

FORMULATION ADVANCEMENTS AND PHARMACOLOGICAL EVALUATION OF  
ALOE SPECIES AND HIBISCUS SABDARIFFA FOR CANCER SUPPORTIVE CARE: A  
COMPREHENSIVE REVIEW (2010-2025)Abdalwali Ahmed Saif<sup>1</sup>, Amina El-Shaibany<sup>2,4</sup>, Mahmoud Mahyoob Alburyhi<sup>1\*</sup>,  
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**ABSTRACT**

**Background:** Cancer supportive care relies on managing symptoms, mitigating treatment side effects, and improving patient quality of life. Herbal supplements containing antioxidant-rich and immunomodulatory botanicals are increasingly integrated into oncological care. **Objective:** To systematically review the pharmaceutical formulation development and pharmacological evaluations of *Aloe* species and *Hibiscus sabdariffa* from 2010 to 2025, establishing a scientific foundation for their use in cancer supportive care. **Methods:** A detailed literature review was conducted analyzing solid dosage formulations, microencapsulation technologies, and extraction optimizations, alongside *in vitro* and *in vivo* evaluations of anticancer, anti-inflammatory, and immunomodulatory mechanisms. **Discussion:** Advanced formulation strategies—including sustained-release matrix tablets, cross-linked hydrogels, and nanoencapsulation—have successfully overcome the physical limitations and instability of *Aloe* and *Hibiscus* extracts. Pharmacologically, *Aloe* species demonstrate profound immunomodulatory and anti-inflammatory properties, while acting as potent bioenhancers. Conversely, *Hibiscus sabdariffa* exhibits direct cytotoxic effects, inducing apoptosis via AMPK activation and generating targeted oxidative stress in cancer cells, alongside significant synergistic antitumor efficacy when combined with conventional chemotherapeutics. **Conclusion:** The integration of modern pharmaceutical formulation technologies with the potent pharmacological activities of *Aloe* and *Hibiscus* extracts yields highly stable, bioavailable, and efficacious herbal supplements. These standardized botanical therapies hold immense promise for enhancing comprehensive cancer supportive care.

**KEYWORDS:** Cancer Supportive Care; *Aloe vera*; *Hibiscus sabdariffa*; Pharmaceutical Formulation; Microencapsulation; Phytopharmacology.

**1. INTRODUCTION**

Cancer supportive care encompasses a continuum of interventions aimed at managing debilitating symptoms, reducing the severe side effects of conventional

treatments, and improving the overall quality of life for oncology patients. In recent years, herbal supplements have gained substantial traction as complementary approaches. Botanicals rich in antioxidants and

immunomodulatory compounds are uniquely positioned to mitigate treatment-related toxicities. This review comprehensively examines the literature from 2010 to 2025 regarding the pharmaceutical formulation and pharmacological validation of two highly promising botanical groups: *Aloe* species and *Hibiscus sabdariffa*.

## 2. *Aloe* Species: Pharmaceutical Formulation and Development

### 2.1 Solid Dosage Forms and Matrix Tablets

Transitioning crude *Aloe* extracts into viable clinical therapies requires robust formulation techniques. Patel developed effervescent tablets incorporating *Aloe vera* extract to enhance palatability and achieve rapid dissolution. Utilizing citric acid and sodium bicarbonate alongside *Aloe vera* gel powder, the tablets disintegrated in under 3 minutes, maintained satisfactory hardness (4–6 kg/cm<sup>2</sup>), and successfully preserved *Aloe* bioactive compounds post-compression.<sup>[1]</sup> Validating oral clinical applications, Fallah Huseini *et al.* conducted a randomized, double-blind, placebo-controlled trial using *Aloe vera* leaf gel capsules (300 mg). Filled using a hand-operated machine, these gelatin capsules demonstrated excellent clinical safety and significantly reduced fasting blood glucose and lipid profiles in diabetic patients.<sup>[2]</sup>

*Aloe vera* has also been heavily utilized as an active excipient. Ranade *et al.* engineered bilayer floating tablets combining amoxicillin and *Aloe vera* gel powder for gastric retention. Using direct compression with HPMC K4M/K100M and effervescent agents, the formulation achieved a floating time of over 8 hours, delivering enhanced gastroprotective activity.<sup>[3]</sup> Similarly, Rahman *et al.* formulated sustained-release curcumin matrix tablets using *Aloe vera* mucilage (5–15% w/w) as a natural solubility enhancer. The freeze-dried *Aloe* polysaccharide fraction significantly improved curcumin dissolution (up to 78% at 8 hours) and increased bioavailability by 200%, establishing *Aloe vera* as a dual release-modifier and bioenhancer.<sup>[4]</sup>

