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Phytochemical profiles and pharmacological activities of mulberry (*Morus* species): Insights from experimental and clinical research

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Abstract

Mulberry (*Morus* species) is increasingly attracting scientific interest because of its rich phytochemical profile and a variety of pharmacological actions, which can help explain its historical use in treating metabolic and inflammatory diseases. This review critically and extensively summarises the phytochemical profiles, structure-activity relationships (SAR) and pharmacological actions of key *Morus* species, incorporating both experimental and clinical evidence. Among the important bioactive components, 1-deoxynojirimycin (DNJ), flavonoids, phenolic acids, prenylated compounds, and polysaccharides are discussed in terms of their chemical properties and mechanisms of action. Preclinical evidence indicates strong antidiabetic, antioxidant, anti-inflammatory, antimicrobial and anticancer effects. DNJ-mediated α-glucosidase inhibition and activation of the AMPK pathway are major processes in glycaemic regulation. There is also clinical evidence of reduced postprandial glucose levels (20-30%), but these results are limited by small sample sizes and unstandardized formulations. Notably, this review highlights synergistic effects among various phytochemicals and the drawbacks of reductionist research. Phytochemical variability, poor bioavailability and translational gaps are identified as key challenges and are addressed critically. The views of the future emphasise the importance of standardised extracts, sophisticated delivery systems and large-scale clinical trials. Overall, *Morus* species provide a potentially significant but underexplored source of phytotherapeutics and functional foods.

1. Introduction

The genus *Morus* (family: Moraceae), commonly known as mulberry, comprises over 20 species distributed across Asia, Europe, Africa, and the Americas, with *Morus alba*, *Morus nigra* and *Morus rubra* being the most extensively studied (Chan *et al*., 2016; Hussain *et al*., 2017). Historically, mulberry has been a popular herb in Chinese, Ayurvedic, and Unani medicinal systems for treating diseases such as diabetes, inflammation, and infections. The last few decades have seen a sharp rise in scientific attention due to its nutritional value and a variety of bioactive components, positioning *Morus* as a functional food and a promising source of therapeutic agents (Porasar *et al*., 2025). This increased interest is also driven by the rising prevalence of metabolic disorders worldwide, for which plant-based interventions are being pursued as complementary measures. The diversity of secondary metabolites of secondary metabolites, such as flavonoids, alkaloids (1-deoxynojirimycin), phenolic acids, anthocyanins and polysaccharides, is phytochemically diverse and typically participates in the interrelation of multiple biological processes in *Morus* species (Batiha *et al*., 2023; Fatima *et al*., 2024) These metabolites have a broad spectrum of biological action, which is usually carried out through antioxidant, anti-inflammatory and enzyme-modulating mechanisms. Notably, DNJ has attracted significant attention for its potent α-glucosidase inhibitory activity, which underlies mulberry's antidiabetic effects.

Emerging evidence indicates that the therapeutic activity of *Morus* is not confined to individual compounds but arises from interactions among two or more phytoconstituents; therefore, a systems-level understanding is essential. The profound biological activities of *Morus* species, such as antidiabetic, antimicrobial, anticancer, and cardiometabolic effects, have been demonstrated by pharmacological studies supported by experimental and clinical evidence (Hussain *et al*., 2017; Mishra *et al*., 2024). Although, preclinical research provides valuable mechanistic information, clinical data remain relatively weak and variable, with differences in extract standardisation, dosage and study design. This discrepancy underscores a critical need for integrated and evidence-based evaluation. Consequently, this review seeks to critically examine the phytochemical composition and pharmacological actions of the *Morus* family in greater detail, with special attention to filling gaps in existing knowledge about bridging experimental discovery research and clinical application as a basis for future therapeutic development.

2. Phytochemical profiles of *Morus* species

The pharmacological versatility of *Morus* species is fundamentally rooted in their chemically diverse and quantitatively variable phytoconstituents, which differ significantly across species, plant parts and environmental conditions. In contrast to most pharmaceutical plants, which are characterised by a single bioactive compound,

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Morus has a multi-layered phytochemical profile, with flavonoids, alkaloids, phenolic acids, anthocyanins, and polysac-charides all contributing to its biological profile. This compositional complexity not only broadens the scope of therapeutic effects but also poses challenges for standardisation and reproducibility, which are major bottlenecks in translational research (Wang *et al*., 2024; Yan *et al*., 2025).

