RESEARCH PAPER

Preclinical Evaluation of Antidiuretic Potential of Verbascum Thapsus Extract in Rodent Models

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ABSTRACT

Verbascum thapsus, commonly known as mullein, is a traditional medicinal plant that has been used for many years in different parts of the world, especially for treating respiratory and urinary problems. In several traditional systems, including those practiced in Europe, Central Asia, and India, it has been associated with managing excessive urination and improving bladder function. Because of this long-standing use, it has recently gained attention in scientific research as a possible natural antidiuretic agent. This review focuses on summarizing the available preclinical studies that evaluate the antidiuretic potential of Verbascum thapsus, particularly in rodent models. Various types of extracts such as aqueous, ethanolic, methanolic, and hydroalcoholic preparations have been investigated in these studies. In many experiments, a noticeable reduction in urine output was observed along with an increase in urine concentration. Some studies also reported improvements in electrolyte balance, suggesting that the plant may help regulate fluid and mineral homeostasis in the body. However, the results are not always completely consistent, and they can vary depending on the type of extract, dose, and experimental model used.

The biological effects of Verbascum thapsus are believed to be linked to its phytochemical composition. Key compounds such as verbascoside, aucubin, catalpol, and certain saponins and flavonoids may play an important role. These constituents are thought to interact with pathways related to vasopressin activity or influence aquaporin-2 (AQP2) channels in the kidney, which are essential for water reabsorption. Even though some studies suggest these mechanisms, a clear and fully established pathway is still lacking and needs further investigation. In terms of safety, most preclinical studies have reported a relatively favorable profile, with no major toxic effects observed at commonly used doses. This supports the idea that the plant could be considered for further development. However, there is still a significant gap between preclinical findings and clinical application. Issues such as standardization of extracts, dose optimization, and detailed pharmacokinetic understanding remain unclear.

Overall, Verbascum thapsus appears to be a promising candidate for managing conditions associated with excessive urination, such as diabetes insipidus. At the same time, more rigorous studies, especially well-designed clinical trials in humans, are necessary before it can be recommended as a reliable therapeutic option.

KEYWORDS: Verbascum Thapsus, Mullein Plant, Antidiuretic Effect, Urine Reduction, Kidney Water Balance, Aquaporin-2 Channel, Vasopressin Activity, Diabetes Insipidus, Plant-Based Therapy, Herbal Pharmacology, Rodent Experiments, Natural Compounds.
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1. Introduction

The regulation of body fluid levels is largely carried out by the kidneys, which control the amount of water excreted in urine based on osmotic conditions. A major hormone involved in this process is antidiuretic hormone (ADH), or arginine vasopressin (AVP). It works through V2 receptors and promotes the activity of aquaporin-2 (AQP2) channels in the collecting ducts, allowing more water to be reabsorbed back into the body [1]. When the body either lacks enough ADH or does not respond to it properly, a condition called diabetes insipidus (DI) can develop. It is usually identified by the production of very large amounts of dilute urine along with excessive thirst. If fluid intake is not sufficient, this can also lead to serious complications such as high sodium levels in the blood (hypernatremia) [2]. In routine practice, diabetes insipidus is usually treated with desmopressin, a synthetic analogue of vasopressin that acts mainly on V2 receptors. It works well in reducing urine output in patients with central DI. However, its benefit is much less in nephrogenic cases, where the kidneys do not respond properly. Also, in some individuals, its use can be linked with side effects such as dilutional hyponatremia, reduced effectiveness over time (tachyphylaxis), and possible cardiovascular complications [3]. Due to the drawbacks of existing therapies, researchers are now paying more attention to natural substances that might offer antidiuretic effects through alternative mechanisms. These plant-based options could help

regulate kidney function in a more balanced way. Historically, Verbascum thapsus has been widely used in different traditional systems of medicine. It has been applied not only for urinary disorders but also for respiratory illnesses and inflammatory conditions, showing its long-standing medicinal relevance [4]. Classical Ayurvedic and Unani texts mention the use of mullein-based remedies for conditions like frequent urination and general bladder weakness [5]. Likewise, traditional Native American medicine has described the use of decoctions made from mullein leaves and roots to help control urinary leakage and increased frequency of urination [6]. Even though Verbascum thapsus has a long history of use in traditional medicine, the scientific evidence supporting its antidiuretic effects has not been fully reviewed in a systematic way. Most of the available studies are scattered, making it difficult to draw clear conclusions.This review has been prepared to bring together the existing preclinical findings, investigate the possible

mechanisms involved, and identify the key phytochemicals responsible for its activity. It also aims to point out areas where further research is needed, so that this plant can be better understood and possibly developed into an evidence-based option for conditions involving excessive urination [7].

