Comparative Anticancer Potential of Artemisia Vulgaris, Cichorium Intybus, and Smilax Glabra: A Review

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Abstract

Cancer remains a leading global health burden, necessitating exploration of alternative therapies. This review comparatively analyzes the anticancer potential of three traditional medicinal plants: Artemisia vulgaris, Cichorium intybus, and Smilax glabra. These plants exhibit diverse bioactive compounds, including flavonoids, terpenoids, and saponins, contributing to antioxidant, anti-inflammatory, antiproliferative, and apoptosis-inducing effects. Specifically, Artemisia vulgaris induces cytotoxicity via mitochondrial dysfunction and caspase activation, Cichorium intybus modulates NF-κB and Wnt/β-catenin pathways to inhibit proliferation, and Smilax glabra induces ROS-mediated apoptosis and modifies the tumor microenvironment. These plants also demonstrate potential in angiogenesis inhibition (e.g., Artemisia vulgaris through VEGF downregulation), immune modulation, and oxidative stress suppression. Despite promising preclinical results, challenges such as bioavailability, extract standardization, and limited clinical trials hinder their clinical translation. Future research should prioritize nano-formulations, synergistic combination therapies, and large-scale clinical studies to validate their efficacy and safety in oncology.

Keywords: *Anticancer, Oxidative Stress, Tumour, Bioactive Compounds, Traditional Medicine, Oncology.*

1. INTRODUCTION AND LITERATURE REVIEW

Cancer represents a major global health crisis, contributing to millions of deaths annually. Despite advancements in conventional cancer treatments like chemotherapy, radiation, and targeted therapies, challenges such as high costs, severe side effects, and drug resistance underscore the need for alternative and complementary approaches. Traditional medicinal plants, with their rich history of therapeutic use, offer a promising avenue for exploration. These plants contain a diverse array of bioactive compounds, including flavonoids, polyphenols, alkaloids, terpenoids, and saponins, known for their antioxidant, anti-inflammatory, and cytotoxic properties. These phytochemicals play pivotal roles in modulating cancer cell growth, inducing apoptosis, inhibiting angiogenesis, and suppressing metastasis. This review focuses on three medicinal plants—*Artemisia vulgaris* (mugwort), *Cichorium intybus* (chicory), and *Smilax glabra* (sarsaparilla)—each with a history of traditional use and emerging evidence of anticancer potential.

1.1. **Artemisia *vulgaris***, a perennial herb from the Asteraceae family, has been used in traditional medicine for digestive, menstrual, and inflammatory conditions. Its phytochemical profile includes flavonoids, coumarins, sesquiterpene lactones, and essential oils. Studies have shown that *A. vulgaris* exhibits anticancer activity through mechanisms such as ROS generation, mitochondrial dysfunction, caspase activation, and VEGF downregulation, leading to apoptosis and angiogenesis inhibition.

1.2. Cichorium *intybus*, also from the Asteraceae family, is widely cultivated and used as a dietary supplement. Traditionally, it has been valued for its hepatoprotective, diuretic, and anti-inflammatory properties. *C. intybus* contains polyphenols, inulin, sesquiterpene lactones, and flavonoids. Its anticancer potential is attributed to its ability to induce apoptosis, arrest the cell cycle, and modulate key signaling pathways like NF-κB, Wnt/β-catenin, and PI3K/Akt. Polyphenols and inulin contribute to antioxidant effects and gut microbiota modulation, respectively, while sesquiterpene lactones interfere with cancer cell proliferation.

1.3. Smilax *glabra*, from the Smilacaceae family, is a staple in Traditional Chinese Medicine (TCM) for its detoxifying, anti-inflammatory, and diuretic effects. Its rhizomes are rich in flavonoids, stilbenes, saponins, and phenolic acids. Research indicates that *S. glabra* exhibits anticancer properties by inducing apoptosis, inhibiting cell proliferation, and suppressing metastasis. Its bioactive compounds modulate signaling pathways like p53, MAPK, and NF-κB, and also modify the tumour microenvironment by reducing hypoxia-induced factors and inhibiting angiogenesis.