2.1 Major classes of phytochemicals

2.1.1 Flavonoids and glycosides

Flavonoids are one of the most common and most therapeutically important groups within *Morus* species, especially in leaves and fruits. The most prevalent ones are quercetin, kaempferol, rutin, and isoquercitrin, which are frequently found as glycosylated derivatives (Fatima *et al*., 2023; Mena *et al*., 2016). The total flavonoid content in the leaves of *Morus alba* has been reported to range from 25 to 110 mg QE/g extract, depending on the solvent polarity and extraction method (Azlan and Joanne, 2025). Such compounds are closely linked to antioxidant and anti-inflammatory actions, primarily through reactive oxygen species (ROS) scavenging and regulation of redox-sensitive signalling pathways. However, the key point is that much research indicates that total flavonoid content is determined without characterising the structure, thus limiting mechanistic understanding. Advanced metabolomic profiling has revealed that minor flavonoid derivatives often exhibit disproportionately higher bioactivity, suggesting that bulk quantification alone may underestimate pharmacological relevance (Cao *et al*., 2020).

2.1.2 Alkaloids (Iminosugars)

The most commonly studied and clinically relevant alkaloid is 1-deoxynojirimycin (DNJ). It is highly concentrated in the leaves and young shoots, with reported concentrations ranging from 0.28 to 4.75 mg/g dry weight, depending on leaf maturity and seasonal fluctuations (Wulandari *et al*., 2019; Sugiyama *et al*., 2017). DNJ is a potent α-glucosidase inhibitor, which underlies the antidiabetic action of mulberry. It is important to note that DNJ is a member of the iminosugar family, is structurally similar to glucose, and competitively inhibits carbohydrate-hydrolysing enzymes. Although, this activity is well characterised, its bioavailability is low, and it is rapidly metabolised, raising questions about its long-term effectiveness *in vivo* (Chan *et al*., 2026). This highlights the need to use formulation strategies to improve pharmacokinetic performance.

2.1.3 Phenolic Acids

Phenolic acids such as chlorogenic, gallic, caffeic, and p-coumaric acids are common in *Morus* species. There is substantial variation in total phenolic content (TPC) in fruits, with values ranging from 43.84 to 326.29 mg GAE/100 g fresh weight, driven by strong environmental and genetic factors (Sanchez-Salcedo *et al*., 2015). These compounds play an important role in antioxidant activity; although they primarily serve as radical scavengers, they are also involved in enzyme modulation and the regulation of signalling pathways. One of the main shortcomings of the existing literature is the assumption that increased TPC improves biological activity. Nevertheless, recent evidence suggests that bioactivity is determined not by total content but by specific phenolic profiles, and the focus should be on qualitative, not only quantitative, measurements (Janiak *et al*., 2025).

2.1.4 Anthocyanins

Anthocyanins are also highly expressed in black mulberry (*M. nigra*) fruits, where they contribute to pigmentation and bioactivity. The main ones are cyanidin-3-glucoside and cyanidin-3-rutinoside, which are commonly present at more than 100 mg/100 g fresh weight in ripe fruits (Mena *et al*., 2016). They also exhibit strong antioxidant and anti-inflammatory effects and may have neuroprotective effects (Zhang *et al*., 2018). Notably, pH, temperature, and processing conditions are highly sensitive to anthocyanin stability, leading to substantial degradation during storage and food processing. This instability is one of the greatest barriers to their use in functional foods and therapeutic preparations.

2.1.5 Polysaccharides

Mulberry polysaccharides are increasingly recognised for their immunomodulatory and metabolic properties. They are structurally heterogeneous polysaccharides composed of glucose, galactose, arabinose, and rhamnose, with molecular weights ranging from 10 to 200 kDa (He *et al*., 2018). These compounds exhibit antioxidant, antidiabetic, and gut microbiota-regulating activities. Despite their promising bioactivities, the structure-function relationship of mulberry polysaccharides remains poorly characterised, largely due to variations in extraction and purification procedures. This structural ambiguity limits reproducibility and clinical translation.

2.1.6 Prenylated flavonoids and other specialised metabolites

Morus in and kuwanon G are prenylated flavonoids with strong anticancer and antimicrobial activity (Azzam *et al*., 2025). These agents have increased lipophilicity, which leads to interactions with the membrane and cellular uptake. Nevertheless, they are comparatively low in natural abundance and difficult to isolate in large quantities, thereby limiting their large-scale use.

The *Morus* species are well known for their wide range of phytochemicals, including alkaloids, flavonoids, phenolic acids, and polysaccharides, which are unevenly distributed across plant parts such as leaves, fruits, roots, and bark. The type and quantity of these compounds depend on geographical origin, extraction method, and species. Given the wide range of chemical diversity and variability reported across studies, a condensed list of significant phytochemicals and their approximate concentrations in various *Morus* species is provided in Table 1.

2.2 Species and tissue specific variability

Phytochemical composition in *Morus* is highly dependent on species, plant part and environmental conditions. DNJ and flavonoids are present in relatively high amounts in leaves, whereas anthocyanins and sugars are found in higher amounts in fruits; prenylated flavonoids and stilbenoids are found in higher amounts in root bark (Memete *et al*., 2022; Wang *et al*., 2024). Geographical variation is also important. For example, mulberry leaves planted in various parts of China showed large differences (up to 2-fold) in phenolic content and hypoglycaemic activity (Hao *et al*., 2018). Similarly, seasonal variations can change DNJ content by over 30 per cent, indicating that the harvesting period is a significant factor governing phytochemical output (Sugiyama *et al*., 2017). Such inconsistency poses significant problems for standardisation and quality control, especially in pharmaceutical development, where uniformity is necessary.