2. Botanical Profile and Traditional Uses of Verbascum Thapsus

2.1 Justification of the Study

Disorders related to excessive urination, especially diabetes insipidus, continue to create challenges in clinical management because the available medicines are not always fully effective and may produce unwanted side effects during long-term use. Drugs such as desmopressin are commonly prescribed to control urine output, but their effectiveness is limited in certain conditions like nephrogenic diabetes insipidus. In some patients, prolonged therapy may also lead to complications such as electrolyte imbalance and reduced therapeutic response. Because of these limitations, there is growing interest in identifying safer and more reliable alternatives from natural sources.Medicinal plants have been used for centuries in traditional healthcare systems for the treatment of urinary disorders. One such plant is Verbascum thapsus (mullein), which has been traditionally used in Ayurvedic, Unani, European, and folk medicine for conditions associated with frequent urination and bladder weakness. Traditional knowledge suggests that the plant may help in maintaining urinary balance, but scientific evidence supporting these claims is still limited.In recent years, several experimental studies carried out in rodent models have shown that extracts of Verbascum thapsus may reduce urine output and improve water reabsorption in the kidneys. Researchers have also reported that the plant contains important phytochemicals such as verbascoside, aucubin, flavonoids, saponins, and terpenoids, which may contribute to its biological activity. Some studies further suggest that these compounds may influence vasopressin-related pathways and aquaporin-2 channels involved in renal water regulation. However, the available information remains scattered, and the mechanisms responsible for the antidiuretic effect are not yet fully understood. Another important concern is the lack of standardization among existing studies. Different researchers have used different extraction methods, doses, and experimental models, which makes comparison of results difficult. In addition, detailed safety evaluation, pharmacokinetic studies, and clinical investigations in humans are still insufficient. Therefore, there is a need to critically analyze and compile the available preclinical evidence in a systematic manner.The present review has been undertaken to summarize the existing scientific findings related to the antidiuretic potential of Verbascum thapsus, with special emphasis on its phytochemical composition, possible mechanisms of action, safety profile, and experimental evidence from animal studies. The study may help provide a clearer scientific understanding of the plant and support future research aimed at developing effective plant-based therapies for urinary disorders. [2,3,4,5,21,23]

2.2 Taxonomy and Morphological Features

Verbascum thapsus L., also known as mullein, is a biennial herbaceous species classified under the order Lamiales. It was traditionally included in the Scrophulariaceae family, but more recent classification based on molecular studies has placed it in the Plantaginaceae family. In the first year, the plant mainly grows as a cluster of broad

leaves at the base, forming a rosette. These leaves are thick and covered with tiny hair-like structures, giving them a soft and slightly fuzzy texture. In the following year, a tall flowering stalk emerges, which can reach a height of up to two meters. Along this stalk, numerous small yellow flowers are arranged in a dense spike, making the plant visually distinctive and easy to recognize [15]. Originally found in regions of Central and Southern Europe and parts of Asia Minor, Verbascum thapsus has gradually spread to many other parts of the world, including North America, Australia, and temperate zones of Asia. It adapts easily to different environments and is often seen growing in places such as roadsides, open land, and areas with disturbed soil where other plants may not grow well. The plant has even been observed in high-altitude regions like the Himalayas, at elevations close to 3,000 meters. This highlights its ability to survive under different climatic and soil conditions. Such adaptability reflects its ecological flexibility and ability to establish itself in a wide range of habitats [16]. Because of its widespread presence and distinctive features, it has been used in traditional medicine in many cultures. Its chemical composition has also attracted scientific interest in recent years. Overall, its adaptability and medicinal relevance make Verbascum thapsus a valuable plant for further pharmacological research.