1.4. Phytochemical Composition

Plant	Key Phytochemicals	Pharmacological Importance
Artemisia *vulgaris*	Flavonoids, terpenoids, sesquiterpene lactones, coumarins	Antioxidant, anti-inflammatory, cytotoxic against cancer cells
Cichorium *intybus*	Polyphenols, inulin, sesquiterpene lactones, flavonoids	Immunomodulatory, anticancer, hepatoprotective
Smilax *glabra*	Flavonoids, saponins, stilbenes, phenolic acids	Antiproliferative, anti-inflammatory, detoxifying properties

2. MECHANISMS OF ANTICANCER ACTION

The anticancer properties exhibited by *Artemisia vulgaris* (*A. vulgaris*), *Cichorium intybus* (*C. intybus*), and *Smilax glabra* (*S. glabra*) are multifaceted, engaging a range of biological pathways that collectively contribute to cancer cell demise, proliferation control, and modulation of the tumour microenvironment. These pathways encompass the induction of apoptosis, the stringent suppression of tumour cell proliferation, the amelioration of oxidative stress and inflammation, and the precise regulation of signaling cascades that govern tumour growth and metastatic potential.

2.1. Induction of Apoptosis:

Apoptosis, or programmed cell death, serves as a critical mechanism for the selective elimination of damaged and cancerous cells. Many cancer cells circumvent this process, leading to unchecked proliferation and tumour progression. The bioactive compounds inherent in *A. vulgaris*, *C. intybus*, and *S. glabra* have demonstrated potent pro-apoptotic effects. Specifically, *A. vulgaris* initiates apoptosis through the disruption of mitochondrial function and the activation of caspase-dependent pathways. Its bioactive constituents, including flavonoids and sesquiterpene lactones, enhance the release of cytochrome c from mitochondria, thereby activating caspase-9 and caspase-3, both pivotal in executing apoptosis. Furthermore, *A. vulgaris* elevates the production of reactive oxygen species (ROS), inducing oxidative stress that triggers apoptotic cascades. *C. intybus* enhances apoptosis by modulating key proteins within the apoptotic pathway, particularly the Bcl-2 family. It curtails the expression of the anti-apoptotic protein Bcl-2 while elevating the levels of the pro-apoptotic protein Bax, thus tilting the balance towards apoptosis. Additionally, polyphenols such as chicoric acid and caffeic acid, found in *C. intybus*, contribute to apoptosis induction by targeting tumour necrosis

factor (TNF)-related signaling. *S. glabra* exhibits strong pro-apoptotic capabilities through the generation of ROS, leading to DNA fragmentation and cell cycle arrest. Stilbenes and flavonoids present in *S. glabra* regulate p53, a critical tumour suppressor protein involved in the DNA damage response. This regulation culminates in increased caspase activation and subsequent cell death, positioning *S. glabra* as a promising candidate for anticancer therapies.

2.2. Inhibition of Cell Proliferation:

Uncontrolled cell proliferation stands as a hallmark of cancer, driven by dysregulated cell cycle progression and aberrant signaling pathways. The phytochemicals within these medicinal plants intervene with key pathways involved in cancer cell proliferation. *A. vulgaris* curtails tumour growth by targeting the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt signaling pathways. These pathways are crucial regulators of cell survival and proliferation. By downregulating Akt phosphorylation and suppressing MAPK activation, *A. vulgaris* diminishes the proliferation rate of cancer cells, leading to cell cycle arrest. *C. intybus* effectively reduces cancer cell proliferation by modulating the nuclear factor kappa B (NF-κB) and Wnt/β-catenin signaling pathways. NF-κB is a key regulator of inflammation-induced tumour growth, and its inhibition by *C. intybus* hampers cancer progression. Similarly, by disrupting the Wnt/β-catenin pathway, *C. intybus* suppresses the expression of cyclin D1 and c-Myc, both essential for cell cycle progression. *S. glabra* exerts its antiproliferative effects by regulating cyclins and cyclin-dependent kinases (CDKs), crucial for cell cycle progression. Bioactive compounds like astilbin and resveratrol derivatives in *S. glabra* downregulate cyclin D and CDK4, inducing G1 phase arrest in cancer cells. This effectively prevents uncontrolled proliferation and facilitates cancer cell elimination.

