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ALFALFA (MEDICAGO SATIVA): PHYTOCHEMISTRY, PHARMACOLOGICAL ACTIVITIES, THERAPEUTIC APPLICATIONS, AND ADVERSE EFFECTS – A COMPREHENSIVE REVIEW

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ABSTRACT

Medicago sativa L., universally referred to as Alfalfa or Lucerne, is a deep-rooted perennial flowering legume belonging to the family Fabaceae. Long celebrated globally as the ―Queen of Forages‖ owing to its unparalleled primary nutrient density, Alfalfa has firmly transcended its agronomic foundations to assume an important standing in contemporary pharmaceutical evaluation and pharmacognostic standardization. This comprehensive review synthesizes the extensive scientific literature regarding the botanical taxonomy, intricate chemical profile, diverse pharmacological landscape, evidence-based clinical utilities, and safety boundaries of *M. sativa*. Extensive phytochemical profiling across decades reveals a structural kaleidoscope of specialized secondary metabolites, most prominently triterpenoid saponins, flavones, isoflavones, coumestans, alkaloids, phytosterols, and unique non-protein amino acids. Modern pharmacological screening has validated its dynamic therapeutic properties, demonstrating robust hypocholesterolemic, anti-diabetic, antioxidant, anti-inflammatory, neuroprotective, hepatoprotective, antimicrobial, and estrogenic activities. Clinically, specialized preparations of Alfalfa hold distinct potential in the complementary management of metabolic syndromes, cardiovascular diseases, atherosclerosis, postmenopausal symptoms, and rheumatoid arthritis. Paradoxically, the safety evaluation of *M. sativa* demands strict

scientific vigilance; the presence of the toxic antimetabolite L-canavanine has been unequivocally linked to the induction and clinical reactivation of systemic lupus erythematosus (SLE) and related autoimmune phenotypes. This manuscript aims to serve as a definitive baseline compilation, balancing the remarkable therapeutic efficacy against documented adverse liabilities to direct future clinical trials and rational formulation engineering.

KEYWORDS: *Medicago sativa*, Alfalfa, Phytochemistry, Triterpenoid Saponins, Isoflavones, L-Canavanine, Systemic Lupus Erythematosus, Anti-arthritic, Neuroprotective, Hepatoprotective.

1. INTRODUCTION

The therapeutic utilization of natural products and medicinal botanicals remains an enduring foundation of global healthcare systems, spanning from primordial Ayurvedic and Traditional Chinese Medicine (TCM) to contemporary evidence-based phytotherapy. Among the extensive plant repositories evaluated in recent decades, *Medicago sativa* L. (Alfalfa), a deep-rooted perennial herb belonging to the family Fabaceae (subfamily Faboideae), stands as an exceptional candidate of profound pharmacological and nutraceutical value.[1]

Originating in the temperate regions of South-Central Asia, notably ancient Persia and Transcaucasia, Alfalfa's agronomic resilience, nitrogen-fixing capacity, and superior macro- and micronutrient density earned it the historical nomenclature —Queen of Forages.[1] Beyond its global deployment in livestock nutrition, its historical medicinal applications are documented across ancient scripts, where it was indicated to manage digestive distress, kidney malfunctions, chronic inflammatory arthritis, low vitality, and lactation failures.[2]

In contemporary pharmaceutical science, *M. sativa* has emerged as an intensive subject of investigation due to its sophisticated, multi-class secondary metabolite matrix. Quantitative and qualitative analyses have demonstrated that the plant functions as a natural bio-factory for complex chemical compounds, including heavily glycosylated triterpenoid saponins, specialized flavones, structural phytoestrogens (isoflavones and coumestans), nitrogenous alkaloids, and unique non-protein amino acids.[1,2] These components operate via intricate synergistic pathways to exert significant cellular effects, including physical entrapment of luminal cholesterol, stimulation of pancreatic insulin release, suppression of pro-inflammatory transcription loops, and catalytic neutralization of reactive oxygen and nitrogen species.[2,3]

However, the pharmacological profile of Alfalfa presents a dual nature that necessitates careful scientific analysis. While its extracts offer substantial therapeutic benefits, the non-protein amino acid L-canavanine poses documented pathological risks, notably the ability to trigger or reactivate serious autoimmune conditions like Systemic Lupus Erythematosus (SLE).[1,4] This comprehensive review is designed to deliver an exhaustive and rigorous analysis of the phytochemistry, pharmacological mechanisms, therapeutic indications, and toxicological thresholds of *M. sativa*, establishing a baseline reference for future drug discovery and clinical application.