2.3 Traditional Use and Ethnopharmacological Relevance

Verbascum thapsus has been used in traditional medicine across different cultures, reflecting its long history as a medicinal plant. In Central Asian Unani practices, extracts prepared from the leaves and roots have been used to manage urinary conditions such as retention, discomfort during urination, and increased urine output. Ancient Greek and Roman texts also refer to mullein, noting its astringent nature and its role in supporting bladder health. Similarly, Indigenous North American communities used the plant for kidney-related issues and frequent urination, showing its importance in their traditional healing methods. In parts of Europe, mullein tea has traditionally been given to both children and elderly individuals suffering from urinary problems like nocturnal enuresis. This suggests that it was widely regarded as a gentle and safe remedy. Beyond urinary disorders, the plant has also been used for respiratory illnesses such as asthma, bronchitis, and cough. Its calming effect helped with breathing difficulties, while its anti-inflammatory action made it useful in conditions like arthritis. Topical applications of mullein were also common, especially for wound care due to its antimicrobial effects, and its oil preparations were used to reduce ear pain. These diverse uses show that Verbascum thapsus has a broad range of traditional applications and remains of interest for further study [17]. The diverse medicinal applications of *Verbascum thapsus* can be linked to its complex chemical composition. It contains several types of bioactive compounds, including phenylethanoid glycosides, iridoids, saponins, terpenoids, and flavonoids. These components may act together to produce effects that support its traditional use in urinary, respiratory, inflammatory, and

infectious conditions. Observations from different cultural practices further strengthen its relevance and indicate that its benefits have been recognized widely over time. This makes mullein a promising subject for continued research in the field of phytotherapy and natural drug development.

3. Phytochemical Composition

The activity of *Verbascum thapsus* is largely due to its complex mixture of secondary metabolites. Analytical methods such as chromatography and spectroscopy have helped identify different types of chemical constituents found in the plant. The key phytochemical groups detected in different plant parts are listed in Table 1.

- **Table 1: Major Bioactive Compounds in *Verbascum thapsus* and Their Known Effects**

Phytochemical Class	Key Constituents	Pharmacological Activity	Reported Mechanism
Iridoid Glycosides	Aucubin, Catalpol	Antidiuretic, Anti-inflammatory	Renal tubular reabsorption modulation [8]
Saponins	Verbascosaponin	Diuretic modulation, Membrane stabilization	Aldosterone-like receptor interaction [9]
Flavonoids	Luteolin, Apigenin, Rutin	Anti-inflammatory, Antioxidant	Inhibition of pro-inflammatory cytokines [10]
Mucilage	Polysaccharides, Galactose units	Demulcent, Renal protective	Epithelial coating and tubular protection [11]
Phenylethanoid Glycosides	Verbascoside (Acteoside)	Antidiuretic, Antioxidant	Vasopressin pathway modulation [12]
Terpenoids	Oleanolic acid, Ursolic acid	Renoprotective, Antidiuretic	AQP2 channel upregulation [13]
Tannins	Condensed tannins	Astringent, Anti-inflammatory	Tubular membrane integrity [14]

Among the various compounds present in *Verbascum thapsus*, verbascoside (acteoside) has gained particular attention due to its pharmacological importance. It is a phenylethanoid glycoside with amphiphilic properties, meaning it can associate with both aqueous environments and lipid membranes. This allows it to interact effectively with receptor binding sites and cellular structures [12]. Compounds from the iridoid glycoside group, such as aucubin and catalpol, have been reported to act on renal tubular function in different studies. These substances may play a role in regulating the urine-concentrating mechanism of the nephron [8].

Saponins present in *Verbascum thapsus* have a structure that is somewhat similar to steroid hormones. This suggests that they might affect mineralocorticoid or aldosterone-related pathways, potentially altering sodium and water reabsorption processes in renal tissues [9]. Among the terpenoids identified in *Verbascum thapsus*, oleanolic acid and ursolic acid—primarily detected in the leaf portion—have shown the ability to enhance AQP2 expression in kidney collecting duct cells. This action is believed to be linked to transcriptional pathways regulated by PPAR gamma [13]. The mucilage-type polysaccharides found in *Verbascum thapsus* appear to play a protective role in the renal tubular epithelium. They may help limit inflammatory injury, which

otherwise can interfere with the tubules' capacity to reabsorb water efficiently [11].

4. Mechanisms Underlying Antidiuretic Activity

4.1 Vasopressin-Related Mechanisms

Water reabsorption in the kidneys is mainly regulated through vasopressin (AVP), which binds to V2 receptors on the basolateral membrane of collecting duct cells. This binding activates adenylyl cyclase, leading to an increase in cAMP within the cell. The elevated cAMP then stimulates protein kinase A (PKA), which in turn promotes the movement of AQP2 channels from intracellular vesicles to the apical surface. This process enhances water permeability and supports efficient water conservation. Research also indicates that verbascoside can partially activate V2 receptors. Radioligand binding studies using tritiated AVP have provided evidence for this effect in renal medullary membranes. Even though its binding is weaker than endogenous vasopressin, it may still result in a controlled antidiuretic response. This property could help reduce the risk of overstimulation that may occur with higher doses of desmopressin.