2.3. Anti-inflammatory and Antioxidant Effects:

Chronic inflammation and oxidative stress are major contributors to cancer progression. Persistent inflammation can induce DNA damage, genetic mutations, and create an immunosuppressive tumour microenvironment. The antioxidant and anti-inflammatory properties of these medicinal plants are pivotal in mitigating these detrimental effects. *A. vulgaris* reduces inflammation by inhibiting pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). It also downregulates cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), enzymes central to the inflammatory response. Additionally, its antioxidant compounds, including flavonoids and terpenoids, neutralize free radicals, thus reducing oxidative stress-induced DNA damage. *C. intybus* displays strong antioxidant activity due to its rich polyphenol content. Polyphenols like chicoric acid, chlorogenic acid, and flavonoids scavenge free radicals, shielding cells from oxidative damage. Furthermore, *C. intybus* suppresses inflammatory mediators like nuclear factor-kappa B (NF-κB), curtailing the expression of cytokines that foster tumour growth. *S. glabra* boosts the activity of antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx), which are essential for detoxifying ROS. Additionally, *S. glabra* suppresses inflammatory responses by inhibiting NF-κB activation and downregulating inflammatory cytokines, thereby reducing the likelihood of cancer development.

2.4. Modulation of the Tumour Microenvironment (TME):

The tumour microenvironment (TME) plays a critical role in cancer progression, metastasis, and resistance to therapy. Various TME components, including immune cells, blood vessels, and the extracellular matrix, support tumour survival. These medicinal plants modulate the TME, making it less favourable for cancer growth. *A. vulgaris* inhibits angiogenesis, the process by which tumours develop new blood vessels to sustain their growth. It does so by downregulating vascular endothelial growth factor (VEGF) and its receptors, thereby impeding

blood vessel formation around tumours. This action limits the supply of oxygen and nutrients to cancer cells, ultimately suppressing tumour growth and metastasis. *C. intybus* enhances immune responses against tumour cells by activating cytotoxic T cells and natural killer (NK) cells. Bioactive compounds like sesquiterpene lactones modulate immune checkpoints, promoting an anti-tumour immune response. This immunomodulatory effect renders *C. intybus* a potential adjunct in cancer immunotherapy. *S. glabra* plays a crucial role in modifying the TME by reducing hypoxia-induced factors. Hypoxia, or low oxygen levels, is a common feature of solid tumours that leads to aggressive cancer behaviour and therapy resistance. *S. glabra* downregulates hypoxia-inducible factor-1α (HIF-1α), thereby suppressing the adaptive mechanisms that tumours use to survive under low oxygen conditions. Additionally, *S. glabra* has been shown to interfere with matrix metalloproteinases (MMPs), enzymes involved in extracellular matrix degradation and cancer metastasis.

2.5 Comparative Evaluation of Anticancer Potential

Plant	Cancer Types Studied	Mechanisms of Action	Potential Applications
Artemisia *vulgaris*	Breast, lung, liver	Apoptosis induction, angiogenesis inhibition	Adjunct to chemotherapy, herbal formulation
Cichorium *intybus*	Colon, prostate, leukemia	Cell cycle arrest, immunomodulation	Dietary supplement, functional food
Smilax *glabra*	Gastric, ovarian, melanoma	Anti-inflammatory, ROS-mediated apoptosis	Phytotherapeutic drug candidate

2.6. Challenges in Translating Medicinal Plant Anticancer Potential to Clinical Practice: Despite promising preclinical results for *Artemisia vulgaris*, *Cichorium intybus*, and *Smilax glabra*, significant challenges hinder their clinical application. Primarily, there's a lack of large-scale clinical trials to validate efficacy and safety in humans, as most studies are limited to in vitro and in vivo models, which don't fully reflect human physiology. Secondly, bioavailability issues plague many bioactive compounds due to poor absorption, rapid metabolism, and low permeability, limiting their therapeutic effectiveness. Lastly, standardization of extracts is difficult due to variability in phytochemical composition caused by factors like plant species, location, and extraction methods, making it challenging to ensure consistent therapeutic effects compared to synthetic drugs.