For traditional medicine standardization, Moein *et al.* formulated film-coated tablets of "Alvoo Fix" (an *Aloe*-based medicine) using wet granulation with PVP K30. They established comprehensive quality control parameters, quantifying aloin content via HPLC and achieving >75% dissolution in 60 minutes.<sup>[5]</sup> Rao *et al.* further validated *Aloe vera* gel powder (10–30% w/w) as an effective natural matrix former for cardiovascular drug delivery, achieving optimal sustained release of eplerenone over 8–12 hours.<sup>[6]</sup>

### 2.2 Analytical Quality Control and Advanced Delivery Systems

To address the long-term stability of *Aloe* markers, Girreser and Wolfram developed a band-selective quantitative HSQC NMR method for *Aloe vera* and *Aloe ferox* solid dosage forms. This advanced technique enabled the simultaneous quantification of acemannan, aloin, and aloin-emodin, revealing specific degradation patterns after 12 months of storage.<sup>[7]</sup>

Exploring systemic efficacy, Na *et al.* demonstrated that orally administered processed *Aloe vera* gel (PAG) capsules containing low molecular weight polysaccharides retained high biological activity, successfully suppressing serum IgE and inflammatory cytokines.<sup>[8]</sup> Additionally, Ashwini *et al.* proved that *Aloe vera* mucilage acts as a highly effective, biocompatible natural binding agent in immediate-release tablets, achieving optimal friability and drug release profiles comparable to synthetic microcrystalline cellulose.<sup>[9]</sup> Jani *et al.* corroborated these release-retarding properties, formulating matrix tablets with processed *Aloe vera* gel that followed Higuchi diffusion-controlled kinetics for up to 12 hours.<sup>[10]</sup>

Recent innovations have focused on overcoming the rapid hydration limitations of native *Aloe* polysaccharides. Irfan developed a citric acid cross-linked *Aloe vera* hydrogel (CL-ALH). Chemical cross-linking at 120°C drastically reduced equilibrium swelling and achieved a precise 24-hour sustained release, maintaining >92% drug content stability for 6 months.<sup>[11]</sup> Furthermore, Tevlek *et al.* pioneered chitosan-encapsulated *Aloe vera* extract nanoparticles (AVE-CSNPS) prepared by ionic gelation. These nanoparticles exhibited an 86.2% encapsulation efficiency, sustained 48-hour release, and provided a 2.8-fold higher cellular uptake, representing a next-generation formulation strategy.<sup>[12]</sup>

## 3. *Aloe* Species: Pharmacological Evaluation

### 3.1 Cytotoxic and Anticancer Mechanisms

The antineoplastic potential of *Aloe* is widely documented. Al-Mahbashi *et al.* evaluated the cytotoxic activities of *Aloe rubroviolacea*, *Aloe vera*, and *Aloe saba* flower extracts against 11 human cancer cell lines. *Aloe vera* exhibited the strongest concentration-dependent growth inhibition (up to 67%), while *A. rubroviolacea* demonstrated moderate antiproliferative capacities (up to 42% inhibition).<sup>[13]</sup> Focusing on specific pathways, Tabolacci *et al.* proved that *Aloe vera* gel exhibits significant anti-melanoma activity. It induced

p53 tumor suppressor protein activation, upregulated the p21 cell cycle inhibitor, triggered caspase-3-mediated apoptosis, and caused G1 phase cell cycle arrest.<sup>[14]</sup>

Evaluating advanced models, Tevlek et al. assessed *Aloe vera* on 3D liver tumor spheroids, demonstrating a powerful 68% growth inhibition compared to only 42% in 2D cultures. Mechanistically, the extract induced profound mitochondrial dysfunction, increased reactive oxygen species (ROS) generation by 3.8-fold, and activated autophagy, establishing its relevance for hepatocellular carcinoma.<sup>[12]</sup>

### 3.2 Immunomodulatory and Anti-inflammatory Effects

*Aloe* species are potent immunomodulators. Liu et al. investigated an *Aloe*-based composition (UP360) in an accelerated aging mouse model. The treatment significantly improved innate and adaptive immunity, increasing NK cell cytotoxicity (2.6-fold), macrophage phagocytosis, and CD4+/CD8+ T cell counts, while preserving the thymus from aging-associated damage.<sup>[15]</sup> Memorial Sloan Kettering Cancer Center's comprehensive review corroborated this, documenting that the polysaccharide acemannan stimulates TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 production in macrophages and acts as a potent immunostimulator via the NF- $\kappa$ B pathway.<sup>[16]</sup>

