo experiments involving animal models. Treatment with mullein extracts was found to lower inflammatory molecules and immune responses via suppression of pro-inflammatory cytokines including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, coupled with an increase in anti-inflammatory cytokines such as IL-10. The results indicate that mullein plays a role in balancing immune responses and defending tissues against infections and inflammation (44). Several exemplary experiments investigating the biological properties of *Verbascum thapsus* are presented in Table 2.

**Table 2.** In Vitro and In Vivo Experiments for Evaluating the Bioactivities of *Verbascum thapsus*

Study Type	Plant Extract	Experimental Model	Key Findings	Reference
In vitro	Ethanollic leaf extract	<i>Staphylococcus aureus</i> , <i>E. coli</i> , <i>Pseudomonas aeruginosa</i>	Demonstrated significant antibacterial activity against both Gram-positive and Gram-negative bacteria	(13)
In vitro	Methanolic extract	Antioxidant assays (DPPH, ABTS)	Showed strong antioxidant activity due to high phenolic content	(43).
In vitro	Aqueous and ethanollic extracts	Bacterial cultures	Extract inhibited microbial growth and disrupted bacterial cell membranes	(13)
In vivo	Leaf extract	Mouse inflammation model	Reduced inflammatory mediators and improved immune response	(44)
In vivo	Phenolic-rich extract	Animal model	Decreased oxidative stress markers and improved antioxidant defense	(43)
In vivo	Plant extract	Murine immune model	Increased macrophage activity and modulated cytokine production (IL-10 increase)	(45)

### Potential Applications of *Verbascum thapsus* in Veterinary Medicine

Natural medicines have become popular among veterinarians as alternative treatment options to enhance the health of animals and prevent infectious diseases (46). One plant that has received much interest in recent years is *Verbascum thapsus*, commonly known as mullein. This plant has shown antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory activities (8). (Table3). It has traditionally been used in the treatment of respiratory conditions, skin infections, and inflammation in animals. The biological activity of this plant is attributed to flavonoids, saponins, and phenolic substances, which act as immunomodulators and help protect the body against infections (47,3)

**Table3.** Potential veterinary applications of *Verbascum thapsus*

Application	Animal Species	Biological Effect	Possible Mechanism	Reference
Respiratory disorders	Cattle, sheep	Expectorant and anti-inflammatory effects	Saponins help mucus clearance and reduce airway inflammation	(8).
Skin infections	Livestock, pets	Antimicrobial activity	Phenolic compounds disrupt microbial cell membranes	(13)
Inflammatory conditions	Farm animals	Reduction of inflammatory mediators	Inhibition of NF-κB and pro-inflammatory cytokines	(47)
Oxidative stress in infections	Various animals	Antioxidant protection	Scavenging of reactive oxygen species (ROS)	(3)
Immune support	Livestock	Immunomodulatory activity	Stimulation of macrophage activity and cytokine regulation	(3)

### CONCLUSION

*Verbascum thapsus* is a potential medicinal plant with great pharmacological potential, which results from its phytochemical constitution. Flavonoids, phenolic acids, iridoid glycosides, and saponins account for the anti-inflammatory, antimicrobial, immunomodulatory, and antioxidative properties of mullein. Experimental data on *V. thapsus* indicates that

this medicinal plant can regulate the inflammatory signaling pathways (e.g., NF-κB and MAPK), inhibiting the production of pro-inflammatory cytokines, and up-regulating IL-10 levels. The biological properties mentioned above may make *V. thapsus* a potential remedy for various types of infectious and inflammatory diseases. Furthermore, the presence of antibacterial and antifungal activity

adds to the potential use of this medicinal plant. While *V. thapsus* possesses high therapeutic potential and shows great promise in this area, more research needs

#### Acknowledgements

N/A

#### Conflict of Interest

The authors declare no conflict of interest.

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