3. Result and Discussion

This manuscript has highlighted the significant anticancer potential of *Artemisia vulgaris, Cichorium intybus,* and *Smilax glabra*, three medicinal plants with a rich history of traditional use. The compilation of preclinical studies demonstrates that these plants exert their anticancer effects through a variety of mechanisms, including the induction of apoptosis, inhibition of cell proliferation, modulation of oxidative stress and inflammation, and alteration of the tumour microenvironment. Specifically, *Artemisia vulgaris* has shown promise in inducing cytotoxicity via mitochondrial dysfunction and caspase activation, effectively targeting various cancer types such as breast, lung, and liver cancers. This plant's ability to downregulate VEGF also suggests its potential in inhibiting angiogenesis, a crucial aspect of tumour growth and metastasis. *Cichorium intybus*, on the other hand, exhibits its anticancer activity by modulating key signaling pathways like NF-κB and Wnt/β-catenin, leading to cell cycle arrest and reduced proliferation, particularly in colon, prostate, and leukemia cells. The plant's rich polyphenol content contributes to its potent antioxidant effects, further enhancing its therapeutic potential.

Smilax glabra distinguishes itself by inducing ROS-mediated apoptosis and modifying the tumour microenvironment through the downregulation of hypoxia-inducible factors, demonstrating efficacy against gastric, ovarian, and melanoma cancers. The modulation of p53 and MAPK pathways by *Smilax glabra* further reinforces its role in controlling cell proliferation and survival.

Despite these promising preclinical results, the translation of these findings into clinical applications faces significant challenges. The variability in phytochemical composition due to factors like plant species, location, and extraction methods complicates the standardization of extracts, hindering consistent therapeutic effects. Furthermore, the limited bioavailability of many bioactive compounds, resulting from poor absorption, rapid metabolism, and low permeability, necessitates innovative delivery strategies. The paucity of large-scale clinical trials also underscores the need for rigorous human studies to validate the efficacy and safety of these plants in oncology. To bridge this gap, future research should prioritize the development of nano-formulations to enhance bioavailability and targeted delivery. Synergistic combination therapies with conventional treatments could also improve efficacy and reduce adverse effects. Moreover, well-designed clinical trials are crucial for establishing optimal dosages, pharmacokinetics, and drug interactions, ensuring the safe and effective integration of these natural agents into mainstream cancer treatments. Ultimately, the exploration of *Artemisia vulgaris, Cichorium intybus,* and *Smilax glabra* offers a promising avenue for developing alternative or complementary cancer therapies, leveraging their diverse mechanisms of action to improve patient outcomes.

4. Future Prospects and Conclusion

To bridge the gap between promising preclinical findings and clinical application, future research should prioritize innovative strategies to enhance the clinical viability of *Artemisia vulgaris*, *Cichorium intybus*, and *Smilax glabra*. Employing nano formulations like nanoparticles, liposomes, and nano emulsions can significantly improve the bioavailability of plant-derived compounds by enhancing solubility, stability, and cellular uptake, enabling targeted drug delivery and minimizing side effects. Synergistic combination therapies with conventional chemotherapy or targeted drugs offer another promising avenue, potentially enhancing efficacy and mitigating adverse effects by sensitizing cancer cells. Crucially, large-scale, well-designed clinical trials are imperative to validate the efficacy and safety of these medicinal plants in humans, establishing optimal dosages, pharmacokinetics, and drug interactions. Establishing robust regulatory frameworks and fostering collaborations between researchers, pharmaceutical industries, and healthcare professionals are essential for translating preclinical successes into mainstream cancer treatments. In conclusion, the exploration of these three plants reveals their significant potential as natural anticancer agents, offering promising alternative or complementary approaches to conventional therapies through their diverse mechanisms of action, including apoptosis induction, proliferation inhibition, antioxidant and anti-inflammatory effects, and tumour microenvironment modulation.

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