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ANDROGRAPHOLIDES, THE ACTIVE PHYTOCHEMICALS OF THE MEDICINAL PLANT *ANDROGRAPHIS PANICULATA* & THEIR IMMUNOMODULATORY EFFECTS

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ABSTRACT: Andrographolides are bioactive compounds derived from the plant *Andrographis paniculata* that have gained attention for their potential as an immune modulator. Research indicates that andrographolides exhibit anti-inflammatory, antioxidant, and immunomodulatory properties. It can enhance the activity of immune cells, such as macrophages and T lymphocytes, and modulate cytokine production, which helps balance immune responses. Clinical studies suggest that andrographolides may be beneficial in treating respiratory infections, reducing inflammation, and potentially providing protective effects against autoimmune conditions. Andrographolides have been shown to inhibit key inflammatory pathways, including the NF-κB, MAPK, and STAT3 signalling pathways, which play crucial roles in the immune response. Andrographolides have been studied in combination with conventional chemotherapy drugs, showing a synergistic effect that enhances the efficacy of chemotherapy while reducing side effects. While results are promising, more extensive clinical trials are necessary to establish its effectiveness and safety for long-term use. Andrographolides show potential as a natural immune-supportive agent, warranting further exploration in integrative health approaches.

INTRODUCTION: Andrographolides extracted from the plant *Andrographis paniculata*. Andrographolides enhance immune response and balance cytokine production. It reduce inflammation by inhibiting pro-inflammatory cytokines and pathways like NF-κB. It protects cells from oxidative stress, contributing to overall health. It exhibits antibacterial and antiviral properties andrographolides explored for respiratory infections, liver health, and autoimmune disorders. Neoandrographolide is a modified form of andrographolide, also derived from *Andrographis paniculata*.

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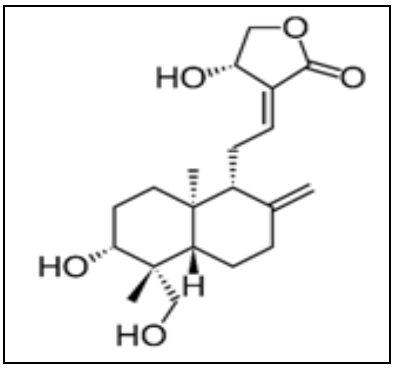
It is similar to andrographolide but with structural modifications that enhance specific properties. Neoandrographolide often shows improved potency compared to andrographolides, particularly in anti-inflammatory and anticancer activities. It modulates immune responses, although specific effects can vary based on its structure. It exhibits potential anticancer effects by inducing apoptosis in cancer cells [1, 2]. Andrographolides and neoandrographolide exhibit significant biological activity, particularly in immunomodulation and anti-inflammatory effects.

Neoandrographolide may offer enhanced therapeutic potential due to its modified structure. Ongoing research continues to explore their mechanisms and applications in health and disease. Recent research has focused on the therapeutic potential of andrographolide in various diseases, including infectious diseases, cancer, diabetes, and inflammatory disorders [2, 3].

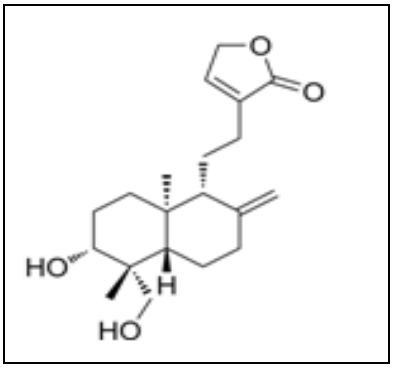
Phytochemical Constituents: Andrographolides are key phytochemical constituents found in the plant *Andrographis paniculata*, but they are not the only compound contributing to the plant's medicinal properties.

Andrographis paniculata contains a range of bioactive phytochemicals that work synergistically or independently to produce therapeutic effects. Andrographolides (Diterpenoid lactone), Primary bioactive compound with anti-inflammatory, anticancer, immunomodulatory, and hepatoprotective effects. Neoandrographolide (Diterpenoid lactone), Provides antioxidant, anti-inflammatory, and cardiovascular protection; supports liver function and reduces oxidative stress. 14-Deoxyandrographolide (Diterpenoid lactone) exhibits anti-inflammatory and antimicrobial effects, particularly helpful in infection control. 14-Deoxy-11, 12-Didehydroandrographolide known for anti-inflammatory and anticancer properties, aiding in immune modulation and cancer cell apoptosis.

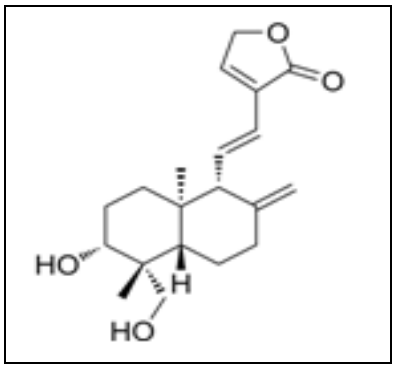
Andrograpanin enhances immune response and reduces inflammation; works synergistically with andrographolide. Flavonoids (e.g., Apigenin, Luteolin) contribute antioxidant, anti-inflammatory, and cardioprotective effects; help reduce oxidative stress and support immunity. Polyphenols Provide antioxidant benefits, aiding in free radical scavenging and enhancing the plant's anti-inflammatory effects [4, 5].



