REVIEW ARTICLE

A comprehensive review on medicinal plants for potential therapeutic applications in breast cancer and sickle cell anemia in women

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Abstract

This review provides insights into the therapeutic advantage of medicinal plants in the management of breast cancer and Sickle cell anemia (SCA) when they occur in women. It underscores the special difficulties faced by women who have both diseases, and the importance of multidisciplinary care among healthcare professionals. The review addresses the positive impact on phytochemicals at work against breast cancer found in curcumin, resveratrol, and epigallocatechin gallate, as well as the growing benefits of phytoestrogens and the selective behaviors of the ligand activity towards estrogen receptors. Moreover, it looks at the traditional and dietary approaches for SCA, paying attention to *Nelumbo nucifera* and *Eichhornia crassipes*, which have anti-sickling effects. The review highlights the role of nutrition, especially vitamin B12, in enhancing the reproductive health of women with SCA. There is a review gap in clinical validation and safety information regarding these plants, especially for pregnant women, which is concerning. Proposed future research focuses on comprehensive clinical trials, safety and efficacy evaluations of herbal blends, and the unification of conventional and alternative medicine for treating breast cancer and SCA in women.

Key words: Breast cancer, medicinal plants and therapies, pharmacology, sickle cell anemia

INTRODUCTION

Recent studies are revealing the intricate connection between breast cancer and sickle cell disease (SCD) in women. Breast cancer is rare in SCD patients because sickled red blood cells (RBC) have a tumor-fighting effect (Nwagu *et al*., 2019). However, as treatments for SCD improve and patients live longer, the chance of developing cancer may increase (Gupta and Guthrie, 2012). One study found no significant difference in breast cancer screening rates between women with and without SCD (Elmileik *et al*., 2024). Still, screening is very important, especially for those with a family history of breast cancer (Nwagu *et al*., 2019). Having both breast cancer and SCD creates unique challenges in diagnosis and treatment, requiring teamwork among oncology, hematology, and other specialists (Güvenc *et al*., 2023). At present, there are no clear guidelines for screening and managing breast cancer in patients with SCD, highlighting the need for more research in this area (Gupta and Guthrie, 2012).

Breast cancer is the most common cancer among women in urban India, but there is a lack of awareness and screening programs, which often leads to diagnoses at later stages (Agarwal and Ramakant, 2008). While some centers offer excellent care, many patients don't get the treatment they need due to limited resources. Having both breast cancer and SCD is rare and creates unique challenges in treatment (Güvenc *et al*., 2023). Women with SCD are generally believed to have a lower risk of breast cancer, but screening remains important, especially for those with a family history (Nwagu *et al*., 2019). A recent study showed no significant difference in breast cancer screening rates between women with SCD and the general population (Elmileik *et al*., 2024). The study also found that body mass index and breast density

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are inversely related in women with SCD, which aligns with what is seen in the general female population.

Due to a lack of awareness, we are unable to recognize the benefits of medicinal plants that offer promising options for treating sickle cell anemia (SCA), a genetic disorder that affects millions worldwide (Islam *et al*., 2024). Several plants, such as *Carica papaya*, *Piper guineense*, and *Cajanus cajan*, have shown anti-sickling properties (Ahajumobi and Asika, 2024). Phytomedicines and nutraceuticals made from these plants can help reduce the frequency of crises and even reverse sickling in lab studies (Imaga, 2013). Traditional healers in Africa and Asia have long used plant-based remedies to manage SCA, providing more affordable and culturally familiar treatment options (Okpuzor *et al*., 2008). Products like Niprisan and Ciklavit, made from plant extracts, have been approved for SCA treatment in Nigeria (Ahajumobi and Asika, 2024). These natural treatments work through antisickling effects, γ-globulin induction, and antiplatelet action (Islam *et al*., 2024). While most research has been done in the lab, there is growing interest in studying these plant compounds in living organisms to better understand their potential for managing SCA (Islam *et al*., 2024).

