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THE SYNERGISTIC POTENTIAL OF ALOE RUBROVIOLACEA AND HIBISCUS SABDARIFFA IN CANCER SUPPORTIVE CARE: A COMPREHENSIVE NARRATIVE REVIEW

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ABSTRACT

Background: The escalating global burden of cancer is compounded by the severe, dose-limiting toxicities associated with conventional chemotherapeutics. In regions with constrained healthcare infrastructure, such as Yemen, there is an urgent need for accessible, effective cancer supportive care. **Objective:** To systematically review the epidemiological landscape of cancer and evaluate the phytopharmacological rationale for utilizing a polyherbal approach—specifically combining endemic *Aloe rubroviolacea* and *Hibiscus sabdariffa*—as a supportive botanical intervention in oncology. **Methods:** A comprehensive literature review was conducted analyzing global and regional cancer statistics, the limitations of current chemotherapies, and the *in vitro* and *in vivo* anticancer, immunomodulatory, and antioxidant mechanisms of *Aloe* and *Hibiscus* extracts. **Discussion:** Conventional cancer treatments inevitably cause systemic toxicities, prompting high utilization of complementary and alternative medicine (CAM). *Hibiscus sabdariffa* exerts potent direct cytotoxic effects, inducing apoptosis via AMPK activation and downregulating pro-inflammatory cytokines. Concurrently, *Aloe rubroviolacea* offers immense hepatoprotective, immunomodulatory, and free radical scavenging capabilities. Integrating these botanicals theoretically produces a multi-target synergy that mitigates oxidative stress and protects normal tissue without compromising antineoplastic efficacy. **Conclusion:** The evidence strongly supports the pharmacological viability of combining *A. rubroviolacea* and *H. sabdariffa*. Rigorously standardized extracts of these plants hold immense promise as a locally sourced, culturally resonant, and highly effective modality for comprehensive cancer supportive care.

KEYWORDS: Cancer Supportive Care; *Aloe rubroviolacea*; *Hibiscus sabdariffa*; Phytopharmacology; Chemotherapy Toxicity; Polyherbalism.

1. INTRODUCTION

1.1 The Global and Regional Cancer Burden

Cancer remains a leading cause of mortality worldwide. In 2022, there were an estimated 20 million new cases and 9.7 million cancer-related deaths globally, a figure projected to surge by 77% to 35 million cases by 2050.[1] The global epidemiological landscape indicates a rapidly growing crisis.[2] The burden is particularly heavy in Asia, which accounts for nearly half of all new cancer cases and over half of global cancer deaths.[1] In the Middle East and North Africa (MENA) region, the World Health Organization (WHO) projects that cancer cases will double to 1.57 million by 2045 due to population aging and high prevalences of obesity,

physical inactivity, and tobacco use.[3] Socioeconomic disparities in this region heavily dictate survival outcomes, with high mortality-to-incidence ratios underscoring poor access to early detection.[4] Breast cancer is the most frequently diagnosed malignancy among women globally[5], but it presents almost a decade earlier in Arab populations compared to Western demographics, necessitating urgent, region-specific screening and care protocols.[6] Furthermore, up to 30% of esophageal and lung cancers in the Middle East are directly attributed to rising trends in cigarette and waterpipe smoking[7], which account for a substantial percentage of total cancer incidence across Gulf Cooperation Council countries.[8]

1.2 Cancer Statistics and Healthcare Challenges in Yemen

In Yemen, the oncology landscape is profoundly compromised by ongoing conflict and infrastructure collapse. In 2020, the crude cancer incidence rate stood at 55.2 per 100,000.[9] By 2022, estimated new cases ranged from 16,525 to over 30,000, revealing massive surveillance uncertainties.[10] The ongoing humanitarian crisis has crippled the health sector, resulting in severe shortages of specialized providers and chemotherapeutic agents.[11] Consequently, late-stage presentation is common; for example, 67% of breast cancer patients in Aden presented with inoperable disease, drastically lowering survival rates.[12]

2. Limitations of Conventional Therapies and the Shift to CAM

While conventional chemotherapy and radiation remain the gold standards of oncological care, they induce severe, non-selective toxicities. Patients routinely suffer from nausea, fatigue, immunosuppression, mucositis, and irreversible organ damage.[13] Over a quarter of patients experience potentially life-threatening toxicities that necessitate treatment discontinuation or severe dose reductions.[14]