Targeting inflammation, Yagi et al. conducted molecular docking which identified Aloesin as a top-performing TNF- $\alpha$  inhibitor. Aloesin effectively suppressed the cyclooxygenase pathway and reduced prostaglandin and histamine release, positioning it as a promising candidate for cancer-related inflammation.<sup>[17]</sup> Li et al. provided a massive review (2020–2025) on *Aloe vera* polysaccharides, affirming that high molecular weight fractions (>400 kDa) exhibit superior immunomodulatory potency, profound COX-2/NF- $\kappa$ B inhibition, and highly effective DPPH radical scavenging.<sup>[18]</sup> Finally, Yanikoglu et al. proved *in vivo* that oral *Aloe vera* formulations significantly reduced allergic airway inflammation, diminished Th2 cytokines, and thinned mucosal thickness, highlighting the therapeutic role of the active component aloin.<sup>[19]</sup>

## 4. *Hibiscus sabdariffa*: Pharmaceutical Formulation and Development

### 4.1 Extraction Optimization and Stability Kinetics

Formulating *Hibiscus sabdariffa* requires managing the thermal sensitivity of its bioactive anthocyanins. A foundational study by Mourtzinis et al. evaluated the thermal stability of *H. sabdariffa* extracts. They

demonstrated that  $\beta$ -cyclodextrin complexation decreased the degradation rate and protected anthocyanins up to 250°C, providing a massive 3.4-fold improvement in thermal stability for solid dosage forms.<sup>[20]</sup> Clinically, early formulation studies by Lin et al. successfully utilized *H. sabdariffa* extract capsules (1g) to significantly reduce serum cholesterol in hypercholesterolemic patients without adverse events.<sup>[21]</sup>

Extraction solvent selection is critical. Sindi demonstrated that aqueous and methanolic extracts yielded the highest anthocyanin content (delphinidin-3-sambubioside and cyanidin-3-sambubioside) and the strongest DPPH antioxidant activity.<sup>[22]</sup> Moving to tablet development, Herrera-Arellano et al. successfully formulated *H. sabdariffa* aqueous extract tablets using wet granulation, achieving excellent friability (<0.8%) and drug content uniformity for use as an antihypertensive adjuvant.<sup>[23]</sup>

Storage stability is heavily reliant on temperature and pH. Sinela et al. investigated anthocyanin degradation kinetics, establishing that isothermal degradation follows first-order kinetics. They calculated half-lives of 90 days at 25°C and 56 days at 40°C, proving that matrix composition and ionic strength are vital for optimizing supplement storage.<sup>[24]</sup>

### 4.2 Microencapsulation and Spray-Drying Technologies

To protect thermolabile compounds, modern formulation relies heavily on microencapsulation. Ridzwan et al. developed spray-dried powders of *H. sabdariffa* ethanolic extracts. Optimized spray drying (inlet 80°C) produced powders with excellent flow properties suitable for direct compression while preserving potent  $\alpha$ -amylase inhibitory activities and high phenolic content.<sup>[25]</sup> Nguyen et al. expanded on this by microencapsulating anthocyanins with a maltodextrin carrier at high temperatures (160°C). The optimal formulation yielded >85% encapsulation efficiency and >93% solubility, effectively protecting the anthocyanins from environmental degradation.<sup>[26]</sup>

Ariestanti et al. successfully explored *H. sabdariffa* calyx extracts as natural colorants and active ingredients, establishing formulation standardizations based on precise anthocyanin content matching for semi-solid and solid dosage forms.<sup>[27]</sup> To optimize initial yields, Yagi et al. determined that infusion and decoction extraction methods yielded 1.5 to 2.1-fold higher total phenolic and anthocyanin contents compared to standard

maceration.<sup>[28]</sup> Idham *et al.* confirmed that spray-drying microencapsulation using a maltodextrin and whey protein isolate matrix (1:3 core: wall ratio) resulted in exceptional post-processing retention (82.6%) and dramatically extended the anthocyanin half-life during high-humidity storage.<sup>[29]</sup>

## 5. *Hibiscus sabdariffa*: Pharmacological Evaluation

### 5.1 Antioxidant and Metabolic Regulation

The pharmacological efficacy of *H. sabdariffa* is driven by its dense phenolic profile. Banwo *et al.* demonstrated that ethyl acetate fractions of the calyces exhibit extreme antioxidant activity (98% ABTS inhibition) alongside powerful  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory actions. This establishes *Hibiscus* as an excellent functional ingredient for targeting oxidative stress and hyperglycemia.<sup>[30]</sup> Suhartika *et al.* evaluated its effects on insulin resistance using network pharmacology, showing that *Hibiscus* downregulates HIF-1 $\alpha$  expression in diabetic models, subsequently lowering cholesterol, triglycerides, and lipid peroxidation while significantly boosting catalase and glutathione activity.<sup>[33]</sup>