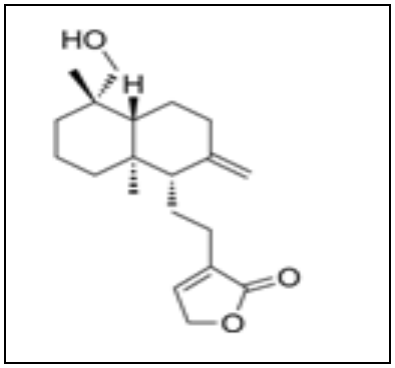
ANDROGRAPHOLIDE



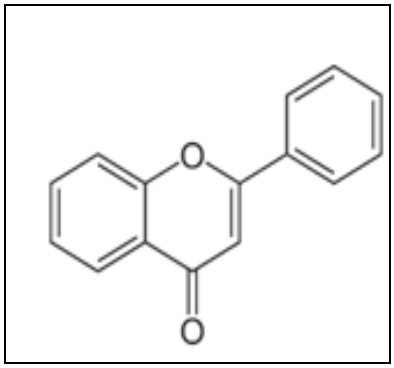
14 – DEOXYANDROGRAPHOLIDE



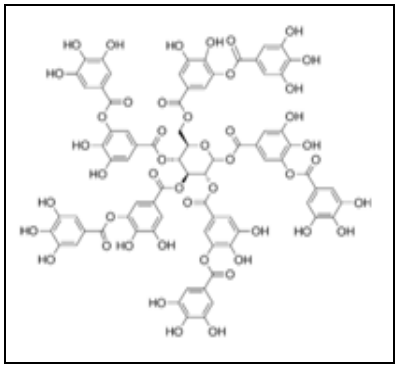
14-DEOXY-11,12-DIDEHYDROANDROGRAPHOLIDE



ANDROGRAPANIN



FLAVONOIDS



POLYPHENOL

Chemistry & Correlatives of Andrographolides: The structure-activity relationship (SAR) of andrographolide provides insights into how specific functional groups contribute to its pharmacological properties. Andrographolide's core structure is a bicyclic diterpenoid lactone with multiple reactive functional groups that play a critical role in its biological activity. The lactone ring, particularly the C-3 and C-4 positions, is essential for andrographolide's anti-inflammatory and anticancer properties. The lactone ring acts as an electrophilic site, enabling interaction with nucleophilic cellular targets (e.g., cysteine residues in proteins) that modulate signaling pathways such as NF-κB, JAK-STAT, and MAPK. The presence of a double bond between C-12 and C-13 is critical for andrographolide's biological activity, particularly its anti-inflammatory effects. It has been observed that saturation of this double bond reduces activity, possibly because the conjugated double bond aids in electron delocalization, increasing reactivity with cellular targets; this double bond also enhances binding to key proteins involved in inflammation and cancer, contributing to its inhibitory effects on these pathways. The C-19 hydroxyl group enhances andrographolide's solubility and contributes to hydrogen bonding interactions with cellular targets.

It also influences andrographolide's pharmacokinetics, affecting bioavailability and plasma half-life. The hydroxyl at C-14 is crucial for anti-inflammatory and immunomodulatory activity. Modifications or removal of this group often result in a marked decrease in bioactivity, indicating its role in the compound's potency. This group enhances the water solubility of andrographolide, improving its cellular uptake. Modifications (e.g., esterification) have been studied to enhance bioavailability while retaining biological activity. Studies have shown that methylation of the hydroxyl groups, especially at the C-3 position, can improve bioavailability while maintaining anti-inflammatory and anticancer activities. Andrographolide derivatives with esterified hydroxyl groups (e.g., succinate esters) have improved pharmacokinetic properties and better cellular uptake, enhancing anti-inflammatory and cytotoxic activities. Excessive modification of hydroxyl groups may reduce the molecule's binding affinity to key proteins. The epoxide group on andrographolide's structure affects its cytotoxic and anti-inflammatory potential. Removal or alteration of the epoxide group reduces activity in many cases, indicating it plays a significant role in protein interactions [6, 7]. Derivatives with retained or modified epoxide groups exhibit improved cytotoxicity against specific cancer cells, as the epoxide group can act as an alkylating agent that covalently modifies cellular proteins. Amine and amide derivatives of andrographolide have shown enhanced anticancer activity with better cell permeability. These modifications aim to improve specificity for cancer cells, often targeting cell proliferation and apoptosis pathways. Halogenated derivatives (e.g., brominated andrographolide) tend to have increased cytotoxicity against cancer cell lines, likely due to enhanced lipophilicity and better cellular uptake. Small modifications, while andrographolide is the primary bioactive constituent, *Andrographis paniculata* contains various diterpenoids, flavonoids, polyphenols, and other compounds that together contribute to its pharmacological profile. This diversity of constituents enables the plant to exert multi-targeted therapeutic effects, making it valuable in traditional and modern medicine [8, 9].

Function of Andrographolides:

14–Deoxyandrographolide: 14-deoxyandro-grapholide, the absence of an oxygen group at the 14th position affects its chemical properties and biological activity. Typically, oxygen-containing functional groups (like hydroxyl or carbonyl groups) influence a compound's polarity, solubility, and ability to form hydrogen bonds, which can impact its interaction with biological targets.

In other andrographolides (e.g., andrographolide itself, which has an oxygen group at the 14th position), this oxygen Increased polarity and water solubility, affecting absorption and bioavailability. Oxygen affects hydrogen bonding potential, influencing binding affinity to proteins and enzymes. It can alter electronic distribution, affecting the compound's reactivity and biological activity. 14-deoxyandrographolide lacks this oxygen group, making it slightly more hydrophobic. This difference influences its membrane permeability, binding to different biological targets, and possibly its overall pharmacokinetic profile and therapeutic effects [9, 10].

14-Deoxy-11,12-Didehydroandrographolide: The absence of an oxygen group at the 14th position alters the polarity and electronic distribution of the molecule. This can affect its ability to interact with biological targets, such as enzymes or receptors, influencing its pharmacological activity. For example, this structural change may enhance its anti-inflammatory or anticancer properties compared to other andrographolides. The presence of a double bond between C-11 and C-12 increases the molecule's rigidity and electron density in that region. This unsaturation can enhance interactions with specific biological targets, potentially growing its bioactivity or altering its mechanism of action. The lack of an oxygen group at C-14 and the double bond between C-11 and C-12 together contribute to the unique biological activities of 14-Deoxy -11, 12 - Didehydroandrographolide, differentiating it from other structurally related diterpenoids. In 14-Deoxy-11, 12-Didehydroandrographolide, the absence of an oxygen group at position 14 (compared to andrographolide) and the presence of a double bond between C11 and C12 influence its biological activity and structural properties. Oxygen-containing functional groups (like hydroxyl or ketone groups) increase the molecule's polarity, affecting water solubility and interactions with biological targets. The absence of oxygen at C14 reduces polarity, potentially enhancing lipophilicity and membrane permeability. The presence or absence of oxygen at C14 may influence binding affinity to enzymes and receptors, altering anti-inflammatory, anticancer, or antimicrobial effects. The double bond at C11-C12 introduces rigidity, affecting molecular interactions with proteins or enzymes. The reduction of oxygenated groups can affect metabolic stability, as hydroxyl or ketone groups are often sites for metabolic modification (e.g., conjugation or oxidation) [11, 12].