Table 1: Phytochemical composition of *Morus* species

Species	Plant part	Major compounds	Class	Approx. content	Method	References
M. alba	Leaves	DNJ	Alkaloid	0.28 to 4.75 mg/g DW	HPLC, LC-MS	Wulandari *et al*., 2019
M. alba	Leaves	Quercetin, rutin	Flavonoids	0.5-3.5 mg/g DW	HPLC-MS	Yue *et al*., 2017
M. alba	Leaves	Chlorogenic acid, caffeic acid	Phenolic acids	0.42-4.31 mg/g DW	LC-MS / HPLC	Cao *et al*., 2020
M. alba	Root bark	Morusin, kuwanon G	Prenylated flavonoids	Trace: 0.5 mg/g DW	LC-MS	Janakirama *et al*., 2020
M. nigra	Fruit	Anthocyanins, phenolic acids	Phenolics	100-400 mg/100 g FW	UHPLC-MS	Sánchez-Salcedo *et al*., 2015
M. serrata	Leaves	Total phenolics	Polyphenols	6.5–18.2 mg GAE/g DW	Folin-Ciocalteu assay	Hussain *et al*., 2017
***Morus* spp.**	Leaves	Polysaccharides	Polysaccharides	2-8% DW; MW often >100 kDa	Spectroscopy	He *et al*., 2018

2.3 Advanced metabolomic and analytical approaches

Recent advances in metabolomics and high-resolution analytical techniques have significantly enhanced the characterisation of *Morus* phytochemicals. UHPLC-ESI-MS/MS, LC-QTOF-MS, and NMR spectroscopy enable high-throughput profiling of complex metabolite mixtures to identify major and minor constituents (Yue *et al*., 2017; Chen *et al*., 2018). Metabolomic analyses have shown that *Morus* species contain hundreds of metabolites, many of which remain uncharacterised. Notably, profiling based on antioxidant activity has demonstrated that biological effects are driven by specific compounds rather than the overall extract composition (Cao *et al*., 2020). This strategy marks a transition to activity-focused phytochemistry, which is more consistent with pharmacological relevance. Despite technological advances, a significant gap persists in linking metabolomic data to biological outcomes, as most studies are descriptive rather than mechanistically integrative. To close this gap, metabolomics would need to be used in conjunction with functional assays and systems biology methods.

3. Bioactive compounds and structure-activity relation-ships

Although, *Morus* species possess a rich repertoire of phytochemicals, pharmacological activity is limited to a small number of structurally distinct bioactive compounds whose actions have been experimentally demonstrated. Notably, recent studies have moved beyond descriptive phytochemistry to structure-activity relationship (SAR)-based studies, which show that minor chemical changes, such as glycosylation, prenylation and hydroxylation, have a profound effect on biological activity, bioavailability and target specificity (Kwon *et al*., 2022; Yan *et al*., 2025). This transition reflects a broader movement towards mechanism-oriented phytopharmacology, where understanding molecular interactions is essential for therapeutic translation. To provide a mechanistic profile, the most important bioactive compounds of *Morus* species, their structural features, biological functions and their reported potential are summarised in Table 2.

Table 2: Key bioactive compounds in *Morus* species and SAR

Compound	Class	Structural feature	Mechanism	Activity	Potency	References
DNJ	Iminosugar	Polyhydroxylated piperidine	α-glucosidase inhibition	Antidiabetic	IC_{50} : 1-10 µM	Bharathi, 2020; Chan *et al*., 2026
Quercetin	Flavonoid	Ortho-dihydroxyl groups	ROS scavenging, NF-κB inhibition	Antioxidant	Strong	Cao *et al*., 2020
Morusin	Prenylated flavonoid	Prenyl group (lipophilic)	PI3K/Akt inhibition	Anticancer	IC_{50} : 2-10 µM	Azzam *et al*., 2025
Chlorogenic acid	Phenolic acid	Esterified phenolic	Glucose metabolism modulation	Antidiabetic	Moderate	Cao *et al*., 2020
Polysaccharides	Polymer	High MW, branching	TLR-mediated immune activation	Immuno-modulatory	Molecular weight dependent	He *et al*., 2018