These limitations have driven a massive shift toward Complementary and Alternative Medicine (CAM). Approximately half of all cancer patients utilize at least one form of CAM during or after standard treatment.[15] CAM encompasses therapies used *alongside* conventional treatments[16], specifically including mind-body practices and biologically based botanical therapies.[17] The use of biologic natural products surges dramatically—from 15.6% to 51.8%—immediately following a cancer diagnosis, primarily as patients seek to cope with side effects, enhance immune function, and adopt a holistic approach to recovery.[18]

3. Cancer Supportive Care and Botanical Interventions

Supportive care encompasses the comprehensive management of the physical, psychological, and metabolic adverse effects of cancer and its treatments.[19] Cancer cachexia, malnutrition, and immunosuppression frequently compromise treatment tolerance. Appropriately timed nutritional and micronutrient supplementation plays a highly recognized role in correcting these deficits and improving overall quality of life.[20] Bioactive phytochemicals from natural products actively improve cancer outcomes by modulating endoplasmic reticulum stress and regulating oxidative injury.[21]

However, botanical supplements must be utilized judiciously. Up to 50% of cancer outpatients consuming CAM experience potential pharmacokinetic interactions with their primary treatments.[22] Specific herbs (e.g., St. John's wort, garlic) significantly modulate cytochrome P450 enzymes, leading to altered chemotherapeutic drug exposures.[23] Consequently, rigorous toxicological assessments and continuous safety monitoring are essential before integrating botanical therapies into mainstream oncological care[24], especially considering that dietary supplements often bypass stringent pre-market FDA approvals.[25]

Historically, medicinal plants have served as vital sources of therapeutic compounds, originating over 25% of modern prescription drugs, including potent antineoplastics like vincristine and paclitaxel.[26] Structurally diverse phytochemicals—alkaloids, flavonoids, and terpenoids—are uniquely capable of modulating the "hallmarks of cancer," such as sustained proliferative signaling and angiogenesis.[27] Furthermore, traditional botanical medicines act as powerful immunomodulators, mitigating treatment-related toxicities through the precise regulation of cytokines, interleukins, and tumor necrosis factors.[28] Integrating these standardized botanical therapies offers an invaluable strategy for comprehensive cancer care, particularly in resource-limited settings.[29] Recent biological reviews confirm that properly formulated herbal therapies effectively alleviate chemotherapy side effects and drastically improve patient tolerance.[30]

4. Pharmacognosy and Therapeutic Potential of *Aloe rubroviolacea*

4.1 Taxonomy, Distribution, and Traditional Uses

Aloe rubroviolacea Schweinf., commonly known as Arabian aloe, is a succulent species belonging to the Asphodelaceae family.[31] It produces thick, blue-green rosettes and dense clusters of waxy orange-red flowers.[32] Endemic to the southwestern Arabian

Peninsula, it thrives on steep rocky slopes above 2,100 meters in Yemen and Saudi Arabia.[33]

Yemen possesses an immensely rich biodiversity, yet its medicinal flora remains largely unexplored scientifically.[34] The traditional ethnomedicine of the region, especially in the highlands and Soqotra Island, relies heavily on local species for primary healthcare.[35] The juice and gel of *A. rubroviolacea* are frequently used by Yemeni healers to treat malaria, intestinal infections, abdominal colic, and inflammatory conditions.[36]

4.2 Phytochemistry and Biological Activities

Recent pharmacological evaluations have unveiled a complex bioactive profile in *A. rubroviolacea*. While *Aloe vera* is globally recognized for its cytotoxicity against cancer lines[37] and its immunomodulatory effects via the polysaccharide acemannan[38], *A. rubroviolacea* demonstrates comparable, yet distinct, promise.[39] Extracts contain high levels of total phenolics and flavonoids, exhibiting potent DPPH radical scavenging activities identical to ascorbic acid.[36] Furthermore, the extracts show profound hepatoprotective and pancreatoprotective effects in CCl_4-induced toxicity models.[36]

Anthraquinones (aloin, aloe-emodin) found across *Aloe* species are known to induce apoptosis and cell cycle arrest through PI3K/Akt and MAPK pathway modulation[40], while suppressing pro-angiogenic VEGF expression.[41] The documented hepatoprotective and extreme antioxidant properties of *A. rubroviolacea* suggest immense potential as a supportive agent capable of neutralizing chemotherapy-induced oxidative tissue damage.[36]