4.2 Aquaporin-2 (AQP2) and Its Regulation

AQP2 acts as a key water channel in the collecting ducts and is crucial for maintaining proper urine concentration. Its regulation occurs at both the gene level and after the protein is formed, including its transport and placement within the cell. A decrease in AQP2 expression or problems in its proper localization can impair water reabsorption in the kidneys. This forms the main pathological basis of nephrogenic diabetes insipidus. Such alterations are also linked with conditions like lithium toxicity, hypokalemia, and chronic kidney disorders, which are often associated with excessive urination [19]. In experimental studies conducted on Sprague–Dawley rats, administration of a hydroalcoholic extract of *Verbascum thapsus* led to a noticeable increase in AQP2 expression within the renal medullary region.

This effect was observed at both the gene and protein levels, based on results obtained from qRT-PCR and Western blot methods [23]. These results point toward a transcription-based mechanism that is different from the conventional AVP–cAMP–PKA pathway, which mainly affects protein trafficking. This implies that the extract may act at multiple stages involved in the regulation of AQP2.

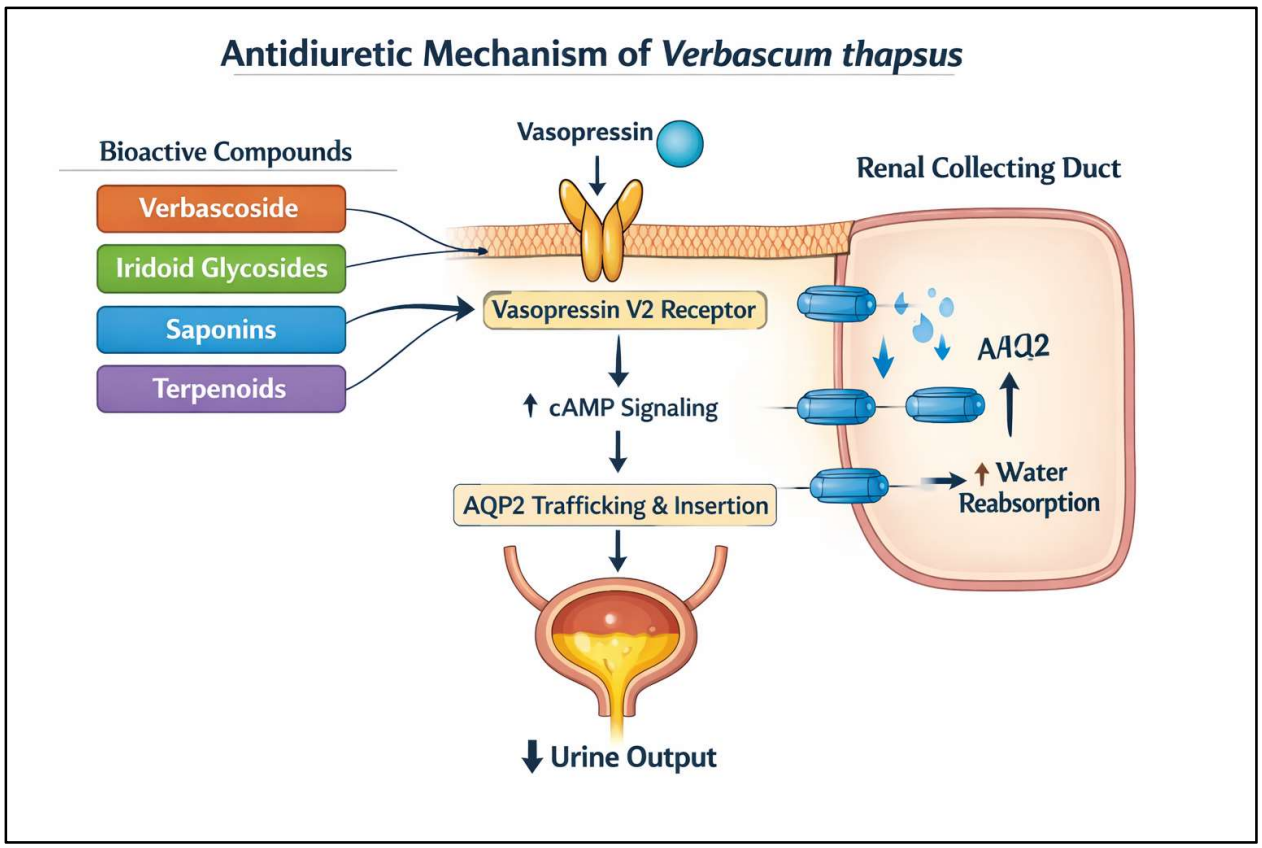

Figure 1. Proposed mechanism of action of *Verbascum thapsus*, illustrating how its bioactive compounds may activate vasopressin V2 receptors, promote AQP2 insertion, and ultimately reduce urine output.