Andrograpanin: Andrograpanin enhances chemokine-induced leukocyte chemotaxis. Specifically, it boosts the movement of leukocytes towards higher concentrations of the chemokine stromal cell-derived factor-1α (SDF-1α) in Jurkat, THP-1, and peripheral blood lymphocyte (PBL) cells. This activity suggests that andrograpanin may contribute to the anti-infective functions of *A. paniculata* by modulating immune cell migration. It exerts anti-inflammatory effects by inhibiting the production of nitric oxide (NO) and pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-12p70, in lipopolysaccharide (LPS)-activated macrophage cells. This inhibition is achieved through the down-regulation of inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokine gene expression levels, suppressing the p38 mitogen-activated protein kinase (MAPK) signaling pathways [13, 14].

Overview of the Research Regarding Andrographolides:

Anti-Inflammatory and Immunomodulatory Properties: Andrographolides have been shown to inhibit key inflammatory pathways, including the NF-κB, MAPK, and STAT3 signaling] pathways, which play crucial role in the immune response. Recent studies highlight its potential in treating chronic inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease (IBD) [15].

Autoimmune Diseases: Studies suggest that andrographolides may modulate the immune response, making it a potential candidate for treating autoimmune diseases like rheumatoid arthritis and multiple sclerosis. In animal models of rheumatoid arthritis, it reduced joint inflammation and cytokine production.

Immunomodulation: Research has shown andrographolide's ability to modulate immune responses by balancing Th1/Th2 immune pathways. This makes it a potential candidate for treating autoimmune diseases and enhancing immune responses in various infections [16, 17].

COVID-19: Some studies have explored using andrographolides asan adjunct treatment for COVID-19 due to its anti-inflammatory and antiviral properties. It is believed to modulate the excessive inflammatory response (cytokine storm) in severe COVID-19 cases.

HIV, Influenza, Hepatitis C: Andrographolides also exhibit inhibitory effects on other viruses by modulating viral proteins or the host's immune response, making it a potential antiviral agent for several viral infections.

Andrographolide has Demonstrated Anticancer Activity Through Several Mechanisms, Including: Inducing apoptosis (programmed cell

death) in cancer cells. Inhibiting cancer cell proliferation by arresting the cell cycle in the G0/G1 or G2/M phase. Suppressing angiogenesis (formation of new blood vessels in tumors) and metastasis (spread of cancer). Studies have explored andrographolide's effects on various cancers, including breast, prostate, lung, colorectal, and pancreatic cancers. It works by modulating several signaling pathways, such as PI3K/Akt, JAK/STAT, and Wnt/β-catenin. Andrographolides are being studied for its protective effects on the cardiovascular system [18]. It is believed to reduce oxidative stress, inhibit inflammation in blood vessels, and protect against ischemia-reperfusion injury (damage caused when blood supply returns to tissue after a period of lack of oxygen). These cardioprotective effects could make it a potential therapeutic agent in conditions like atherosclerosis, hypertension, and myocardial infarction. Emerging research points toward andrographolide's neuroprotective properties, particularly in protecting neurons from oxidative stress and inflammation. This is relevant to neurodegenerative diseases like Alzheimer's and Parkinson's.

In animal models, andrographolides have shown promising results in improving cognitive function and reducing neuroinflammation. Andrographolides have demonstrated antibacterial properties against both Gram-positive and Gram-negative bacteria. Research highlights its potential in managing antibiotic-resistant bacterial infections. Studies have reported andrographolide's efficacy against parasites such as Plasmodium falciparum (the parasite responsible for malaria) and Leishmania species, suggesting its potential as an antimalarial and antileishmanial agent [19].

Hepatoprotective and Antioxidant Properties:

Liver Protection: Andrographolides are noted for its hepatoprotective effects, particularly in preventing liver damage caused by toxins, drugs, or alcohol. It helps restore liver function and reduces inflammation and oxidative stress in the liver.

Antioxidant Activity: By neutralizing free radicals, andrographolides may also protect against oxidative damage at the cellular level, making it beneficial for conditions driven by oxidative stress, such as liver diseases, neurodegeneration, and cardiovascular disorders [20].

Potential in Metabolic Disorders:

Anti-Diabetic Effects: Research indicates that andrographolides can improve glucose metabolism, increase insulin sensitivity, and protect pancreatic β-cells, making it a promising candidate for type 2 diabetes management.

Anti-Obesity: Andrographolide's ability to inhibit adipogenesis (fat cell formation) and enhance lipid metabolism suggests its potential role in obesity treatment. Andrographolides modulate the immune system through multiple pathways, primarily involving the regulation of pro-inflammatory cytokines and signaling cascades [21].

Inhibition of NF-κB Pathway: The NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway is a critical regulator of immune and inflammatory responses. Andrographolides modulate the immune system mainly by inhibiting this pathway. Under normal conditions, NF-κB is held in the cytoplasm in an inactive state bound to its inhibitor, IκBα. Pro-inflammatory stimuli like TNF-α or pathogens activate IκB kinase (IKK), which phosphorylates IκBα, leading to its degradation and subsequent release of NF-κB. The free NF-κB then translocates to the nucleus, promoting the transcription of pro-inflammatory genes, including cytokines (like IL-6, TNF-α), chemokines, and adhesion molecules. Andrographolides inhibit the phosphorylation and degradation of IκBα, thereby preventing NF-κB translocation to the nucleus. This reduces the transcription of pro-inflammatory cytokines and mediators, thereby attenuating the inflammatory response [22].

Suppression of JAK/STAT Pathway: The JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling pathway plays a key role in cytokine-mediated immune responses. In this pathway, cytokines bind to their receptors and activate JAKs, which then phosphorylate the STAT proteins. Phosphorylated STATs dimerize and move into the nucleus, where they drive the expression of genes related to inflammation and immunity [23]. Andrographolides interfere with the JAK/STAT pathway by inhibiting the phosphorylation of STAT proteins (particularly STAT3), thus preventing the expression of pro-inflammatory genes such as IL-6 and IL-1β.