There are more basic plants for the treatment of breast cancer and SCDs, such as *Nelumbo nucifera* Garetn., Holy basil, and *Eichhornia crassipes,* but we can focus on using the plant *N. nucifera* Garetn. and *E. crassipes*. *N. nucifera* Gaertn, commonly known as lotus, shows promising potential in treating breast cancer. Studies have found that its leaf extract can stop the growth of new blood vessels and the spread of breast cancer cells by lowering connective tissue growth factor-mediated PI3K/AKT/ERK signaling (Chang *et al*., 2016). Two active compounds, liensinine and nuciferine, help slow breast cancer cell growth and prevent bone loss by causing cancer cells to die and stopping the development of bone-destroying cells (Kang *et al*., 2017). Aporphine alkaloids from *N. nucifera*, such as nuciferine, nor-nuciferine, and roemerine, fight breast cancer through several targets and pathways, according to network pharmacology and molecular docking studies (Adrian *et al*., 2024). *N. nucifera* also has various health benefits, including anticancer, antioxidant, and anti-inflammatory effects, thanks to its many plant compounds (Alok Bhardwaj and Modi, 2016). These results show that *N. nucifera* has strong potential as a treatment for breast cancer. Water hyacinth (*E. crassipes*), though invasive, has shown potential medicinal uses because of its bioactive compounds (Uamai *et al*., 2024). Although it is not specifically used to treat SCA, it reflects the growing interest in plant-based treatments. Several African medicinal plants like *C. papaya*, *P. guineense*, and *C. cajan* have shown promise in managing SCA (Ahajumobi and Asika, 2024). These plants contain chemicals that help prevent sickling of RBCs, offering hope for safe and effective treatments (Imaga, 2013). A study in Cameroon found that traditional healers use 12 plant species to treat SCA, with the Euphorbiaceae family being the most common (Yembeau *et al*., 2022). The bark and seeds of these plants are often used in different ways. Many of these plants have polyphenols and alkaloids, which may provide antioxidant and anti-sickling benefits (Yembeau *et al*., 2022).

HIGHLIGHTS

1. Dual Disease Challenge: Breast cancer is uncommon in sickle cell disease (SCD) women, but increases as survival in SCD advances
2. Both need to be addressed by multidisciplinary management; no official guidelines are available
3. Therapeutic Potential of Plants:
   A. Breast Cancer: *N. nucifera* (Lotus): Angiogenesis and metastasis inhibition through connective tissue growth factor-mediated suppression of PI3K/AKT/ERK; bio-actives such as liensinine, nuciferine, and roemerine inhibit cancer proliferation and bone loss
   B. Curcumin: Anti-proliferation, anti-metastasis, and improves chemo response
   C. Resveratrol: Suppresses invasion pathways and increases chemo efficacy
   D. Epigallocatechin gallate: Pro-apoptotic, anti-inflammatory, lowers radiation skin toxicity
   E. Phytoestrogens: ERβ binding preference implies potential protective function; "Phyto SERMs" concept evolving
   F. Adaptogens (Ashwagandha, Rhodiola, Siberian ginseng): Antistress, boost energy, possibly augment anticancer therapy.

Sickle cell anemia (SCA): Plants with anti-sickling potential: *Carica papaya*, *Piper guineense*, *Cajanus cajan*, *Nigella sativa*, *Moringa oleifera*, turmeric, and fenugreek. Mechanisms: Inhibit sickle hemoglobin (HbS) polymerization, free radical scavenging, and red blood cell count increase. Preparations such as Niprisan and Ciklavit are already marketed in Nigeria.

Women's Health Focus: SCD has severe effects on reproductive health – ovarian sickling, diminished ovarian reserve, pregnancy at risk (↑ preeclampsia, pre-term delivery, stillbirth). Vitamin B12 essential for SCD fertility – enhances oocyte quality, mitigates oxidative stress, and preserves nitric oxide synthesis for reproductive function.

Gaps and Research needs: Clinical Trials: Well-powered, large-scale RCTs on plant therapies in breast cancer and SCD – particularly in women and pregnant patients. Safety Data: Particularly in pregnancy; present evidence is too limited. Standardization: Established phytochemical profiles, dosing regimens for reproducible effects. Mechanistic Clarity: Pharmacology detail to inform safe combinations with mainstream therapies.

PATHOPHYSIOLOGY

SCD is a mono-gene disorder resulting in the production of sickle hemoglobin, which polymerizes when deoxygenated, resulting in the destruction of RBCs (Steinberg, 2008). This results in a complex pathophysiology characterized by chronic hemolytic anemia, vasculopathy, and vaso-occlusive crises (VOC) (Steinberg, 2008; Elion *et al*., 2010). Recent work has elucidated the contribution of RBC dehydration, abnormal adhesion to vascular endothelium, inflammation, and abnormalities of vascular tone in the pathophysiology of SCD (Elion *et al*., 2010). Progress in the treatment of SCD, mainly with hydroxyurea, has increased the life expectancy of patients and, with it, the challenge of malignancy, one of which is an increase in breast cancer (Gupta and Guthrie, 2012). Rarely, breast cancer and SCD have coexisted, causing a unique diagnostic and treatment consideration, which necessitates cooperation from oncology, hematology, and other specialties (Güvenc *et al*., 2023). The breast cancer and sickle cell anemia were identified via different protein and molecule as cell progression explained in graphical representation of Fig 1. However, guidelines for screening and managing breast cancer in SCD patients are currently lacking (Gupta and Guthrie, 2012).

Main Protein

BUB1 – a mitotic checkpoint kinase involved in chromosome segregation during cell division; often implicated in cancer progression.