2. BOTANICAL CHARACTERIZATION AND TAXONOMY

Medicago sativa is a deeply anchored perennial legume capable of surviving up to two decades in well-drained, temperate, or semi-arid soils due to its specialized taproot system, which can penetrate depths exceeding 4 to 6 meters into the subterranean strata.[1] Structurally, the plant is characterized by erect or semi-prostrate herbaceous stems arising from a central woody crown, reaching an average height of 30 to 100 cm. The leaves are arranged alternately and are uniformly trifoliate. Each individual leaflet is oblong, obovate, or oblanceolate, measuring 10 to 30 mm in length, with finely serrated margins restricted primarily to the upper third of the lamina.

The inflorescence manifests as a dense, axillary raceme encompassing 10 to 35 distinctly papilionaceous flowers. Corolla coloration is highly polymorphic, displaying vibrant shades of purple, lavender, violet, yellow, cream, and white, depending on the specific cultivar, genetic variation, and environmental conditions.[1] Following entomophilous pollination, primarily mediated by solitary bees, the ovary develops into a tightly coiled or spiral-shaped legume seed pod containing 2 to 8 kidney-shaped, yellowish-brown seeds. Taxonomically, the plant is classified under the kingdom Plantae, division Tracheophyta, class Magnoliopsida, order Fabales, family Fabaceae, tribe Trifolieae, and genus *Medicago*, which comprises approximately 83 distinct species distributed globally.[5,9]

3. PHYTOCHEMICAL COMPOSITION

The vast pharmacological profile of *Medicago sativa* is a direct consequence of its rich and highly integrated chemical matrix. Research confirms that the distribution and exact concentrations of active compounds vary significantly across the plant's roots, leaves, stems, sprouts, and seeds.[1]

3.1 Triterpenoid Saponins

Triterpenoid saponins represent the most prominent class of biologically active secondary metabolites within *M. sativa*, accumulating in substantial quantities within both aerial components and deep root networks.[6] Chemically, these complex amphiphilic glycosides feature a highly hydrophobic 30-carbon triterpene aglycone core (sapogenin) linked covalently to one or more hydrophilic oligosaccharide chains composed of glucose, galactose, rhamnose, xylose, or arabinose units.[2, 6] Analytical protocols have successfully mapped over 33 distinct saponin molecules within the plant.[2] The major aglycone cores include Medicagenic Acid (a highly oxygenated di-carboxylic triterpene imparting potent antimicrobial activity), Hederagenin and Bayogenin (pentacyclic triterpenoid structures essential to cell membrane interactions), and Soyasapogenols A, B, and E (highly lipophilic aglycones linked to systemic metabolic regulation).

3.2 Flavonoids and Phytoestrogens

The foliar parts of Alfalfa contain a rich profile of polyphenolic compounds, specifically flavones and structural phytoestrogens.[1] The primary free and glycosylated flavones isolated include tricin, apigenin, luteolin, and chrysoeriol. Beyond these standard phenolics, *M. sativa* serves as one of the richest sources of phytoestrogens — non-steroidal plant compounds structurally analogous to endogenous mammalian 17β-estradiol.[1,10] These are divided into two primary subclasses: Coumestans, represented primarily by coumestrol and 4'-O-methylcoumestrol, and Isoflavones, including genistein, daidzein, formononetin, and biochanin A.[10,11]

3.3 Alkaloids and Nitrogenous Compounds

Alfalfa synthesizes several basic nitrogenous compounds. The principal alkaloids present are the pyridine-type betaines, namely stachydrine and l-homostachydrine, primarily localized within the green forage and leaves.[2] Additionally, the seeds and young germinating sprouts contain high concentrations of L-canavanine, a non-protein sulfur-free amino acid that functions as a structural analog of the essential amino acid L-arginine, with documented implications for autoimmune reactivity.[1,4]