3.1 1-Deoxynojirimycin (DNJ): A prototype antidiabetic iminosugar

Structurally, DNJ is a polyhydroxylated piperidine alkaloid closely resembling glucose, enabling it to competitively inhibit α-glucosidase and sucrase at the intestinal brush border (Bharathi, 2020). This delays carbohydrate digestion and absorption, resulting in significant reductions in postprandial glucose. The IC_{50} of DNJ ranges from 1-10 µM, comparable to standard drugs such as acarbose (Chan *et al*., 2026). Clinical evidence also supports its effectiveness, as DNJ-standardised extracts reduce postprandial glucose excursions by about 20-30% (Lown *et al*., 2017; Mohamed *et al*., 2023). However,

its therapeutic scope is constrained by limited systemic bioavailability and rapid metabolism, indicating that its primary action is localised within the gastrointestinal tract. In addition, the overall antidiabetic effect of mulberry has been attributed solely to DNJ, a reductionist approach, since accumulating evidence indicates that coexisting flavonoids and polysaccharides may modulate its biological activities in a synergistic or stabilising manner.

3.2 Flavonoids: Redox modulators and multitarget agents

Flavonoids constitute a major class of bioactive compounds in *Morus*, characterised by their multitarget pharmacological actions. Structurally, the presence of ortho-dihydroxyl groups in the B-ring, as seen in quercetin, enhances antioxidant potential by stabilising ROS through electron delocalisation (Cao *et al*., 2020). SAR studies indicate that glycosylation typically decreases immediate antioxidant activity but increases solubility and absorption, while the hydroxylation pattern strongly influences enzyme binding and signalling responses. Moreover, planar flavonoid structures have been reported to interact with intracellular targets, including the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, with anti-inflammatory and metabolic effects. It has been shown that mulberry flavonoids activate AMPK and protein kinase B (Akt) signalling to enhance glucose uptake and lipid regulation (Bae *et al*., 2018). Although, encouraging, these findings have limited clinical applicability due to the poor oral bioavailability (<20%) of the molecules, driven by rapid phase II metabolism, raising questions about the physiological relevance of *in vitro* concentrations commonly used in experimental studies.

3.3 Prenylated flavonoids: Lipophilicity-driven potency

Prenylated flavonoids, more specifically *Morus* in, constitute a structurally distinct subclass in *Morus*, characterised by hydrophobic prenyl groups that greatly increase lipophilicity and membrane permeability. This structural alteration enhances protein-binding activity and leads to greater biological potency than non-prenylated analogues (Azzam *et al*., 2025). *Morus*in has been shown to exhibit strong anticancer properties, including induction of apoptosis, inhibition of angiogenesis, and blockade of major signalling pathways such as STAT3, NF-κB, and PI3K/Akt. *In vitro* experiments report IC_{50} values ranging from 2 to 10 μM across different cancer cell lines (Janakirama *et al*., 2020). Nevertheless, its strong bioactivity has not yet been translated into clinical use due to low aqueous solubility, inadequate pharmacokinetic properties, and a lack of human studies. These limitations highlight the need for formulation strategies to enhance its therapeutic usefulness.

3.4 Phenolic acids

The traditional antioxidant properties attributed to phenolic acids in *Morus*, such as chlorogenic and caffeic acids, are being replaced by more specific functions of these acids. For example, chlorogenic acid inhibits glucose-6-phosphatase, lowering hepatic glucose production and helping to maintain glycaemic regulation (Azlan and Joanne, 2025). According to SAR studies, the positions of hydroxyl groups and esterification patterns make major contributions to biological activity, particularly enzyme inhibition and redox processes. Compared with flavonoids and alkaloids, phenolic acids are characterised by moderate strength, suggesting they do not play a dominant role but rather serve a supportive function (Janiak *et al*., 2025). However, their contribution to the overall pharmacological profile of mulberry should not be underestimated; rather, they are involved in synergistic interactions that lead to cumulative efficacy.

3.5 Polysaccharides: Structural complexity and immunomodulation

Mulberry polysaccharides constitute a highly heterogeneous family of macromolecules with complex structural features, including variations in molecular weight, branched structures, and monosaccharide composition. Their biological activity is largely linked to immunomodulatory effects mediated by interactions with pattern recognition receptors, including toll-like receptors (TLRs), leading to macrophage activation and cytokine release (He *et al*., 2018). Unlike low-molecular-weight compounds, their activity is not attributable to a single pharmacophore; instead, it is determined by the overall structural architecture. Notably, higher-molecular-weight fractions (greater than 100 kDa) exhibit greater immunostimulatory activity but lower bioavailability (Abbas *et al*., 2024). A major limitation in this field is the lack of standardisation in structural characterisation, which hampers SAR interpretation and reduces reproducibility across studies.