### 5.2 Anticancer Mechanisms and Apoptosis

*Hibiscus* extracts possess profound, selective anticancer mechanisms. Chiu *et al.* elucidated that *Hibiscus* extract selectively induces pro-oxidant effects specifically in MCF-7 breast cancer cells. It altered the intracellular redox status by deeply depleting antioxidant enzymes (SOD, catalase, glutathione peroxidase) and increasing MDA lipid peroxidation 4.2-fold, triggering oxidative stress-mediated apoptosis while protecting normal, healthy cells.<sup>[31]</sup>

Tsai *et al.* investigated the specific apoptotic signaling pathways of *Hibiscus* anthocyanins in colorectal cancer cells. The extracts heavily activated AMPK signaling (2.8-fold increase), inhibited the Akt survival pathway, induced mitochondrial dysfunction (cytochrome c release), and triggered Fas-mediated extrinsic apoptosis via caspase-8 and caspase-3 activation. *In vivo* dietary supplementation in mice remarkably reduced polyp numbers by 54% and size by 67%.<sup>[32]</sup> A comprehensive review by Ahmed *et al.* synthesized this evidence, confirming that *Hibiscus* induces apoptosis, triggers G1 and G2/M phase cell cycle arrest, inhibits VEGF-mediated angiogenesis, and prevents metastasis via MMP-2/9 downregulation across oral, breast, lung, colon, and leukemia cell lines.<sup>[34]</sup>

### 5.3 Synergistic and Immunotherapeutic Potential

The combination of *Hibiscus* with conventional therapies highlights its supportive care value. Ezcurra-Hualde *et al.* demonstrated that intratumoral administration of *H. sabdariffa*-derived anthocyanins produced massive tumor mass reductions. Crucially, combination with doxorubicin achieved highly synergistic effects (88.2% tumor growth inhibition). Mechanistically, the extract reversed chemotherapy-induced immunosuppression, enhanced CD8+ T cell tumor infiltration, increased NK cell activity, and induced long-term immune memory.<sup>[35]</sup> Lastly, Nogueira da Cruz comprehensively reviewed its selective cytotoxicity, documenting that *Hibiscus* specifically targets ER $\alpha$ -positive breast cancer cells. It heavily downregulates ER $\alpha$  expression, triggers apoptosis via Bax/Bcl-2 modulation, suppresses NF- $\kappa$ B nuclear translocation, and inhibits COX-2, proving its immense, multifaceted value in hormone-dependent cancers.<sup>[36]</sup>

Preformulation study is a stage before preparing drugs is the stage of compatibility between excipients and the drug, and after that the various pharmaceutical forms are prepared according to compatibility. The method of preparing drugs from industrial sources applies to natural sources, taking into account that natural sources need to be studied from the beginning, as there is no information available. Therefore, the study must be in accordance with the system of studying compatibility preformulation, then studying the formulation, evaluation, and stability study of pharmaceutical forms in novel drug delivery systems. Formulating natural sources and herbal extracts as advanced drug delivery systems that have been developed and formulated in different pharmaceutical dosage forms and therapeutic doses appropriate to the type of diseases such as acute, chronic, or emergency cases and the principles and strategies of treating them, whether direct, auxiliary, or preventive treatment. They are distinguished by their safe and effective natural drug use according to scientific studies determined by pharmacognosy and pharmaceutical formulation Scientists.<sup>[37-68]</sup>

## 6. CONCLUSION

The rigorous pharmaceutical and pharmacological evaluation of *Aloe* species and *Hibiscus sabdariffa* from 2010 to 2025 firmly establishes their vital role in cancer supportive care. Pharmaceutical advancements—ranging from targeted microencapsulation and citric acid cross-linked hydrogels to optimized effervescent and sustained-release matrix tablets—have successfully mitigated the physical instability and poor solubility of

these crude extracts. Pharmacologically, these botanical formulations offer immense therapeutic value; *Aloe* provides critical immune modulation and hepatoprotective antioxidant defenses, while *Hibiscus sabdariffa* delivers targeted cytotoxic, pro-apoptotic, and synergistic anti-tumor effects. Together, standardized formulations of these plants offer a scientifically validated, reproducible, and highly effective complementary approach to mitigating treatment toxicities and improving oncology patient outcomes.

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