Branches from BUB1:
- Left: BUB54.1 → BUBBL
- Right: PHUbi/CO2 → COUBL1.

Middle Link

BUBBL → RUVBL1 → COUBL1 (Protein-protein interaction pathway).

Inhibitors

- BAY81811600322 (drug candidate for BUBBL or RUVBL1 inhibition)
- CB64 (compound interacting in the pathway, possibly targeting RUVBL1)

Function

These interactions could represent therapeutic targets for drug inhibition to suppress tumor cell growth.
1. Cell A (red textured) – possibly an initial infectious or abnormal cell
   Treated with Drug 1 → transforms into
2. Cell B (red textured sphere) – intermediate stage
   Treated with Drug 2 → transforms into
3. Cell C (smooth red) – further modified or damaged cell
4. Pink spiky cell (D) – may be a different variant or stage of the main cell type
5. Blue spotted cell (E) – likely a cell undergoing apoptosis or other cytoplasmic changes
6. Pink smooth cell (F) – possibly a final, inactivated, or dead cell.

The central white strip represents a sequence of transformations or reactions between cell types. Arrows indicate the direction of progression or influence. The background outline of the lungs suggests this may relate to lung biology, respiratory infection, or cancer. All the pathology of breast cancer and sickle cell anemia were briefed in flow chart in figs 2 and 3.

MEDICINAL PLANTS FOR BREAST CANCER IN WOMEN

Phytochemicals and their Anti-tumor Mechanism

The anticancer potential found in many medicinal plants is mainly due to them having many different types of phytochemicals. These are naturally occurring compounds belonging to various classes, such as flavonoids, carotenoids, polyphenols, saponins, phenolic compounds, terpenoids, and glycosides, which contribute to the biological activities of the plant.

The phenolic compounds, for example, are the most common group of secondary metabolites in plants and are synthetized through the phenylpropanoid pathway. They are well-known in scientific circles to be highly potent in antioxidants, which help plants fend off pests, diseases, and ultraviolet rays. This antioxidant ability is also useful in human health as they may help to scavenge free radicals that could cause damage to cells and other diseases. Tricyclic isoprenoids or triterpenoids comprise a diverse class of triterpenes bearing different functional groups. Plant development, growth, and stress responses are regulated by these compounds.

In human medicine, terpenoids have important medical, food, and chemical applications, antimicrobial, and anti-cancer activity. Green plant-derived flavonoids have become increasingly popular due to their remarkable pharmacological and nutraceutical attributes, such as potent antioxidant, anti-carcinogenic, and anti-inflammatory effects, and are widely studied throughout the world.

Several well-studied herbal compounds have demonstrated significant antitumor properties and distinct mechanisms of action in breast cancer shown in fig 4 and explained:

Curcumin is derived from *Curcuma longa* (turmeric), has been reported to exert anti-proliferative, pro-apoptotic, anti-metastatic, and anti-angiogenic effects. These effects are at least in part the result of the modulation of several molecular

Table 1: Medicinal plants for sickle cell anemia

Plant name	Traditional use/origin	Reported effects/ benefits	Key phytochemicals (if known)	Current research status	Specific safety notes
Cajanus cajan (Pigeon pea)	Nigeria, widespread	Prevents/reduces sickling, anemia treatment, and anti-sickling molecules.	Two specific molecules in stem.	Preclinical: Identified anti-sickling molecules. Limited clinical research.	Gastrointestinal symptoms reported in some patients.
Carica papaya	Nigeria, widespread	Anti-sickling activities.	Not specified.	Preclinical: Most reported species with anti-sickling activity.	Not specified.
Terminalia catappa	Nigeria, widespread	Anti-sickling activities.	Not specified.	Preclinical: Most reported species with anti-sickling activity.	Not specified.
Ceiba pentandra	DR Congo	"Blood tonic" beverage.	Not specified.	Traditional use. Limited scientific validation.	Not specified.
Alchornea cordifolia	DR Congo	"Blood tonic" beverage.	Not specified.	Traditional use. Limited scientific validation.	Not specified.
Moringa oleifera	Africa	Anti-urolithiasis, SCD treatment.	Phytochemicals.	Traditional use. Limited scientific validation.	Not specified.
Nigella sativa	Widespread	Antioxidant qualities.	Not specified.	Traditional use. Limited scientific validation.	Not specified.
Niprisan (Polyherbal)	Nigeria	Anti-sickling.	From *Syzygium aromaticum*, *Piper guineense*, *Aframomum melegueta*, *Sorghum bicolor*, *Pterocarpusosun*.	Clinical: Passed Phase IIA and IIB trials, widely used.	Associated with headaches.
Aloe vera (*Aloe barbadensis*)	Widespread	Prevents sickling, decreases vaso-occlusive/ pain crises.	Not specified.	Review suggests potential. Further research needed.	Fever and diarrhea reported.
Lemongrass (*Cymbopogon citratus*)	Eastern Uganda, widespread	Increases red blood cell counts, manages SCD.	Not specified.	Traditional use. Study showed RBC increase (not SCD specific).	Fever and diarrhea reported.
Garlic	Widespread	Antioxidant effects, prevents dense cell growth.	Not specified.	Review suggests effectiveness. Further research needed.	Nausea, vomiting, facial flushing reported.
Turmeric (*Curcuma longa*)	Widespread	66.81% reversal of sickled RBCs *in vitro*.	Anthocyanins, organic acids.	Preclinical: Strong *in vitro* evidence.	Not specified.
Fenugreek (*Trigonella foenum-graecum*)	Widespread	61.28% reversal of sickled RBCs *in vitro*.	Anthocyanins, organic acids.	Preclinical: Strong *in vitro* evidence.	Not specified.