By suppressing STAT3 activation, andrographolides modulate immune cell activity and promote an anti-inflammatory environment.

Modulation of MAPK Pathway: The MAPK (mitogen-activated protein kinase) pathway is another crucial regulator of immune responses, including inflammation and cell differentiation. The MAPK pathway includes several kinases, such as ERK, JNK, and p38, which respond to extracellular stimuli like cytokines or stress signals. These kinases, when activated, phosphorylate transcription factors that control the expression of inflammatory genes. Andrographolides inhibit the activation of JNK and p38 MAPK, which reduces the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. By blocking this pathway, andrographolides help to reduce the inflammatory responses in various immune-mediated conditions [24].

Activation of Nrf2/ARE Pathway: The Nrf2 (nuclear factor erythroid 2–related factor 2) pathway is a key regulator of the antioxidant response, which is closely linked to immune modulation and inflammation. Under normal conditions, Nrf2 is bound to its repressor protein, Keap1, in the cytoplasm.

Upon activation by oxidative stress or other stimuli, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it binds to the antioxidant response element (ARE) in the DNA, promoting the expression of antioxidant enzymes such as glutathione S-transferase (GST) and heme oxygenase-1 (HO-1).

Andrographolides enhance the activation of the Nrf2/ARE pathway, thereby boosting the production of antioxidant enzymes. This helps reduce oxidative stress and associated inflammation, contributing to its immuno-modulatory effects. By reducing oxidative stress, it also indirectly suppresses immune activation and inflammatory cytokine production [25].

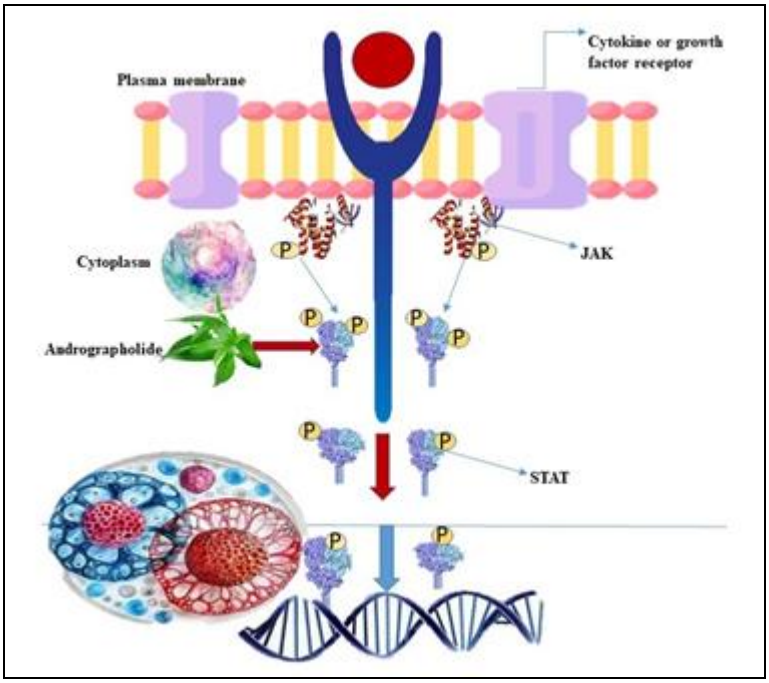


FIG. 1: DIAGRAM OF ACTIVATION OF PATHWAY

Suppression of Pro-Inflammatory Cytokines: Andrographolides directly reduce the production of various pro-inflammatory cytokines and chemokines, which are key players in immune responses. TNF-α a potent pro-inflammatory cytokine involved in systemic inflammation. IL-6 Plays a major role in acute inflammation and in the transition to chronic inflammation.IL-1β another pro-inflammatory cytokine that mediates immune and inflammatory responses.MCP-1 a chemokine that recruits monocytes to sites of inflammation. Andrographolides reduce these cytokines by inhibiting the transcription factors (like NF-κB and STAT3) that regulate their production.

This helps in controlling excessive inflammation and immune activation.

Th1/Th2 Balance Modulation: Andrographolides also influence the balance between Th1 and Th2 immune responses, which is important in various autoimmune and allergic diseases. Th1 cells promote cell-mediated immunity and are typically involved in responses to intracellular pathogens like viruses. However, excessive Th1 responses are associated with autoimmune diseases. Th2 cells promote humoral immunity (antibody production) and are involved in allergic reactions and responses to extracellular pathogens.

Andrographolide's Action: Research suggests that andrographolides help maintain a balanced Th1/Th2 response. It reduces the Th1-driven inflammatory response by decreasing the production of Th1 cytokines (like IFN-γ) and enhances regulatory T cell (Treg) function, promoting immune tolerance and reducing the risk of autoimmunity [26].

Influence on Tregs (T cell) and M1/M2 Macrophage Polarization: Regulatory T Cells are essential for maintaining immune tolerance and preventing autoimmune diseases. Andrographolides promote T cell function, helping to suppress excessive immune responses and inflammation.

Macrophage Polarization: Macrophages exist in two main states.

M1 Macrophages: Pro-inflammatory and involved in pathogen clearance and tissue damage.

M2 Macrophages: Anti-inflammatory and involved in tissue repair and resolving inflammation. Andrographolides shift the balance from M1 to M2 macrophages, reducing inflammation and promoting tissue repair, which is beneficial in chronic inflammatory and autoimmune conditions. Andrographolides have most prominent role on liver. Andrographolides have demonstrated significant hepatoprotective activity in various studies, making it a compound of undivided attention for liver health.

Antioxidant Properties: Andrographolides exhibit strong antioxidant properties, which help reduce oxidative stress in liver cells. Neutralizing free radicals protects hepatocytes from damage caused by toxins and inflammatory processes.

Reduction of Liver Enzymes: Research has shown that andrographolides can lower elevated liver enzymes (such as ALT and AST), indicators of liver damage. This suggests its potential to improve liver function and health.

Anti-inflammatory Effects: Andrographolides can inhibit pro-inflammatory cytokines and pathways, reducing inflammation in the liver. This is particularly beneficial in conditions like fatty liver disease and hepatitis, where inflammation plays a key role in disease progression.