3.4 Primary and Nutritional Constituents

From a nutritional perspective, the green leaf meal of *M. sativa* provides high-quality protein (18–25% dry weight), containing a balanced ratio of all essential amino acids, including

leucine, isoleucine, lysine, valine, phenylalanine, and tryptophan.[2] Furthermore, it contains a comprehensive vitamin and mineral matrix including Phytonadione (Vitamin K^1), Tocopherol (Vitamin E), Ascorbic Acid (Vitamin C), Thiamine (B^1), Riboflavin (B^2), Pyridoxine (B^6), Calcium, Magnesium, Iron, Zinc, and Potassium.[2,3]

4. PHARMACOLOGICAL ACTIVITIES AND MOLECULAR MECHANISMS

The diverse phytochemical matrix of *Medicago sativa* interacts with multiple physiological targets, resulting in a wide spectrum of validated pharmacological properties. Recent systematic reviews confirm that flavonoids, isoflavones, and triterpenoid saponins dominate its bioactivity landscape through redox modulation, membrane perturbation, receptor engagement, and suppression of NF-κB/MAPK signaling.[9,12]

4.1 Hypocholesterolemic and Anti-Atherosclerotic Activity

The primary mechanism driving Alfalfa's hypocholesterolemic effect involves its triterpenoid saponins.[1] These amphiphilic molecules possess a high physical affinity for cholesterol and bile acids within the gastrointestinal tract. Upon ingestion, the hydrophobic saponin core binds directly to dietary cholesterol and endogenous bile salts in the intestinal lumen, forming heavy, insoluble, non-absorbable micellar complexes. This prevents cholesterol reabsorption across the brush border membrane of enterocytes, promoting its elimination through fecal excretion.

To compensate for the loss of intestinal bile acids, the hepatic architecture is forced to upregulate the expression of cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme that drives the conversion of endogenous hepatocyte cholesterol into primary bile acids. Concurrently, hepatocytes increase LDL receptor surface expression to clear circulating LDL-cholesterol from the bloodstream. This dual action significantly reduces total serum cholesterol, LDL-C, and atherogenic apolipoprotein B (ApoB) metrics, without inducing harmful changes in HDL-C fractions.[1,7]

4.2 Anti-Diabetic and Insulinotropic Activity

Extensive in vivo and in vitro evaluations have confirmed that aqueous and ethanolic extracts of *M. sativa* possess prominent anti-diabetic and insulinotropic properties.[2,3] When administered orally, active fractions stimulate the structural release of insulin from clonal pancreatic β-cells via a mechanism that mirrors pharmaceutical sulfonylureas. At the

peripheral tissue level, Alfalfa enhances glucose homeostatic disposal by upregulating the transcription and translocation of GLUT-4 vesicles into skeletal muscle and adipose cells. Furthermore, specific polyphenolic components act as competitive inhibitors against intestinal α-glucosidase and pancreatic α-amylase enzymes, slowing carbohydrate breakdown and reducing postprandial blood glucose spikes.[2,3,8]

4.3 Antioxidant and Radical Scavenging Activity

The highly oxygenated phenolic rings and hydroxyl groups of apigenin, luteolin, and tricin found in Alfalfa act as potent electron donors capable of neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS).[2,13] Beyond direct chemical scavenging, Alfalfa extracts trigger intracellular pathways that enhance the expression of endogenous antioxidant enzymes. This upregulation is primarily achieved through the activation of the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) transcription loop, leading to increased cellular production of Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx). This comprehensive enzymatic enhancement effectively protects lipid bilayers from peroxidation and prevents oxidative DNA strand breaks.[2,13]

A 2022 experimental study by Raeeszadeh et al. confirmed that the alfalfa methanolic extract (AME) significantly reduced oxidative stress markers in rat hepatic tissue following nicotine-induced injury, demonstrating significant restoration of SOD, CAT, and GPx levels and reduction in malondialdehyde (MDA) content, providing direct pharmacological evidence for its hepatoprotective-antioxidant mechanism.[13]