pathways relevant to cancer development. In addition, curcumin has been demonstrated to have the potential to overcome endocrine resistance in breast cancer and increase the sensibility of conventional chemotherapies such as docetaxel and paclitaxel. Its application in the clinic is greatly hampered by the low bioavailability, quick metabolism, and poor water solubility, which is been overcome by high- end delivery systems like nanoparticle formulations.

Resveratrol is an anti-oxidant polyphenol in grapes, peanuts, and red wine act as anti-inflammatory and anticancer substance. Research has proved that it reduces the invasion of breast cancer cells by blocking certain signaling pathways and boots the chemotherapy agent effects.

Epigallocatechin gallate (EGCG), which is found mainly in green tea, is known for its strong antioxidant,

Table 2: Safety and efficacy herbal remedies for sickle cell disease

Category	Details	Specific Examples/Notes	Key research limitations
Overall reported efficacy	-38.5% of participants reported symptom improvement. Pooled efficacy nearly 100% higher among users versus controls.	All included studies reported improvement in general health and reduced crisis frequency.	Not statistically significant (P<0.01, but CI 0.99–4.32). High risk of publication bias.
Overall reported side effects	-22.9% of participants reported side effects. Pooled adverse effects 48% lower among users versus controls.	Range of safety concerns: 5.6% to 31.9%. Common: gastrointestinal symptoms (diarrhea, vomiting, abdominal distension), fever, headaches.	Not statistically significant (P<0.01, but CI 0.26-1.05). High risk of publication bias.
Specific plant-associated side effects	-*Zanthoxylum chalybeum* bark extract: Higher WBC counts, squamous cell growths in rats. *Carissa edulis* root/ bark extracts: Mild renal, hormonal, hematological changes in rats. Niprisan: Headaches. *Cajanus cajan*: Gastrointestinal symptoms. *Aloe barbadensis*, *Zingiber officinale*, *Cymbopogon citratus*, Forever Living products, GNLD supplements, ginseng products: Fever and diarrhea.	Animal studies indicate adverse events at higher doses. Human data often self-reported.	Limited long-term safety data. Small sample sizes in primary studies.
Plants with No Reported Side Effects	- *Petiveria alliacea*, *Chenopodium ambrosioides*, *Entandrophragma utile*	These plants had no side effects reported in the reviewed studies.	Lack of reported side effects does not equate to proven safety, especially with limited studies.
Research Limitations	Small sample sizes of primary studies. High risk of publication bias. Lack of statistical significance for pooled efficacy and safety. Insufficient high-quality clinical trials. Unknown long-term effects.	More extensive controlled studies with better-defined endpoints are required to inform clinical use.	These limitations prevent definitive conclusions on overall safety and efficacy.

anti-inflammatory, and anti-tumor effects. It leads to apoptosis, causes blocks in cells reproducing, and stops the growth and spread cancer in breast cancer. EGCG reduces both the number and seriousness of radiation skin change in through radiation therapy for breast cancer.

Withania somnifera (Ashwagandha) has strong potential to fight tumors. That stops aerobic glycolysis, assists in returning from Epithelial-Mesenchymal Transition, and only stimulates apoptosis and reactive oxygen species (ROS) formation in cancer cells, leaving normal breast epithelia unharmed. It disrupts mitochondria and affects the ways of two major pathways, p53 and estrogen receptor (ER). Thymoquinone in *N. sativa* inhibits several cancers-related pathways, stimulated cell death, holds back cancer cell from spreading, and manage significant signaling molecules.

Hormonal Influences and Phytoestrogens in Breast Cancer

The role of phytoestrogens, plant compounds structurally similar to human estrogen, in breast cancer has been a subject of considerable debate and evolving scientific understanding. Historically, women diagnosed with breast cancer, particularly those with hormone-receptor-positive disease, were often advised against consuming phytoestrogens due to concerns that these compounds might stimulate alpha ERα, which are known to drive the proliferation of hormone-responsive cancers.