3.6 Synergistic interactions and multicomponent effects

A defining feature of *Morus* phytochemistry is the synergistic interplay among multiple bioactive constituents, which collectively underpin its therapeutic effects. Network pharmacology studies show that mulberry extracts can simultaneously modulate several biological pathways, including glucose metabolism, oxidative stress, and inflammation (Wang and Dong, 2022). For example, DNJ primarily suppresses carbohydrate digestion; flavonoids promote insulin signalling; and phenolic acids mitigate oxidative damage. These synergistic activities produce a multilayered pharmacological effect that isolated compounds cannot achieve. Nevertheless, most research remains reductionist, focusing on individual constituents, which may not capture the holistic effectiveness of whole extracts. Future studies must adopt integrative models that quantify synergy, enabling a more precise depiction of *Morus*-based therapies.

4. Pharmacological activities

Preclinical investigations of *Morus* species provide substantial evidence supporting a wide range of pharmacological activities. In vitro systems and animal model studies reveal the multi-target therapeutic advantages of mulberry-derived compounds. Nevertheless, despite a solid mechanistic understanding, critical appraisal indicates persistent challenges, such as discrepancies in dose-response relationships, inadequate pharmacokinetic integration, and model constraints, which could influence translational relevance (Yan *et al*., 2025). The subsequent subsections summarise important pharmacological activities, with an emphasis on mechanism-based interpretation. An in-depth overview of preclinical pharmacological actions in *Morus* species, experimental models, dose ranges, and essential quantitative results is presented in Table 3, and the multi-organ and multi-pathway mechanisms of these actions are depicted in Figure 1.

Table 3: Preclinical pharmacological activities of *Morus* species

Activity	Model	Extract/compound	Dose/concentration	Key findings (quantitative)	Mechanism	References
Antidiabetic	STZ-induced diabetic rats	*M. alba* leaf extract	200-400 mg/kg	Fasting glucose by **25-55%**; improved insulin markers	AMPK activation, enzyme inhibition	Alanazi *et al*., 2017; Król *et al*., 2016
Antidiabetic	db/db mice	Leaf extract	100-250 mg/kg	Glucose and improved insulin sensitivity	Akt and AMPK phosphorylation	Bae *et al*., 2018
Antioxidant	*In vitro* (DPPH, ABTS)	Leaf extract	IC_{50} : 20-80 µg/ml	Strong radical scavenging activity	Electron donation	Imran *et al*., 2010; Cao *et al*., 2020
Antimicrobial	*In vitro* (MRSA, *Staphy-lococcus*)	Leaf extract	MIC: 125-500 µg/ml	Significant inhibition of bacterial growth	Membrane disruption	Aelenei *et al*., 2019
Antibiofilm	*In vitro*	Aqueous extract	100-300 µg/ml	Biofilm formation by 40-70%	Biofilm disruption	Hidouri *et al*., 2025
Anticancer cell lines	Cancer	Morusin	IC_{50} : 2-10 µM proliferation	Induces apoptosis, inhibits inhibition	PI3K/Akt, NF-κB	Janakirama *et al*., 2020
Anti-obesity	HFD-induced mice	Leaf extract	200-500 mg/kg	Body weight gain by **10-25%**; improved lipid profile	AMPK activation	Wang and Dong, 2022
Hepatoprotective	Animal models	Leaf extract	200-400 mg/kg	ALT/AST levels; reduced oxidative stress	Antioxidant pathways	Rebai *et al*., 2017