4.4 Anti-Inflammatory and Immunomodulatory Activity

Alfalfa significantly suppresses the production of key pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and inducible Nitric Oxide Synthase (iNOS). This action occurs via targeted downregulation of the NF-κB signaling cascade.[14] By preventing the phosphorylation and subsequent degradation of IκB, Alfalfa blocks the nuclear translocation of NF-κB, effectively shutting down the transcription of acute inflammatory genes. Aboul Naser et al. (2024) further demonstrated that the butanol fraction of *M. sativa* seeds significantly reduced IL-1β, TNF-α, PGE2, and CRP levels in CFA-induced arthritic rats, supporting its potential in managing rheumatoid arthritis through IL-1 receptor blockade.[15]

4.5 Neuroprotective Activity

Recent mechanistic investigations have positioned *M. sativa* as a promising neuroprotective agent. Pre-treatment with alfalfa methanolic extract significantly reduced cerebral infarct size, xanthine oxidase activity, $O^{-}2$ production, and thiobarbituric acid-reactive substances (TBARS) in an ischemia-reperfusion model, while restoring reduced glutathione and tissue sulfhydryl levels.[16] A comprehensive 2025 review exploring Alfalfa's role against neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease confirmed that its flavonoid and saponin-rich profile attenuates neuroinflammation, reduces oxidative stress-mediated neuronal apoptosis, and modulates cell survival signaling pathways, including PI3K/Akt.[17] Additionally, M. sativa-derived polysaccharides have demonstrated measurable neuroprotective effects attributed to their antioxidant capacity and free radical quenching potential.[18]

4.6 Hepatoprotective Activity

The hepatoprotective profile of *M. sativa* has been validated in multiple experimental models. Its phytoestrogenic compounds and flavonoids demonstrate significant capacity to lower serum ALT/AST levels, upregulate glutathione S-transferase expression, and reduce hepatic malondialdehyde accumulation.[12,13] These effects operate through the concurrent suppression of oxidative lipid peroxidation and NF-κB-driven inflammatory cascades within the hepatic parenchyma, providing cytoprotection against both chemical-induced and inflammatory hepatocellular injury.

4.7 Antimicrobial Activity

Medicagenic acid and related saponin fractions isolated from *M. sativa* display potent, broad-spectrum antimicrobial activity.[2,19] These amphiphilic saponin molecules interact with phospholipid bilayers of microbial cell membranes, inducing osmotic instability, membrane permeabilization, and subsequent leakage of intracellular contents. Furthermore, *M. sativa* Defensin 1 (MsDef1), a cysteine-rich antifungal peptide, has demonstrated potent broad-spectrum antifungal activity against fungal pathogens and has recently been explored as a potential tumor sensitizer in chemotherapy applications.[20]

4.8 Anti-Arthritic Activity

Emerging preclinical evidence strongly supports the anti-arthritic potential of *M. sativa*. Alfalfa seed metabolomic constituents significantly modulated inflammatory mediators,

oxidative stress markers, and genetic disturbance parameters in CFA-induced arthritic rats, particularly via IL-1 receptor pathway blockade.[15] The isoflavone constituents genistein and coumestrol have been shown to suppress synoviocyte proliferation through NF-κB pathway inhibition, while phenolics such as chlorogenic acid stimulate osteoblast genesis, inhibit osteoclast genesis, and balance RANK/RANKL/OPG signaling, collectively easing rheumatoid arthritis-related cartilage degradation.[9,15]

5. THERAPEUTIC APPLICATIONS

Based on its validated pharmacological activities, *Medicago sativa* can be effectively utilized across several key therapeutic areas as summarized in Table 1.

Table 1: Therapeutic applications of *Medicago sativa* with corresponding bioactive constituents.

Therapeutic Domain	Primary Bioactive Profile	Clinical Indication / Application
Cardiovascular Care	Triterpenoid Saponins, Phytosterols, Tricin	Management of hyperlipidemia, reduction of arterial plaque formation, and prevention of coronary atherosclerosis.
Endocrinology	Coumestrol, Genistein, Daidzein	Relief from postmenopausal hot flashes, night sweats, and prevention of postmenopausal osteoporotic bone loss.
Metabolic Control	Hydrophilic plant complexes, Chromium	Adjunctive glycemic regulation in Type-2 Diabetes Mellitus and management of metabolic syndrome.
Hematology	Phytonadione (Vitamin K_1)	Supportive therapy for bleeding disorders, correction of hypoprothrombinemia, and promoting healthy blood coagulation.
Neuroprotection	Polyphenols, Saponins, Phytoestrogens	Attenuation of oxidative neuronal damage and neuroinflammation in ischemia-reperfusion and neurodegenerative models.
Hepatoprotection	Flavonoids, Tocopherol, Phenolic acids	Protection against chemical-induced hepatocellular injury; reduction of ALT/AST and hepatic lipid peroxidation.
Rheumatology	Genistein, Chlorogenic acid, Saponins	Reduction of joint inflammation, synoviocyte proliferation, and cartilage degradation via NF-κB and IL-1R blockade.