However, a more nuanced understanding has emerged from contemporary research. This shift in perspective stems from the discovery of two distinct types of ERs: ERα and ERβ. While ERα is indeed associated with proliferative effects in breast tissue, ERβ is believed to exert an anti-proliferative influence. New studies indicate that phytoestrogens exhibit a higher affinity for binding to ERβ than to ERα. This differential binding suggests that if phytoestrogens preferentially activate ERβ, they could potentially reduce cancer growth and recurrence rather than promoting it. This fundamental change in understanding has led some researchers to propose renaming these compounds "PhytoSERMs" (Selective ER Modulators) to accurately reflect their selective action on ERs. This re-evaluation underscores the dynamic nature of scientific knowledge and the critical need for continuous reassessment of traditional medical advice in light of new

Table 3: Sickle cell disease's (SCD) effects on female reproductive health and associated complications

Category	Specific impact/ complication	Underlying mechanisms	Contributing factors
Fertility Issues	Reduced Reproductive Lifespan	Ovarian sickling, ischemia, reperfusion injury, chronic hypoxia to ovaries.	Frequent ovarian sickling, vascular occlusion, inflammation leading to ovarian dysgenesis and premature ovarian failure.
	Impaired Oocyte Quality and Quantity	Oxidative stress, telomere shortening, mitochondrial dysfunction, granulosa cell apoptosis.	Chronic transfusion and hemochromatosis (iron overload) from blood transfusions.
	Gonadal Hypofunction	Direct impact of SCD on ovarian function.	Hydroxyurea (may damage ovaries), Opioids (may lower hormone levels), Non-steroidal anti-inflammatory drugs (may reduce ovulation).
Pregnancy Complications (Maternal)	Increased Pain Crises	Increased metabolic demand, blood viscosity, and hypercoagulability.	Pregnancy-induced physiological changes, stress on already affected organs.
	Severe Anemia	Increased demands on bone marrow to produce red cells.	Aggravation of pre-existing anemia.
	Acute Chest Syndrome	Vaso-occlusion in lungs.	Increased susceptibility to infections.
	Serious Infections (Pneumonia, Sepsis)	Impaired immune function in SCD, increased susceptibility during pregnancy.	Increased complement activation in pregnancy combined with SCD.
	Pre-eclampsia	Endothelial damage, inadequate vascularization of evolving embryo.	SCD is a vascular disease, increased risk of utero-placental insufficiency.
	Renal Complications	Increased renal demands during pregnancy superimposed on existing kidney injury from SCD.	Injury to glomeruli, tubules, and renal vasculature in SCD.
Pregnancy Complications (Fetal/Perinatal)	Pre-term Birth	Compromised uteroplacental circulation, chronic fetal hypoxia.	Vaso-occlusion in placenta (villous fibrosis, necrosis, infarction).
	Low Birth Weight/ intrauterine growth restriction	Chronic fetal hypoxia, inadequate vascularization.	Impaired nutrient and oxygen delivery to fetus.
	Stillbirth	Severe maternal complications, placental insufficiency.	High risk of fetal growth restriction.
	Opioid Exposure	Maternal pain management.	Infants may need monitoring for withdrawal symptoms.

mechanistic discoveries. It also highlights the importance of receptor selectivity in the development of therapeutic agents.

Specific phytoestrogen-containing plants include:

Soy (Glycine max) and red clover (Trifolium pratense)

These plants contain isoflavones such as genistein and daidzein, which are preferential agonists for ERβ. Beyond their estrogenic activities, these compounds also modulate P450 enzymes involved in estrogen metabolism, exhibit anti-inflammatory effects, and may suppress DNA methylation, potentially reactivating tumor suppressor genes. While most clinical trials suggest that isoflavones in dietary supplements are safe and do not show estrogenic effects on breast or endometrial tissues, some studies have indicated an estrogenic or proliferative effect in premenopausal women, emphasizing the need for individualized assessment.

Black cohosh (Actaea racemosa)

A popular and effective herbal medicine for menopausal symptoms, Black Cohosh was initially considered a phytoestrogen. However, current understanding suggests it primarily acts on neurotransmitter pathways in the brain, helping to alleviate hot flashes and improve mood and sleep without adversely affecting estrogen-sensitive pathways.