Protection against Drug-Induced Toxicity: Studies have indicated that andrographolides can protect the liver from damage caused by certain drugs and toxins, such as acetaminophen. It helps in preventing necrosis and apoptosis of liver cells.

Fibrosis and Cirrhosis Prevention: Some research suggests that andrographolides may help prevent liver fibrosis and cirrhosis by inhibiting hepatic stellate cells' activation and promoting antifibrotic factors' expression.

Regeneration of Liver Cells: There is evidence that andrographolides may promote the regeneration of liver cells, aiding recovery from liver injury and enhancing overall liver function.

Clinical Relevance: While many studies are preclinical (*in-vitro* or animal models), these findings highlight the potential of andrographolides as a therapeutic agent for liver diseases. Clinical studies are needed to confirm its efficacy and safety in humans [27].

Andrographolides have garnered attention for their potential neuroprotective effects, with several studies exploring its mechanisms and therapeutic implications.

Protection against Excitotoxicity: Some studies suggest that andrographolides can protect neurons from excitotoxicity caused by excessive stimulation of glutamate receptors. This protection could help prevent neuronal death associated with conditions like Alzheimer's and Parkinson's diseases.

Promoting Neurogenesis: Research indicates that andrographolides may stimulate neurogenesis, generating new neurons, which could be beneficial in recovery from brain injuries and age-related cognitive decline.

Modulation of Neurotransmitters: Andrographolides may influence levels of neurotransmitters, potentially improving mood and cognitive function.

Protective Effects in Animal Models: Various animal studies have demonstrated that andrographolides can reduce cognitive deficits and brain damage in models of neurodegeneration, providing a basis for its potential therapeutic use.

The safety and bioavailability of andrographolides have been subjects of research, revealing essential insights for their use in therapeutic applications. Generally, andrographolides are considered safe at moderate doses. Animal studies have shown low acute toxicity, but excessive doses may lead to adverse effects such as gastrointestinal issues or liver toxicity. Limited clinical trials have reported mild side effects like nausea and diarrhoea. More extensive studies are needed to confirm its long-term safety in humans. Andrographolides may interact with certain medications (e.g., anticoagulants or immunosuppressants), so caution is advised, especially in patients taking other treatments one of the main challenges with andrographolides and its low oral bioavailability. Factors contributing to this include poor solubility and extensive first-pass metabolism. Research has explored various formulation strategies to enhance bioavailability, including nanoparticles, liposomes, and complexation with other substances (like cyclodextrins). Studies indicate that the peak plasma concentration of andrographolides occur within a few hours after administration, but its rapid elimination can limit its therapeutic effects. Different dosage forms (e.g., extracts, capsules) may influence bioavailability, and optimal dosing regimens are still being investigated.

Liposomal formulations of andrographolides offer several beneficial effects that enhance their therapeutic potential. Liposomes can encapsulate andrographolides, protecting it from degradation in the gastrointestinal tract and enhancing its absorption. This leads to higher bioavailability compared to standard formulations. Liposomes can be engineered to target specific tissues or cells, allowing for more effective delivery of andrographolides to sites of action, such as inflamed or damaged tissues. By improving the targeted delivery and reducing systemic exposure, liposomal formulations may minimize potential side effects of higher doses of free andrographolides. Encapsulating andrographolides in liposomes can protect them from oxidative degradation and enhance its stability, making them more effective over time. Nanoparticle formulations of Andrographolides can be engineered to cross the blood-brain barrier more effectively, making them particularly useful for neuroprotective applications. Nanoparticles can be co-loaded with other therapeutic agents, creating synergistic effects that may enhance the overall efficacy of treatment. Nanoparticle formulations can be adapted for various routes of administration, including oral, intravenous, or topical, providing flexibility in treatment options [28].

Anti-inflammatory Activity of Andrographolide: Andrographolides, a diterpenoid lactone derived from *Andrographis paniculata* (commonly known as the "King of Bitters"), have demonstrated significant anti-inflammatory activity in numerous studies. Andrographolides reduce the levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β. By inhibiting these signalling molecules, andrographolides help reduce inflammation in various tissues. Andrographolides inhibit the NF-κB (nuclear factor-kappa B) pathway, which plays a crucial role in the inflammatory response. NF-κB activation leads to the expression of genes involved in inflammation, including cytokines, chemokines, and enzymes like COX-2 and iNOS. Andrographolides suppress NF-κB activation, thereby reducing inflammation. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) enzymes are elevated in inflammatory conditions. Andrographolides have been shown to downregulate COX-2 and iNOS, thereby reducing the production of pro-inflammatory prostaglandins and nitric oxide. It can inhibit mitogen-activated protein kinase (MAPK) pathways involved in cellular responses to inflammatory stimuli.

Suppressing MAPK signaling helps modulate inflammation and immune responses. Andrographolides modulate immune cell activity, particularly T cells, and has been found to reduce the infiltration of neutrophils and macrophages in inflamed tissues. This helps prevent excessive immune response and tissue damage.

Mechanism of Anti inflammatory Action: Andrographolides, a diterpenoid lactone isolated from *Andrographis paniculata*, exhibits strong anti-inflammatory effects. Andrographolides suppress the activation of nuclear factor-kappa B (NF-κB), a critical transcription factor in inflammatory processes. NF-κB normally activates genes responsible for producing pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. By inhibiting NF-κB, andrographolides reduce the transcription of these cytokines, thereby dampening inflammation. By blocking NF-κB and other inflammatory pathways, andrographolides lower the expression and release of cytokines like TNF-α, IL-1β, and IL-6, which mediate the immune response. This action reduces inflammatory signaling and infiltration of immune cells at inflammation sites. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are enzymes that contribute to inflammation by producing prostaglandins and nitric oxide, respectively. Andrographolides have been shown to inhibit the expression of COX-2 and iNOS, reducing the production of these inflammatory mediators. Andrographolides also inhibit the NLRP3 inflammasome, a protein complex that plays a crucial role in the innate immune response by promoting the maturation and release of pro-inflammatory cytokines like IL-1β. By inhibiting NLRP3 activation, andrographolides can reduce the inflammatory response at a cellular level [28].