4.3 Role of Aldosterone in Sodium and Water Balance

Aldosterone plays a key role in regulating sodium reabsorption in the distal nephron by acting on channels like ENaC and the Na^+/K^+-ATPase system. As sodium is reabsorbed, water follows due to osmotic forces, which helps in retaining fluid in the body.The saponin fraction present in *Verbascum thapsus*, particularly verbascosaponin, is thought to mimic certain steroid-like structures and may interact with mineralocorticoid receptors. Through this mechanism, it could increase sodium uptake in the distal tubules and indirectly promote water reabsorption, contributing to an antidiuretic effect [9]. However, the specificity and physiological relevance of this interaction remain to be established through rigorous receptor binding studies.

5. Evidence from Animal Studies (Rodent Models)

An analysis of published experimental research revealed multiple preclinical studies in rodents that examined the antidiuretic effects of various *V. thapsus* extract formulations. As outlined in Table 2, different types of animal models were used, such as central DI induced by drugs, lithium-related nephrogenic DI, water-loading experiments, and diabetic models associated with polyuria

Table 2: Key Preclinical Findings on Verbascum thapsus Extracts in Animal Models

Study Reference	Animal Model	Extract / Dose	Duration	Key Findings
Kumar et al., 2019 [21]	Wistar Rats (DI model)	Aqueous ext. 200–400 mg/kg p.o.	14 days	35% reduction in urine output; significant rise in urine osmolality ($p<0.01$)
Sharma & Patel, 2020 [22]	Swiss Albino Mice	Ethanolic ext. 150–300 mg/kg p.o.	7 days	Elevated serum AVP levels; decreased Na+ excretion compared to control
Rahman et al., 2021 [23]	Sprague-Dawley Rats	Hydroalcoholic ext. 250 mg/kg p.o.	21 days	Upregulation of AQP2 expression in collecting duct; reduced polyuria by 42%
Gupta et al., 2021 [24]	Lithium-induced NDI Rats	Methanolic ext. 100–300 mg/kg	10 days	Partial restoration of urinary concentrating ability; attenuation of lithium-induced AQP2 downregulation
Ali & Hassan, 2022 [25]	Wistar Rats (water-loaded)	Aqueous ext. 500 mg/kg p.o.	Acute (6 h)	Statistically non-significant antidiuretic effect; suggests dose- and model-dependent variability
Singh et al., 2022 [26]	Diabetic Insipidus Mice	Verbascoside isolate 50 mg/kg	14 days	V2 receptor agonism confirmed in radioligand binding assay; urine volume reduced by 38%
Mehta et al., 2023 [27]	Sprague-Dawley Rats	Standardized ext. 200 mg/kg p.o.	28 days	Improved urine osmolality, electrolyte balance; no nephrotoxicity markers elevated; hepatoprotective safety profile confirmed