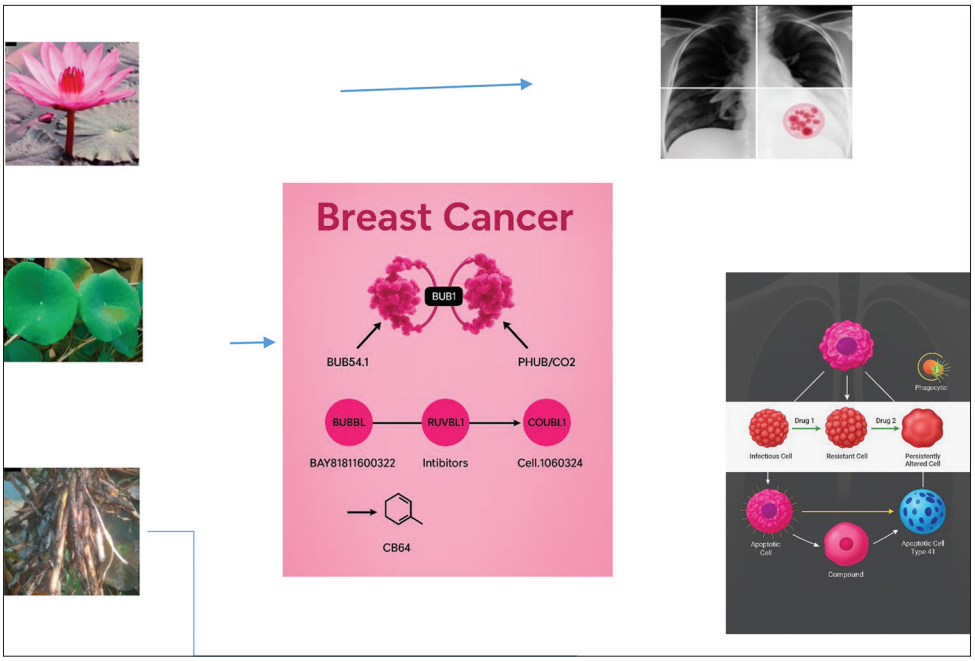

Figure 1: Graphical abstract for breast cancer and sickle cell anemia

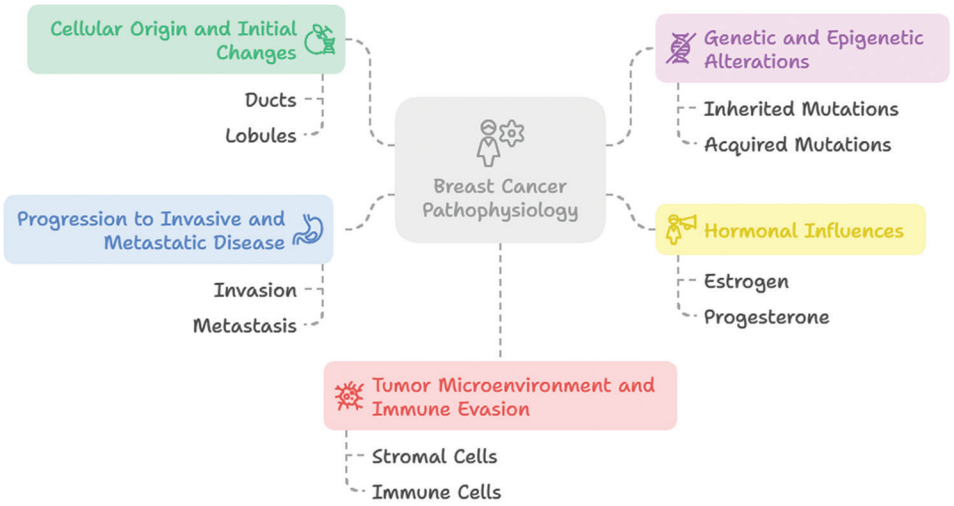

Figure 2: Pathophysiology of breast cancer

Despite this, current medical guidance often advises against its use in breast cancer patients or those undergoing endocrine therapy. This creates a notable contradiction, as clinical studies have indicated that Black Cohosh may enhance the activity of Tamoxifen and reduce menopausal symptoms like joint aches, night sweats, hot flashes, and low mood when used concurrently. This ongoing debate highlights a significant disconnect between emerging research and established clinical guidelines, underscoring the urgent need for additional well-designed clinical studies to clarify its safety and efficacy in this patient population.

Other botanicals with estrogenic activities

Other plants such as Hops (*Humulus lupulus*), Licorice (*Glycyrrhiza* species), Kudzu (*Pueraria lobata*), Rhubarb (*Rheum rhaponticum*), Chasteberry (*Vitex agnus-castus*), Flaxseed (*Linum usitatissimum*), and Dong Quai (*Angelica sinensis*) are also discussed for their estrogenic or hormone-modulating properties. Their relevance to breast cancer prevention or treatment varies, with some showing potential protective effects linked to hormonal, chemical, inflammatory, and/or epigenetic pathways, while others require more definitive evidence regarding their safety and efficacy in this context.