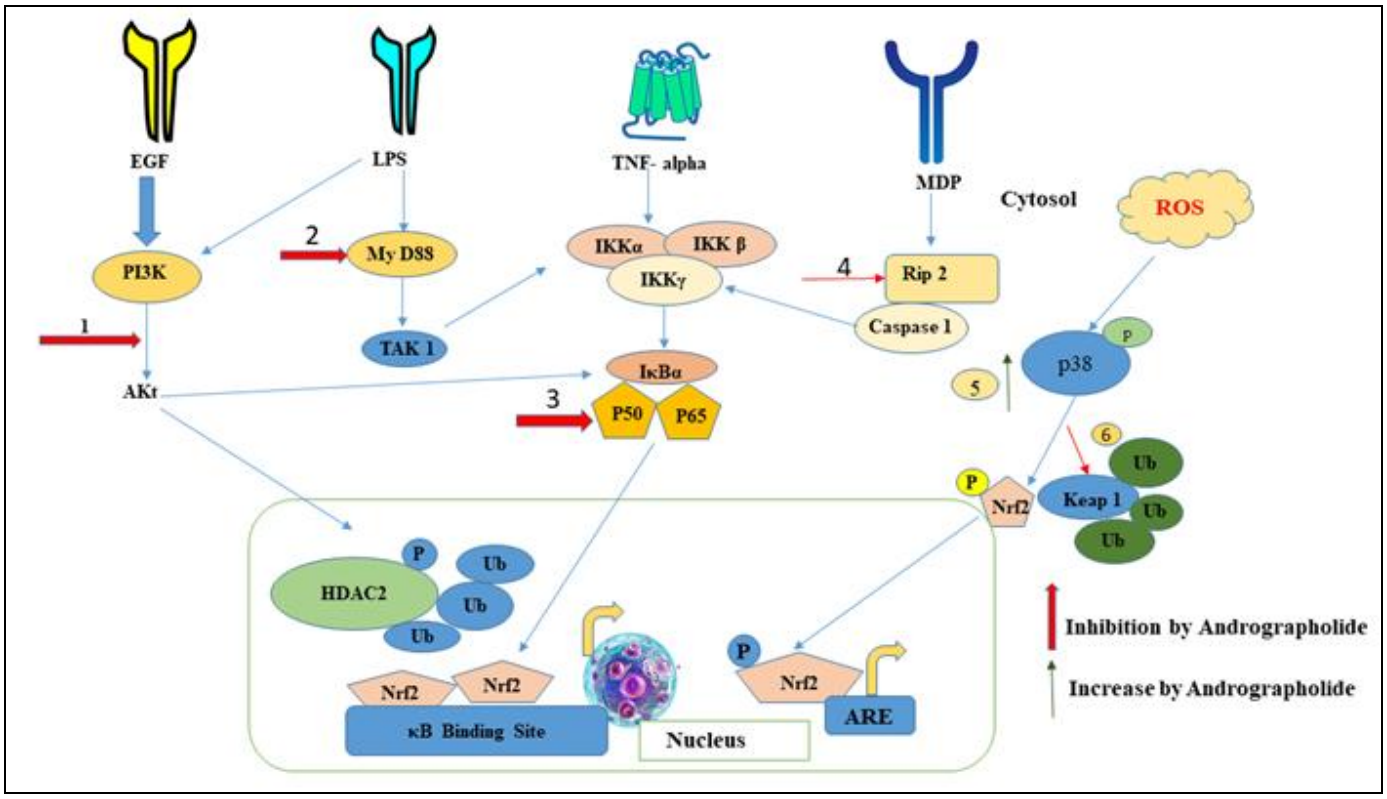


FIG. 2: DIAGRAM OF ANTI-INFLAMMATORY ACTION

Anticancer Effect of Andrographolide: Andrographolides exhibit significant anticancer properties, primarily through its influence on cell signaling pathways, apoptosis, and inhibition of cancer cell proliferation. It promotes apoptosis (programmed cell death) in cancer cells *via* intrinsic and extrinsic pathways. It activates caspase enzymes (such as caspase-3 and caspase-9) and promotes mitochondrial dysfunction, releasing cytochrome c, which further triggers cell death. This apoptosis-inducing effect reduces tumor cell survival. Andrographolides inhibit various growth-promoting pathways, such as PI3K/Akt/mTOR and MAPK, which are often

over activated in cancer cells. By blocking these pathways, andrographolides reduce cell proliferation and tumor growth, especially in cancers like breast, prostate, and lung cancer. Angiogenesis, the process by which tumors form new blood vessels to supply oxygen and nutrients, is critical for cancer progression. Andrographolides inhibit vascular endothelial growth factor (VEGF) expression and other angiogenic factors, thereby restricting the blood supply to the tumor and slowing its growth. It suppresses metastatic and invasive capabilities of cancer cells by downregulating matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which play a role in breaking down the extracellular matrix. This effect limits cancer cells' ability to spread to other parts of the body. It modulates tumor suppressor proteins, such as p53, which is often inactivated in cancer cells. By activating p53, andrographolides enhance cell cycle arrest and apoptosis, thereby inhibiting tumor growth. It also upregulates p21, a cyclin-dependent kinase inhibitor, leading to cell cycle arrest in the G1 phase. It can enhance immune responses against cancer cells. It activates immune cells, such as T cells and natural killer (NK) cells, which contribute to the destruction of cancer cells. This immune-modulating effect adds an additional layer of anticancer activity, especially in immunogenic tumors. Cancer cells often have higher levels of reactive oxygen species (ROS), contributing to mutation, proliferation, and survival. Andrographolides can reduce oxidative stress, lowering ROS levels and reducing the mutations and signaling supporting cancer growth. Andrographolides have been shown to suppress oncogenes like MYC and BCL-2, which are commonly overexpressed in cancers. By downregulating these oncogenes, andrographolides limit cancer cell survival and reduces resistance to apoptosis [28].

Toxicology of Andrographolide: Andro-grapholides, are bioactive compound derived from *Andrographis paniculata*, is widely recognized for its pharmacological benefits, including anti-inflammatory, antiviral, and anticancer properties. Studies on acute toxicity indicate that andrographolides have a relatively high safety margin. Animal models have shown that high doses (up to several grams per kilogram) do not result in significant lethality or acute toxic responses. The LD50 (lethal dose for 50% of subjects) for andrographolides in rodents is generally high, suggesting low acute toxicity. Prolonged administration of andrographolides at therapeutic doses has not demonstrated significant toxic effects in most animal studies. However, some studies have indicated potential hepatotoxicity and nephrotoxicity when used at high or prolonged doses. Signs of liver enzyme elevation and histopathological changes have been observed in high-dose chronic exposure, warranting caution in long-term use.