5. Pharmacognosy and Anticancer Mechanisms of *Hibiscus sabdariffa*

5.1 Taxonomy, Distribution, and Traditional Uses

Hibiscus sabdariffa L. (roselle) is a Malvaceae family member utilized across global traditional medicine systems.[42] The fleshy calyces of the *altissima* variety are traditionally employed to treat hypertension, liver disorders, and inflammatory complaints.[43] Folk medicine preparations exhibit established diuretic, choleretic, and antipyretic properties.[44]

5.2 Phytochemistry and Pharmacological Properties

Roselle calyces are exceptionally rich in organic acids (hydroxycitric, malic, and tartaric acids) and phenolic compounds (protocatechuic acid, chlorogenic acid).[45] These constituents impart significant biological activities, including antimicrobial and hepatoprotective effects.[46] Clinical meta-analyses confirm that *H. sabdariffa* supplementation yields potent antihypertensive effects, significantly lowering both systolic and diastolic blood pressure.[47]

5.3 Anticancer Mechanisms

Substantial molecular evidence demonstrates the direct anticancer potential of *H. sabdariffa*. Protocatechuic acid (PCA) triggers apoptosis in leukemia, breast, and prostate cancer cells via reactive oxygen species (ROS) generation and mitochondrial dysfunction.[48] Crude extracts exhibit selective cytotoxicity, preferentially inducing death in MCF-7 breast cancer cells while sparing normal, healthy tissue.[49] Furthermore, gossypetin (a major flavonoid) exerts anti-metastatic properties by upregulating the Bax/Bcl-2 ratio and arresting the G2/M phase cell cycle through ERK and NF-κB pathway regulation.[50,51] Anthocyanins derived from *Hibiscus* strongly induce apoptosis in colorectal cancer cells through AMPK activation and Fas-mediated caspase-8 activation.[52]

6. The Synergistic Potential of Polyherbal Regimens

Combining *A. rubroviolacea* and *H. sabdariffa* offers a powerful synergistic mechanism for cancer supportive care. Synergy in phytomedicine occurs when the combined therapeutic effect of multiple bioactives significantly exceeds the sum of their isolated effects.[53]

Hibiscus sabdariffa contributes direct cytotoxic and pro-apoptotic effects via AMPK activation and ROS generation. Simultaneously, *Aloe rubroviolacea* provides essential immunomodulatory, antioxidant, and hepatoprotective properties. This "multi-target" combination fundamentally addresses the complex hallmarks of cancer while protecting healthy tissues. Furthermore, the organic acids in *Hibiscus* potentially enhance the aqueous solubility and bioavailability of *Aloe* polysaccharides. Together, this combination mitigates the severe hepatic and oxidative toxicities caused by conventional chemotherapy, ultimately improving patient quality of life.

7. Standardization and Delivery Optimization of Herbal Extracts

To transition these traditional remedies into clinically viable therapeutics, rigorous standardization is mandatory. The application of advanced extraction technologies, such as optimized response surface methodology, guarantees maximum recovery of bioactive phytoconstituents.[54] Validated quality control approaches—utilizing HPLC and GC-MS—ensure batch-to-batch reproducibility, which is essential to confirm consistent marker compound concentrations and clinical credibility.[55]

Advancing herbal medicine requires overcoming inherent phytochemical instability.[56] Comprehensive

stability testing protocols protect photosensitive and oxygen-sensitive compounds from rapid degradation.[57] To ensure maximum therapeutic efficacy, novel pharmaceutical techniques focus on enhancing stability and solubility.[58] Utilizing technologies like microencapsulation fundamentally protects thermolabile compounds (such as anthocyanins) and ensures the controlled, highly bioavailable delivery of lipophilic constituents.[59] Implementing these rigorous standardization protocols elevates traditional Yemeni ethnobotany into the realm of evidence-based pharmaceutical science.

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.[59-90]

8. CONCLUSION

The integration of botanical therapies into modern oncology provides a vital solution to the dose-limiting toxicities of conventional chemotherapy. The literature robustly validates the pharmacological efficacy of *Hibiscus sabdariffa* as a potent apoptotic and anti-inflammatory agent, and *Aloe rubroviolacea* as a powerful antioxidant and hepatoprotective botanical. Their combined application offers a synergistic, multi-target approach that safely mitigates oxidative stress and protects normal tissue without compromising antineoplastic action. By subjecting these endemic and widely cultivated plants to rigorous pharmaceutical standardization, researchers can develop an accessible, highly effective, and culturally resonant supportive care intervention for cancer patients in resource-constrained environments like Yemen.

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