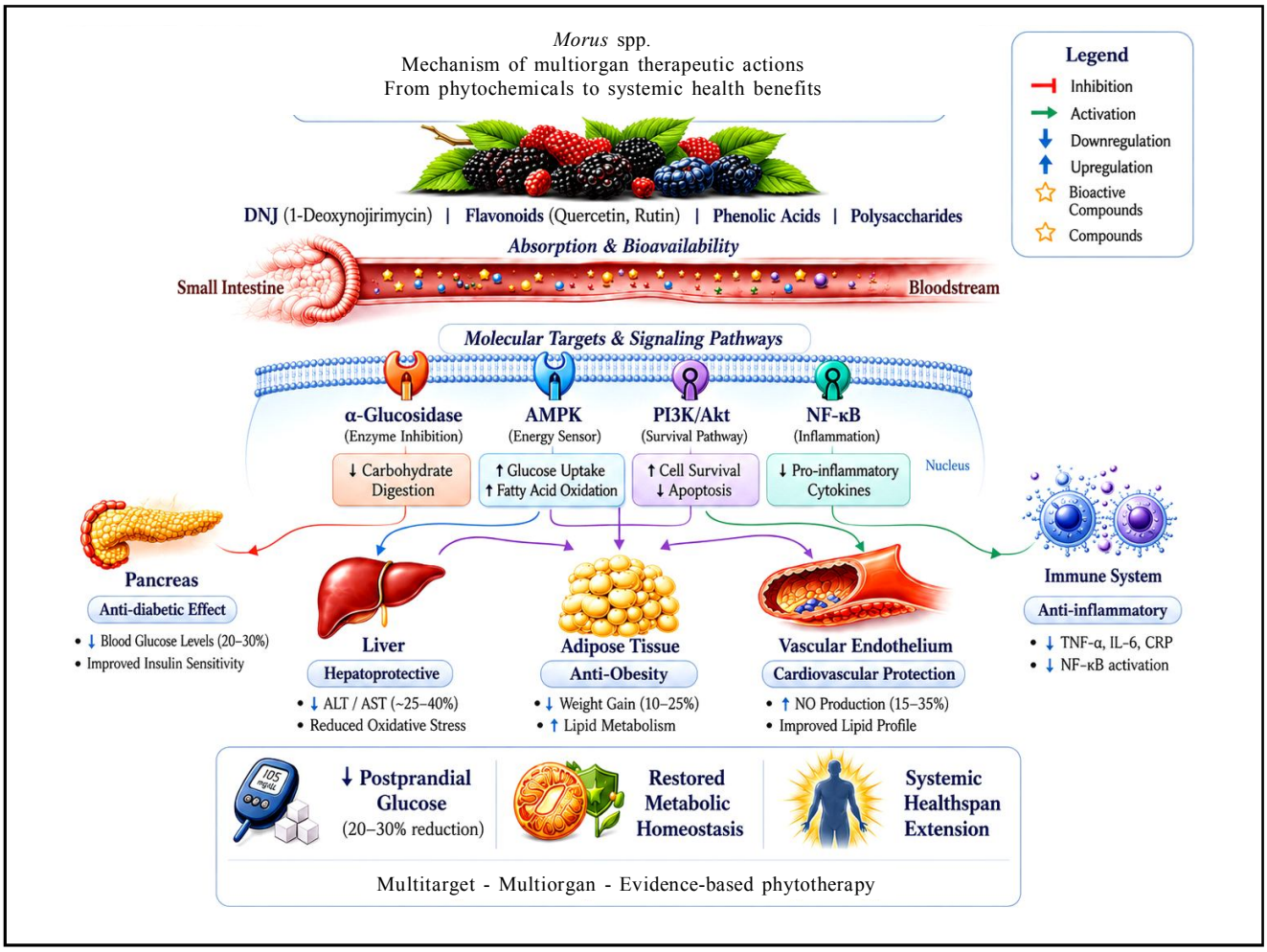

Figure 1: Mechanism of multiorgan therapeutic actions of *Morus* spp. phytochemicals.

4.1 Antidiabetic activity

The antidiabetic effect of *Morus* species has been the most widely researched and repeatedly proven pharmacological effect. Experimental studies using streptozotocin-induced diabetic rats and genetic models such as db/db mice have demonstrated significant reductions in fasting blood glucose levels of 30%-60%, along with improvements in insulin sensitivity and glycated haemoglobin (Alanazi *et al*., 2017; Krol *et al*., 2016). These impacts are mediated, respectively, by inhibition of carbohydrate-digesting enzymes (α-glucosidase and α-amylase), activation of AMPK and Akt signalling pathways, and inhibition of hepatic gluconeogenesis (Bae *et al*., 2018; Lv*et al*., 2022). Additionally, mulberry-derived alkaloids, such as sangzhi alkaloids, have shown glucose-lowering effects comparable to those of standard antidiabetic drugs in experimental studies (Chen *et al*., 2025). Despite these promising outcomes, a major limitation is the reliance on high extract doses (often >200 mg/kg) and simplified disease models, which may not accurately reflect human metabolic conditions.

4.2 Antioxidant and anti-inflammatory activities

The *Morus* species exhibit high antioxidant and anti-inflammatory activities, largely attributed to their high phenolic and flavonoid profiles. *In vitro* tests consistently show strong free radical-scavenging effects, with IC_{50} values usually below 50 ug/ml (Imran *et al*., 2010; Cao *et al*., 2020). These effects translate into reduced oxidative stress *in vivo*, as evidenced by lower malondialdehyde (MDA) levels and increased activity of endogenous antioxidant enzymes, including superoxide dismutase (SOD) and catalase (Krol *et al*., 2016). The anti-inflammatory activity is mediated by inhibition of the NF-κB signalling pathway and suppression of pro-inflammatory cytokines such as TNF-α and IL-6. A critical drawback is the excessive reliance on chemical antioxidant assays, which lack physiological relevance and can overestimate *in vivo* effectiveness by failing to account for absorption and metabolism.

4.3 Antimicrobial and antibiofilm activities

Mulberry extracts have shown significant antimicrobial activity against a wide range of microorganisms, including drug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA). Studies indicate minimum inhibitory concentrations (MICs) of 125 to 500 µg/ml for *M. alba* leaf extracts against *Staphylococcus* species (Aelenei *et al*., 2019). In addition, mulberry extracts exhibit pronounced antibiofilm activity, inhibiting biofilm formation by more than 60% in pathogenic bacteria (Hidouri *et al*., 2025). These effects are attributed to membrane disruption, inhibition of nucleic acid synthesis, and enhanced effects of traditional antibiotics. However, most of the evidence is based on *in vitro* studies, and little of it has been validated in animal models of infection, which limits clinical extrapolation.