Adaptogenic Herbs for Supportive Care

Adaptogens are a unique class of herbs that enhance the body's ability to "adapt" to stress, whether physical, chemical, or biological. For women recovering from breast cancer

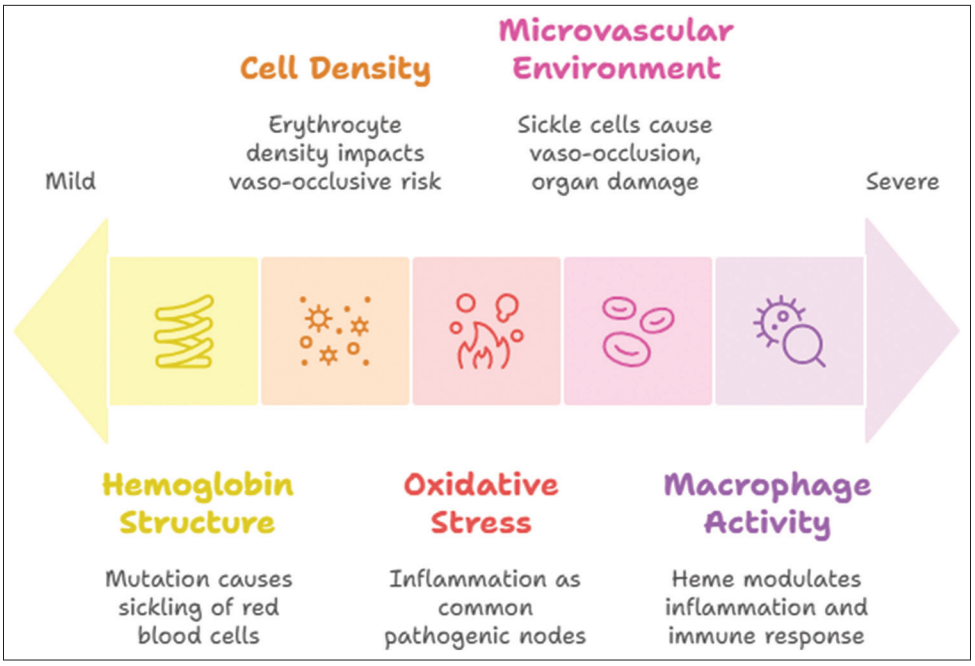

Figure 3: Pathophysiology of sickle cell anemia

or undergoing treatment, these herbs can be particularly beneficial in managing the physiological and emotional toll of the disease and its therapies.

Ashwagandha (W. somnifera)

Studies suggest that Ashwagandha may possess anti-proliferative properties and could assist in suppressing breast cancer recurrence. Beyond its potential direct anticancer effects, it is highly valued for promoting a sense of calmness, reducing anxiety, protecting against physiological and emotional stress, and improving sleep quality – all crucial aspects of supportive care during cancer treatment.

Rhodiola (Rhodiola rosea)

This adaptogen is prized for its capacity to improve energy levels, mood, cognitive function, and mental focus. It also exhibits cardio-protective and anti-cancer qualities. However, it is important to note that Rhodiola might influence specific liver enzymes, potentially altering the metabolism and levels of certain drugs, including Tamoxifen. The precise benefit or risk of this interaction remains uncertain and warrants careful consideration.

Siberian ginseng (Eleutherococcus senticosus)

Known for its ability to boost energy and improve mental focus, Siberian Ginseng also possesses immunomodulatory, antioxidant, and anti-cancer properties. It is crucial for patients and practitioners to differentiate it from Asian Ginseng (*Panax ginseng*), which is a distinct plant species with phytoestrogenic properties. Misidentification or misuse could lead to unintended hormonal effects, emphasizing the need for precise botanical identification and expert consultation.

Current Research Landscape and Challenges

The current research landscape for medicinal plants in breast cancer is characterized by significant preclinical promise alongside considerable challenges in clinical translation. Numerous herbal extracts and their isolated phytochemicals have demonstrated promising effects in inhibiting tumor proliferation, metastasis, angiogenesis, and drug resistance in various *in vitro* and *in vivo* preclinical studies. This extensive preclinical evidence provides a strong foundation for further investigation.

Nevertheless, there is still little integration of these plant-based treatments into standard oncology procedures. The lack of standardized dosing guidelines and the inherent variability in herbal formulations, which can result in inconsistent therapeutic outcomes, are major challenges. In addition, the systemic efficacy of many promising compounds, like resveratrol and curcumin, is limited by their high metabolism and low bioavailability in the human body. Notwithstanding these obstacles, certain substances, such as EGCG and curcumin, have advanced to clinical trials and are frequently investigated as supplemental therapies to improve the effectiveness of traditional treatments or lessen their adverse effects. In fact, some herbal remedies have demonstrated synergistic effects with hormone therapy and traditional chemotherapy, which may improve therapeutic results while reducing toxicity. Continued research that combines modern pharmacological techniques with traditional knowledge is essential to overcome these challenges and develop safer,