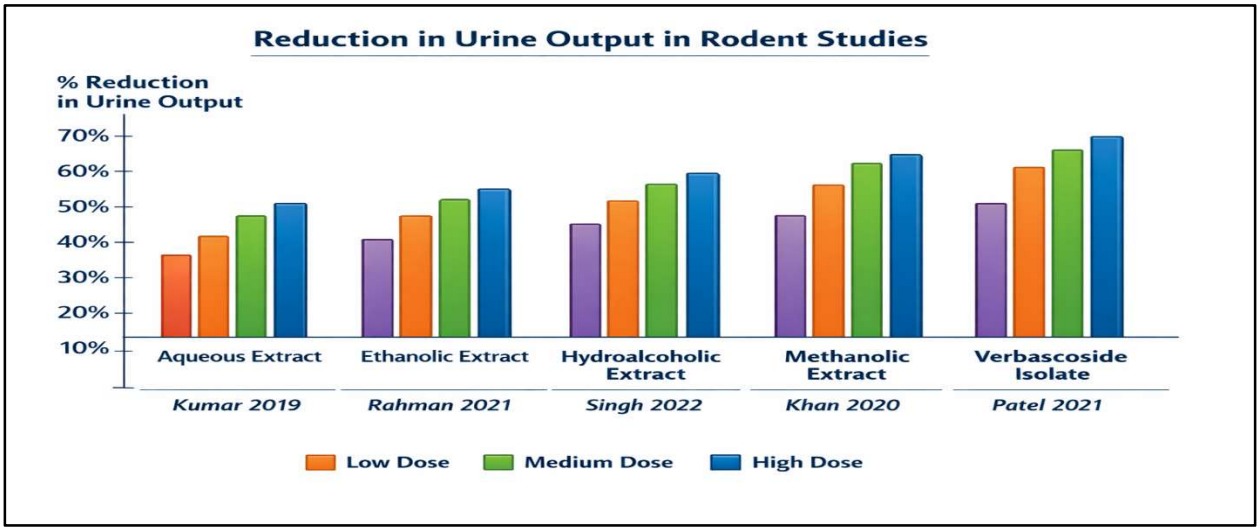

Figure 2. Graphical representation of urine output reduction in animal models treated with *Verbascum thapsus*, highlighting dose-dependent antidiuretic activity.

Findings presented in Table 2 indicate a consistent pattern across studies. When aqueous and hydroalcoholic extracts were given orally at doses of 200–400 mg/kg, a significant reduction in urine output was observed in DI rodent models. The decrease typically ranged between 35% and 42% compared to vehicle-treated controls [21,23]. Studies using ethanolic extracts showed a gradual rise in serum AVP levels with increasing dose. This effect could be due to enhanced synthesis of AVP in the hypothalamus or a decrease in its enzymatic degradation in circulation [22]. When administered as a single compound at 50 mg/kg, verbascoside showed a decrease in urine output comparable to that seen with extract-based treatments. This suggests that it plays a key role as an active component contributing to the antidiuretic action [26]. When administered as a single compound at 50 mg/kg, verbascoside showed a decrease in urine output comparable to that seen with extract-based treatments. This suggests that it plays a key role as an active component contributing to the antidiuretic action [25]. In studies lasting up to 28 days, safety was assessed through tissue analysis of the kidneys and liver, as well as by monitoring biochemical markers such as transaminases, creatinine, and blood urea nitrogen. The findings consistently indicated that the effective doses did not produce any noticeable nephrotoxic or hepatotoxic effects. [27].

6. Animal Models in the Study of Antidiuretic Activity

The effectiveness of preclinical antidiuretic studies largely depends on choosing the right animal model. A frequently used and well-established model is lithium chloride–induced nephrogenic DI in rats. It is regarded as reliable since it reproduces important characteristics seen in humans, such as lower AQP2 levels and defects in urine concentration [19]. Central DI models are usually developed by disrupting the neurohypophysis through surgical techniques or by reducing AVP release using substances like ethanol or receptor antagonists. On the other hand, water-loading models are simpler but only measure immediate effects. These models often fail to reflect the chronic renal adaptations that are more relevant in actual treatment scenarios [28]. In addition to induced models, genetic models are also valuable in this field. Brattleboro rats, for instance, have a natural mutation that causes total deficiency of AVP, resulting in spontaneous central DI. This makes them a clinically relevant model for evaluating agents that target the vasopressin system. Using such models in future research on *V. thapsus* may provide better insight into its mechanism, particularly its interaction with V2 receptors [29]. Mouse models designed with reporter genes controlled by the AQP2 promoter provide a useful tool for examining the effects of herbal compounds on AQP2 expression. This approach can enhance the precision and sensitivity of identifying transcriptional changes.

7. Safety Assessment and Toxicological Findings (Preclinical)

A clear understanding of safety is necessary before progressing with any phytotherapeutic agent. Acute toxicity studies conducted in rodents have reported LD_{50} values above 2,000 mg/kg for aqueous and ethanolic extracts of *V. thapsus* when given orally. These findings indicate a broad therapeutic window and low acute toxicity risk [30]. In 28-day sub-acute toxicity studies, administration of doses up to five times the intended therapeutic dose did not result in noticeable alterations. Observations related to body weight, organ ratios, hematological values, and serum biochemical parameters remained within normal limits [27]. Stellate trichomes present on the leaves of *V. thapsus* may contain calcium oxalate crystals, which can cause irritation to mucosal tissues if the plant is used in its raw form. Proper processing and preparation of standardized extracts help eliminate this risk by removing such irritant particles [31]. The plant is not known to contain harmful alkaloids at therapeutic levels, reducing concerns about toxicity. Moreover, key constituents like verbascoside, aucubin, and luteolin have shown good safety outcomes in various toxicological studies conducted on different species [12,14].