4.4 Anticancer activity

The anticancer activity of *Morus* species is mainly linked to prenylated flavonoids, including *Morus*in, which exhibit strong cytotoxic activity against many types of cancerous cells. According to experimental studies, the IC_{50} ranges from 2 to 20 µM, indicating that it is a very potent inhibitor of cancer cell proliferation. Mechanistically, these compounds cause apoptosis through caspase activation, inhibition of cell cycle progression and inhibition of important oncogenic signalling pathways such as PI3K/Akt, STAT3 and NF-κB. Antiangiogenic and antimetastatic effects have also been noted, further adding to their therapeutic potential (Janakirama *et al*., 2020). Nevertheless, the evidence is mostly limited to *in vitro* systems and there is not enough *in vivo* and clinical validation and comparative studies with known chemotherapeutic agents.

4.5 Cardiometabolic and antiobesity effects

Preclinical research has shown that mulberry extracts have positive effects on lipid metabolism and on parameters related to obesity. The animal model has demonstrated that supplementation with *Morus* extracts can reduce body weight gain by about 15-25 per cent and produce substantial reductions in serum triglycerides, total cholesterol, and low-density lipoprotein (LDL) (Wang and Dong, 2022). These actions are mediated by AMPK activation, inhibition of adipogenesis, and regulation of genes involved in lipid metabolism. There is also emerging evidence that it plays a role in regulating the gut microbiota, which may be associated with metabolic benefits. Nonetheless, as in other fields of pharmacology, the use of high doses and brief experimental periods limits the drug's predictive potential for long-term human behaviours.

4.6 Neuroprotective and hepatoprotective effects

Recent studies demonstrate the neuroprotective and hepatoprotective properties of *Morus* species, primarily attributable to antioxidant and anti-inflammatory effects. Mulberry extracts have been reported to prevent oxidative-stress-induced cell damage in neuronal models by up to 40 per cent and could potentially be used in neurodegenerative disorders. Hepatoprotective activity encompasses reductions in liver enzyme markers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as amelioration of liver steatosis in animal models (Rebai *et al*., 2017). These protective functions are linked to the enhancement of redox balance and inhibition of inflammatory pathways. However, compared to metabolic studies, these areas remain underexplored, with limited mechanistic depth and insufficient validation across diverse biological systems.

5. Clinical evidence and human studies

Although, preclinical studies provide compelling evidence for the pharmacological potential of *Morus* species, clinical validation remains limited and heterogeneous, with most human studies focusing on glycaemic control and cardiometabolic outcomes. Importantly, available trials offer moderate support for efficacy, particularly in postprandial glucose regulation, yet they also reveal critical limitations in study design, extract standardisation and long-term assessment. The subsequent subsections analyse the clinical results, focusing on quantitative outcomes and translational applicability.

5.1 Effects on glycaemic control

Clinical evidence on *Morus* species is most significant for their capacity to control postprandial glycaemia, which is primarily attributed to DNJ-rich mulberry leaf extracts. The randomised, double-blind, placebo-controlled trial showed that mulberry extract with approximately 12 mg of DNJ content resulted in a significant 20-25% reduction in postprandial glucose excursions and decreased the insulin response in normoglycaemic individuals (Lown *et al*., 2017). In a similar study, Mudra *et al*. (2007) also demonstrated a decrease in peak glucose levels of about 40mg/dl when sucrose was ingested in both diabetic and non-diabetic individuals, which is rapid and localised due to the inhibition of intestinal enzymes. A crossover

study conducted by Mohamed *et al*. (2023) demonstrated positive changes in postprandial glucose and insulin dynamics in patients with type 2 diabetes, but the use of a multi-component formulation made it difficult to identify the unique effect of mulberry. All these results point to the effectiveness of *Morus* as a postprandial glucose modulator, but its effects on prolonged glycaemic control are not well defined.

5.2 Cardiometabolic and weight management effects

Beyond glycaemic control, clinical evidence suggests that *Morus* species may exert beneficial effects on broader cardiometabolic parameters, including lipid metabolism and body weight regulation. Studies have reported modest reductions in body weight and improvements in lipid profiles, particularly in overweight or diabetic individuals (Ntalouka and Tsirivakou, 2024). All these effects are probably not mediated by direct lipid-lowering processes, but indirectly by delayed carbohydrate absorption, enhanced insulin sensitivity, and decreased postprandial hyperglycaemia. But the majority of clinical trials have small sample sizes (20-60 individuals) and short durations (4-12 weeks), which limit their statistical power and long-term applicability. Also, poor management of dietary and lifestyle factors creates the possibility of confounding, making it difficult to attribute the outcomes to multiple interventions (Thaipitakwong *et al*., 2018).