Organ-Specific Toxicity:

Liver Toxicity: The liver is the primary site for metabolism and biotransformation of andrographolides and high doses may lead to hepatic stress. Some high-dose animal studies have noted increased liver enzymes (such as ALT and AST) and mild liver histological changes, indicating potential hepatotoxicity.

Kidney Toxicity: High doses of andrographolides have shown evidence of nephrotoxicity, with reported changes in kidney function markers and histopathological alterations in renal tissue under excessive or prolonged exposure.

Clinical use of *Andrographis paniculata* extracts containing andrographolides have generally been safe, with few reported adverse effects when used at recommended dosages. The most common side effects include mild gastrointestinal discomfort, headache, and allergic reactions. Reports of severe toxicity are rare but may occur with excessive dosages or in sensitive individuals.

Inflammatory Lung Diseases: COPD involves chronic inflammation, oxidative stress, and tissue remodeling. Reduces inflammation by downregulating pro-inflammatory cytokines (e.g., TNF-α, IL-6). Alleviates oxidative stress by enhancing antioxidant enzyme activity. Modulates airway remodeling through inhibition of matrix metalloproteinases (MMPs). Asthma is characterized by airway hyperreactivity, inflammation, and mucus overproduction. It suppresses Th2-mediated immune responses, reducing IL-4, IL-5, and IL-13 levels and inhibits NF-κB and STAT6 pathways, which are critical in asthma pathogenesis, eases airway hyperreactivity,

and prevents mucus hypersecretion. ARDS (Acute respiratory distress syndrome) involves severe inflammation and lung damage, often triggered by infections or trauma. IPF (Idiopathic Pulmonary Fibrosis) involves progressive lung scarring due to chronic inflammation and fibroblast activation and inhibits fibroblast proliferation and collagen deposition, slowing fibrosis. Attenuates TGF-β1 signaling, a key pathway in fibrotic processes. Lung cancer involves uncontrolled cell growth and inflammation-driven tumor progression. Induces apoptosis in cancer cells via activation of caspase pathways and reduces tumor-related inflammation and angiogenesis. May enhance the effectiveness of chemotherapy and reduce side effects. Pulmonary TB involves chronic inflammation and immune dysregulation caused by Mycobacterium tuberculosis. Enhances macrophage-mediated pathogen clearance. Modulates immune responses to prevent excessive inflammation and exhibits antimicrobial activity against TB and other respiratory pathogens.

Autoimmune Disorder: Andrographolides, are bioactive compound from *Andrographis paniculata*, has shown potential in modulating cellular pathways implicated in autoimmune disorders. Its effects are largely mediated through its influence on inflammatory signaling cascades, immune cell activity, and oxidative stress pathways. Andrographolides are potent inhibitor of the NF-κB pathway, a central regulator of inflammation and immune responses.

It prevents the phosphorylation and degradation of IκBα (an NF-κB inhibitor), thereby inhibiting the nuclear translocation of NF-κB. This action reduces the transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), chemokines, and adhesion molecules, which are elevated in autoimmune disorders such as rheumatoid arthritis and multiple sclerosis. Janus kinase (JAK), signal transducer and activator of transcription (STAT) signaling, andrographolides reduce cytokine-mediated immune responses. This modulation helps suppress the excessive activity of Th1 and Th17 cells, which are often hyper activated in autoimmune diseases. Andrographolides activate nuclear factor erythroid 2–related factor 2 (Nrf2), which is crucial for cellular defense against oxidative stress.

Enhanced Nrf2 activity promotes the expression of antioxidant enzymes like hemeoxygenase-1 (HO-1) and glutathione peroxidase, protecting cells from oxidative damage in autoimmune disorders. Inhibitor of the NF-κB pathway, a central regulator of inflammation and immune response. Andrographolides modulate TLR signaling, particularly TLR4, which is involved in recognizing danger-associated molecular patterns (DAMPs) and initiating immune responses. This action dampens innate immune activation and the subsequent inflammatory cascade. It suppresses the differentiation and proliferation of pro-inflammatory T cell subsets (Th1 and Th17) and enhances regulatory T cells (Tregs). This helps restore immune balance and prevent autoimmune tissue damage. Andrographolides reduce NLRP3 inflammation activation, which is linked to the release of IL-1β and IL-18, potent mediators of inflammation in autoimmune diseases [27].

Antitumor Effect: Andrographolides induce apoptosis via the intrinsic mitochondrial pathway by increasing the Bax/Bcl-2 ratio and activating caspase-9 and caspase-3. Endoplasmic Reticulum Stress triggers ER stress, leading to apoptosis through the upregulation of CHOP and caspase-12. It inhibits cell cycle progression, particularly at the G1/S or G2/M phases, by downregulating cyclins (e.g., Cyclin D1) and cyclin-dependent kinases (CDKs) while upregulating CDK inhibitors such as p21 and p27.

By suppressing NF-κB activity, andrographolides decrease the transcription of genes associated with cell survival and proliferation, such as Bcl-2 and survival. PI3K/Akt/mTOR Pathway inhibits the PI3K/Aktsignalling cascade, reducing tumor growth and survival. MAPK/ERK It modulates MAPK/ERK signaling to suppress oncogenic proliferation.

Andrographolides inhibit vascular endothelial growth factor (VEGF) and its receptor-mediated signalling, reducing tumor angiogenesis. It downregulates hypoxia-inducible factor-1α (HIF-1α), a critical driver of tumor vascularization under hypoxic conditions. It reduces metastasis by inhibiting matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, essential for extracellular matrix degradation and tumor

invasion. Andrographolides also modulate epithelial-to-mesenchymal transition (EMT) markers, decreasing N-cadherin and vimentin while increasing E-cadherin [29, 30]. Reactive Oxygen Species (ROS) induces ROS accumulation in cancer cells, leading to oxidative stress and subsequent apoptosis. Healthy cells are less affected, highlighting its selective cytotoxicity. Andrographolides enhance antitumor immunity by stimulating the activity of cytotoxic T cells and natural killer (NK) cells. It modulates the tumor microenvironment, reducing immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [26].