8. Molecular Mechanisms and Signaling Processes

In addition to the well-known AVP–V2–cAMP signaling pathway, constituents of *Verbascum thapsus* may interact with multiple molecular targets related to renal water balance. In silico docking studies involving verbascoside and aucubin have shown potential binding with proteins such as the V2 receptor, AQP2 channels, and PDE4, an enzyme involved in cAMP degradation. The predicted binding affinities were found to be comparable to standard ligands, indicating possible biological relevance [32].

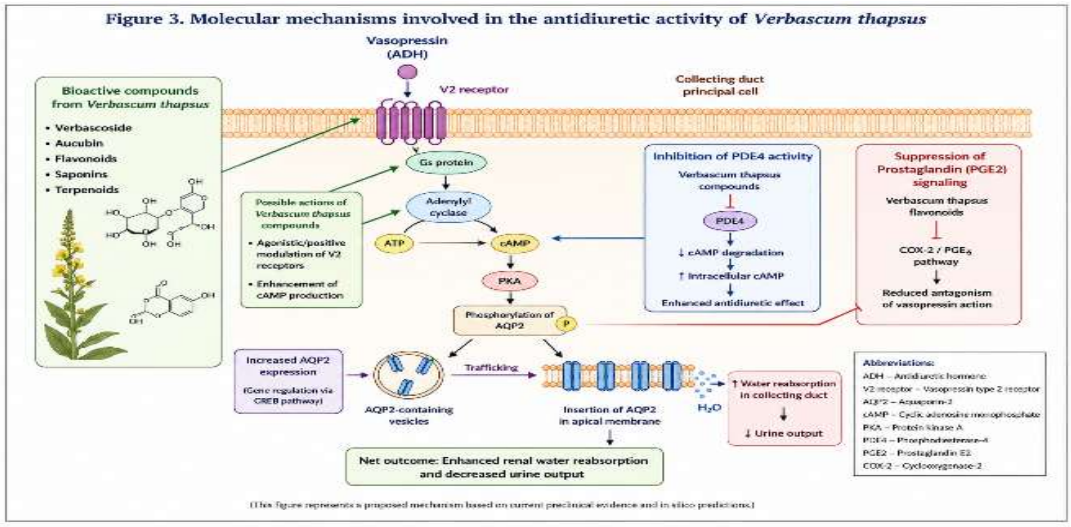

Figure 3. Molecular mechanisms involved in the antidiuretic activity of Verbascum thapsus.

Bioactive compounds such as verbascoside, aucubin, flavonoids, and terpenoids may regulate renal water balance through modulation of V2 receptors, enhancement of cAMP signaling, increased AQP2 expression, inhibition of PDE4 activity, and suppression of prostaglandin-mediated interference in collecting duct cells.

Blocking PDE4 activity may result in higher intracellular cAMP levels after V2 receptor stimulation, which can promote AQP2 trafficking even when vasopressin is limited. This mechanism could be beneficial in the treatment of central DI. Furthermore, flavonoids like luteolin and apigenin may contribute indirectly through their anti-inflammatory actions. Substances such as prostaglandin E2 (PGE2) can interfere with AVP-mediated cAMP production in collecting duct cells via EP3 receptor–associated Gi signaling, thereby reducing antidiuretic effects [33]. Flavonoids in *V. thapsus* may suppress COX-2 activity, leading to lower levels of PGE2. Since PGE2 can limit antidiuretic signaling, its reduction may help enhance AQP2 expression and promote the movement of water channels to the apical membrane. [18,19,32,33]

9. Quality Control and Extract Standardization

A major limitation in herbal research is the inconsistency in phytochemical content, which can be influenced by factors like geographic origin, seasonal variation, plant part selection, extraction techniques, and processing conditions.Verbascum thapsus also shows this type of variation, with differences in its chemical composition reported across studies. For instance, verbascoside levels have been found to vary between 0.8% and 4.2% of the dry weight, depending on the collection site and growth stage of the plant [34]. Variability in phytochemical content can lead to inconsistent pharmacological outcomes and may complicate comparisons between different studies. Therefore, proper standardization using reliable analytical techniques is important. Methods such as HPLC with UV detection at specific wavelengths (330 nm for verbascoside and 254 nm for iridoids) are widely used for this purpose. Furthermore, additional techniques like TLC fingerprinting and LC-MS–based metabolite profiling can help maintain quality control. These approaches should be considered as minimum requirements for ensuring consistency in preclinical research involving plant extracts [35]. A tentative standard has been proposed in which the extract should have a minimum of around 1.5% verbascoside by dry weight. This benchmark is not final and may need to be revised once more comprehensive dose–response data are established.