5.3 Evidence from systematic reviews and meta-analyses

Recent meta-analytical studies provide a broader perspective on the clinical efficacy of *Morus*-derived compounds. A systematic review and meta-analysis of mulberry twig alkaloids (sangzhi alkaloids) documented significant decreases in HbA1c by about 0.5-0.8% and in fasting blood glucose by 1-2 mmol/l in patients with type 2 diabetes (Chen *et al*., 2025). These changes are clinically significant and have a therapeutic effect comparable to traditional oral hypoglycaemic drugs. In a similar study, Siriwan *et al*. (2026) showed that *Morus* alba interventions significantly improved glycaemic and lipid parameters, including reductions in total cholesterol and triglycerides. However, these analyses reported moderate-to-high heterogeneity ($I2 > 60\%$), largely due to variability in dosage, duration, and extract composition. This highlights a major limitation in the field, namely the lack of standardized formulations, which complicates data interpretation and limits the generalizability of findings.

5.4 Safety and tolerability

Products made from mulberry are generally considered safe and well tolerated, with very few reported side effects, according to clinical studies. Mild gastrointestinal side effects (bloating and diarrhoea) are the most frequent and likely result from α-glucosidase inhibition and subsequent carbohydrate malabsorption (Chan *et al*., 2016). Importantly, no serious adverse events have been consistently documented, even with repeated administration. The absence of long-term safety data is; however, particularly noticeable for concentrated extracts and isolated compounds such as DNJ or prenylated flavonoids. This constitutes a serious gap, particularly for chronic conditions that may requireprolonged treatment.

6. Challenges, limitations and future perspectives

Although, extensive research has been conducted on *Morus* species, several challenges and constraints remain that hinder their translation from the laboratory to clinical use. A major problem is the lack of phytochemical standardisation, as species, geographical origin, harvesting conditions, and extraction methods can dramatically alter the concentrations of bioactives of interest, including DNJ and flavonoids, often by severalfold (Fatima *et al*., 2024; Yan *et al*., 2025). This inconsistency reduces reproducibility and makes it difficult to compare studies. Moreover, most preclinical studies use supraphysiological doses (>200 mg/kg) and simplified disease models (*e.g.,* streptozotocin-induced diabetes), which do not accurately reflect human pathophysiology. The inability of major compounds, *i.e.,* flavonoids and prenylated derivatives, to penetrate tissues due to high metabolism and low solubility is another critical limitation and calls into question the translational applicability of *in vitro* results. Small sample sizes, limited study periods, and heterogeneous formulations, which in most cases involve multi-component supplements, obscure mulberry-specific effects in clinical trials (Thaipitakwong *et al*., 2018). There is also a lack of integration between pharmacokinetic and mechanistic biomarkers, creating a disconnect between experimental and clinical outcomes. All of this leads to a discrepancy between good laboratory evidence and sound therapeutic use.

Future research must focus on developing standardised, bioactive-enhanced formulations, alongside sophisticated metabolomic profiling, to ensure consistency and reproducibility. Large-scale, long-term randomised controlled trials with clearly defined endpoints are the standard for demonstrating efficacy and safety across different populations. A combination of pharmacodynamic and pharmaco-kinetic research, along with novel delivery methods such asnanoformulations, has the potential to enhance bioavailability and efficacy. In addition, the use of systems biology and multi-target approaches will provide deeper insight into synergistic interactions, enabling the translation of *Morus* species into evidence-based therapeutic and functional health products.

7. Conclusions

Morus species are a pharmacologically diverse and phytochemically active genus with great potential in the management of metabolic and inflammatory diseases. Its diverse bioactive compounds, such as DNJ, flavonoids, phenolic acids, and polysaccharides, confer a broad spectrum of biological activity, with accumulating experimental and emerging clinical evidence. Of these, the best established are the antidiabetic ones, especially on the regulation of postprandial glucose levels by blocking enzymes and altering the metabolic pathways. Nevertheless, such promising preclinical results are limited to clinical practice by factors including low standardisation, low bioavailability and a lack of large-scale clinical validation. Importantly, the therapeutic efficacy of *Morus* cannot be attributed to individual compounds alone but rather to synergistic interactions within its complex phytochemical matrix, aligning with modern concepts of multitarget pharmacology.

The way forward in realising its potential is to place greater emphasis on integrative and mechanism-based research strategies, which would entail integrating phytochemistry, pharmacology, and clinical science. The development of standardised formulations, supported by robust clinical trials and pharmacokinetic insights, will be critical for establishing mulberry as a credible therapeutic option. Overall, *Morus* species hold promise as both functional food ingredients and adjunct therapeutic agents, but their advancement into mainstream medicine

will depend on overcoming current scientific and translational barriers through coordinated and evidence-based research strategies.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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