6. ADVERSE EFFECTS, CONTRAINDICATIONS, AND TOXICITY

While *Medicago sativa* offers widespread therapeutic potential, unstandardized or excessive clinical administration carries specific toxicological risks that require careful medical oversight.

6.1 Induction and Exacerbation of Autoimmune Diseases (SLE)

The most significant clinical risk associated with Alfalfa is its documented ability to induce or reactivate Systemic Lupus Erythematosus (SLE) and related autoimmune conditions.[1,4] This severe adverse effect is driven by the non-protein amino acid L-canavanine, which is

highly concentrated within the seeds and raw sprouts.[1] L-canavanine serves as a direct structural analogue of L-arginine. During human protein synthesis, cellular tRNA fails to differentiate between the two molecules, resulting in the mistaken incorporation of L-canavanine in place of L-arginine into nascent polypeptide chains. This amino acid substitution disrupts the tertiary and quaternary folding of resulting proteins, creating abnormal neo-antigens. When these modified proteins are presented to the immune architecture, they trigger an aggressive autoimmune response characterized by the generation of anti-nuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies, leading to widespread T-cell dysfunction, B-cell hyperactivity, and severe inflammatory attacks on healthy host tissues.[4]

6.2 Estrogenic Disruptions

Because of elevated concentrations of coumestrol and related phytoestrogens, the prolonged or high-dose intake of Alfalfa supplements can disrupt reproductive hormone homeostasis.[10,11] Clinical signs include mastalgia, unexpected menstrual irregularities, and altered luteinizing hormone surges. Furthermore, Alfalfa preparations are contraindicated in patients with a history of estrogen-sensitive malignancies, such as breast, ovarian, or uterine carcinomas, and should not be co-administered with pharmaceutical anti-estrogens (e.g., Tamoxifen) or oral contraceptives due to competitive receptor binding.

6.3 Anticoagulant Drug Interactions

Alfalfa naturally synthesizes substantial quantities of Phytonadione (Vitamin K_1), which acts as an essential cofactor for the hepatic γ-glutamyl carboxylase enzyme, driving the activation of clotting factors II, VII, IX, and X. Consequently, the consumption of Alfalfa supplements directly counteracts oral Vitamin K antagonists, most notably Warfarin. This herb-drug interaction significantly lowers the International Normalized Ratio (INR), reduces prothrombin time, and sharply increases the risk of dangerous thromboembolic events in patients requiring therapeutic anticoagulation.[7]

7. CONCLUSION

Medicago sativa represents a highly valuable natural repository of diverse, biologically active phytochemicals. Its scientifically validated capacity to lower serum lipids, improve pancreatic insulin release, suppress pro-inflammatory signaling pathways, exert neuroprotective and hepatoprotective effects, and mitigate oxidative stress confirms its significant potential for

integration into modern pharmaceutical formulations and functional foods. The expanding body of evidence from 2020 to 2025 has particularly reinforced its anti-arthritic, neuroprotective, and hepatoprotective dimensions, moving the plant's clinical relevance well beyond traditional indications.

However, its complex biochemical profile presents clear clinical challenges — specifically L-canavanine-induced autoimmunity, significant herb-drug interactions with oral anticoagulants, and estrogenic disruption at high doses. To safely harness the full therapeutic potential of Alfalfa, future pharmacogenetic research must focus on optimizing specialized extraction protocols designed to selectively isolate beneficial saponin and flavonoid fractions while completely removing toxic anti-nutritional compounds, ensuring both high efficacy and patient safety in clinical applications.

8. CONFLICT OF INTEREST

The authors declare that they have no competing financial or personal interests that could influence the objectivity or integrity of the research presented in this manuscript.

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