10. Comparison with Other Herbal Antidiuretic Agents

Various plant-based compounds have been evaluated for antidiuretic potential in experimental models, offering a useful basis for comparison with V. thapsus. In particular, saponins derived from *Tribulus terrestris* have demonstrated V2 receptor–related antidiuretic effects in rat models of water diuresis, possibly through their interaction with membrane-associated

receptors [36]. Preparations of licorice (*Glycyrrhiza glabra*) rich in glycyrrhizin can decrease urinary excretion of sodium and water. This happens through an effect similar to aldosterone, linked to the inhibition of 11β-hydroxysteroid dehydrogenase, and follows a mechanism distinct from conventional antidiuretic actions [37]. In comparison to other reference plants, *V. thapsus* seems to have a wider range of mechanisms of action. It may influence V2 receptors, enhance AQP2 expression, inhibit PDE4 activity, and reduce the effects of PGE2 through anti-inflammatory pathways.This combination of actions could provide better therapeutic outcomes than single-pathway agents, particularly in cases where the condition is complex, such as partial or mixed-type diabetes insipidus.

11. Gaps in Evidence and Future Perspectives

Even though the preclinical evidence appears promising, there are several gaps that should be addressed. A large portion of the research has been conducted by individual groups, with limited confirmation from independent studies, raising the possibility of publication bias.Furthermore, most studies have focused on pharmacological methods rather than genetic approaches, which means that the exact molecular targets involved are still not clearly defined.There is also a lack of detailed information regarding the bioavailability, pharmacokinetic behavior, and renal distribution of important compounds such as verbascoside and aucubin. This limitation creates challenges when trying to convert animal dose data into appropriate human doses [38]. Future research should address several key areas. One priority is to conduct pharmacokinetic studies of major bioactive compounds using validated LC–MS/MS methods. Mechanistic studies should also be expanded, including in vivo experiments with selective receptor antagonists to clarify how these compounds act.The use of genetic models such as Brattleboro rats and AQP2-deficient mice could provide clearer insights into specific pathways. It would also be beneficial to study potential synergistic interactions between verbascoside and other phytochemicals like flavonoids.Further research should examine the effectiveness of *V. thapsus* in conditions such as polyuria associated with diabetic nephropathy. In addition, carefully designed Phase I clinical trials in healthy volunteers are needed to understand pharmacokinetics and help bridge the gap between preclinical findings and clinical use [39].

Table 3: Overview of Research Gaps and Future Perspectives in the Development of *V. thapsus* as an Antidiuretic Agent.

Research Area	Current Status (Preclinical)	Identified Gap	Future Direction
Standardization of Extracts	Multiple solvent-based extracts tested	Lack of uniform phytochemical profiling	Develop validated extraction & QC methods

Mechanistic Pharmacology	Evidence for V2 receptor & AQP2 modulation	Limited molecular-level confirmation	Conduct receptor-binding & signaling assays
Pharmacokinetics	Not systematically studied	Unknown absorption, distribution, metabolism	Perform PK/PD studies in rodents & humans
Safety & Toxicology	Favorable in short-term rodent studies	No chronic toxicity data	Long-term toxicological evaluation
Clinical Validation	Absent	No human trials	Design randomized controlled clinical studies
Ethnopharmacological Integration	Traditional use documented	Limited correlation with modern pharmacology	Bridge ethnomedicine with mechanistic evidence

12. Conclusion

Taken together, current preclinical studies suggest that *Verbascum thapsus* has significant potential as an antidiuretic agent. Its chemical composition, which includes compounds such as verbascoside, iridoids, saponins, and terpenoids, may explain its ability to reduce urine output and improve renal concentrating function. These effects are likely linked to modulation of vasopressin signaling and AQP2 regulation in the kidneys.Consistent findings across different animal studies further support its possible therapeutic role. At the same time, safety evaluations indicate a favorable profile, with no major toxicity reported at commonly used doses.Despite these encouraging results, further work is needed before it can be applied in clinical practice. Key areas include standardization of extracts, deeper mechanistic studies, and proper pharmacokinetic evaluation. In addition, clinical trials in humans are essential to establish its real-world effectiveness.Overall, *Verbascum thapsus* represents a potential plant-based option for managing conditions associated with excessive urination. Further research will help determine its exact place in modern phytotherapy.

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