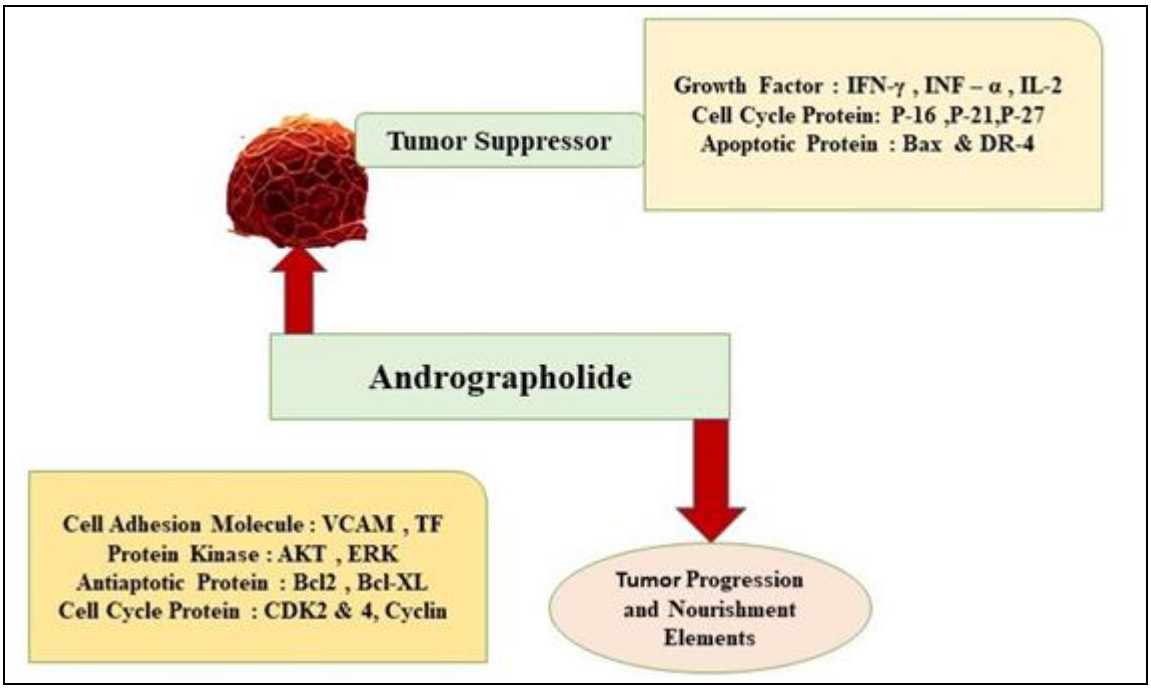


FIG. 3: ANTITUMOR EFFECT OF ANDROGRAPHOLIDE

Preclinical and Clinical Evidence: Priclinical Studies of andrographolides have shown efficacy against various cancers, including breast, lung, colon, prostate, liver, and pancreatic cancers, *in-vitro* and *in-vivo*. Although preclinical data are promising, clinical trials on andrographolides as antitumor agent are limited. Early-phase studies have indicated tolerability and potential efficacy when used alone or as an adjunct to chemotherapy. Andrographolides enhance the efficacy of conventional chemotherapeutic agents (e.g., cisplatin, doxorubicin) by sensitizing tumor cells to these drugs, reducing drug resistance, and mitigating chemotherapy-induced toxicity [29].

CONCLUSION: Andrographolides demonstrate significant potential as an immunomodulator, supported by both preclinical and clinical evidence. Its ability to regulate immune responses stems from its impact on multiple molecular pathways. Andrographolides have shown promising results in reducing inflammation and improving outcomes in viral infections like influenza, dengue, and COVID-19. Its ability to modulate cytokine production is particularly relevant in managing cytokine downpours. It stimulates the immune system by enhancing macrophage activity, lymphocyte proliferation, and antibody production. This dual effect of suppressing hyperactive immune responses while supporting baseline immunity positions it as a balanced immunomodulator. Preliminary studies suggest its ability to downregulate aberrant immune responses in autoimmune conditions (e.g., rheumatoid arthritis) without significantly compromising overall immunity. Andrographolides hold promise as a complementary therapy in managing inflammatory and immune-related diseases. However, more clinical trials are essential to define standardized dosages, safety parameters, and its full therapeutic potential.

Future Prospects: The future prospects of andrographolides are therapeutic agent are promising due to its broad spectrum of biological activities. Andrographolide's low bioavailability

can be addressed through advanced drug delivery technologies, such as nanoparticles, liposomes, and prodrug formulations. Development of sustained-release formulations to enhance therapeutic effects and compliance. Andrographolides in combination with existing drugs (e.g., antivirals, anti-inflammatory agents, or chemotherapeutics) to improve efficacy and reduce side effects. Deeper investigation into molecular pathways modulated by andrographolides, such as its effects on NF-κB, STAT3, and oxidative stress-related mechanisms. Understanding genetic factors influencing individual responses to andrographolides to enable personalized medicine approaches. With advancements in pharmaceutical sciences and a growing interest in plant-based therapeutics, andrographolides could play a significant role in the future of medicine.

Current research of Andrographolides: A 2024 study investigated andrographolide's anti-inflammatory activity compared to common nonsteroidal anti-inflammatory drugs (NSAIDs). The research revealed that andrographolides effectively inhibited the release of pro-inflammatory cytokines such as IL-6, TNF-α, and IFN-γ in lipopolysaccharide (LPS) and interferon-γ induced RAW264.7 cells. This cytokine-inhibiting activity was associated with the downregulation of the NF-κB pathway, suggesting andrographolide's potential as a therapeutic agent against cytokine storms. Another study explored the binding affinities of andrographolides and its derivative, 14-deoxy-11,12-didehydroandrographolide, with key COVID-19 proteins, including 3CLpro, PLpro, and the spike protein. The findings indicated strong interactions, particularly with papain-like protease (PLpro), suggesting potential antiviral properties. Network pharmacology analysis further elucidated pathways of immunomodulation, highlighting andrographolide's role in modulating immune responses [31].

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