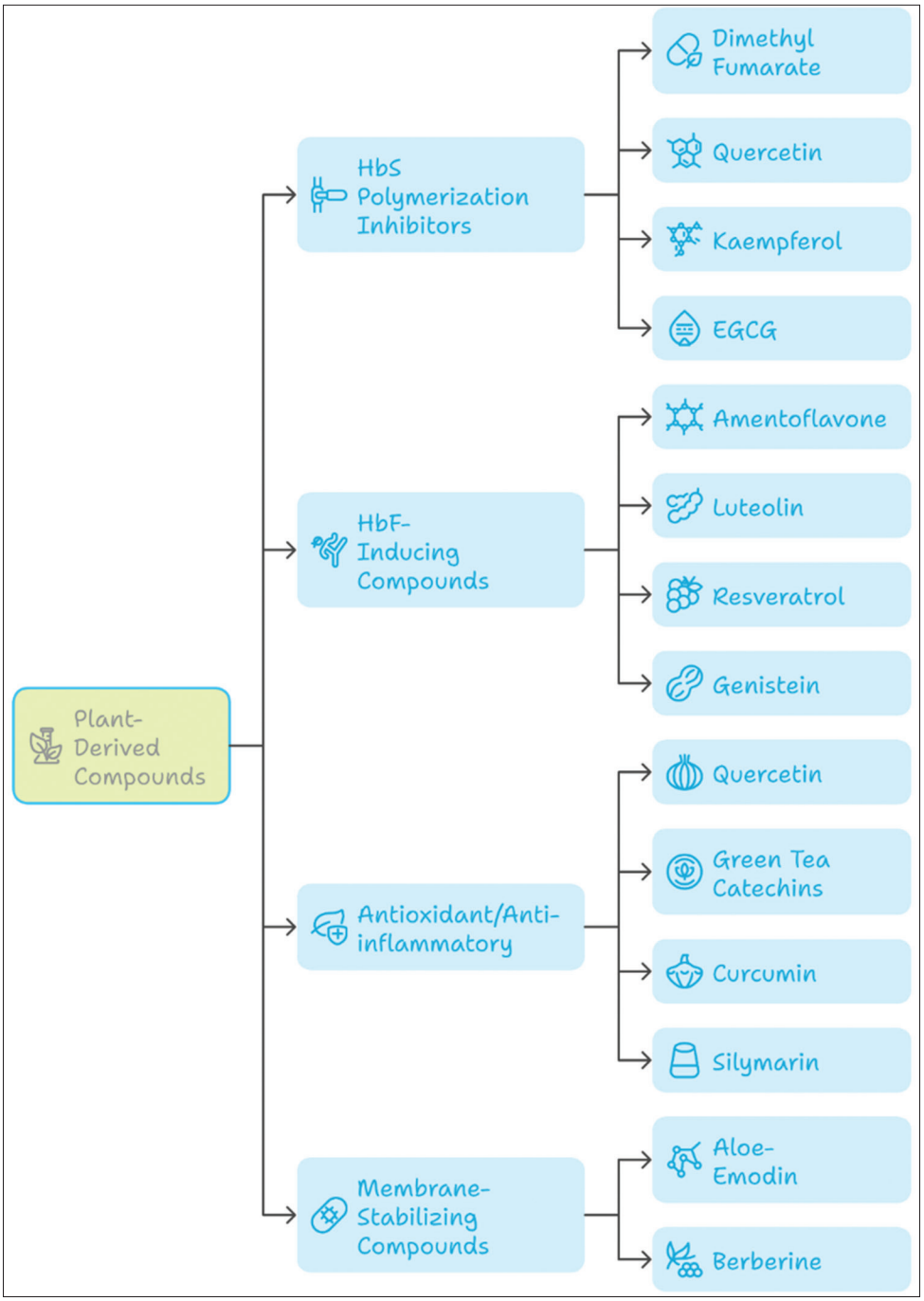

Figure 4: Plant-derived compounds for sickle cell anemia

more effective, and personalized therapeutic strategies for breast cancer.

MEDICINAL PLANTS FOR SCA IN WOMEN

Traditional and Nutritional Interventions

In many parts of the world, particularly in Africa, traditional healers have long relied on a vast array of native medicinal foods derived from plants for the management of SCD. These conventional treatments often enjoy higher popularity than modern medications, reflecting a deep-rooted cultural acceptance and accessibility. However, the traditional reliance on verbal transmission of this knowledge carries the inherent risk of its loss for future generations, underscoring the importance of documentation and scientific validation.

Beyond traditional herbal remedies, nutritional interventions play a crucial role in SCD management. Nutritional deficiencies are known to contribute to the severity of SCD, increasing interest in dietary supplements. Individuals with SCD often require higher caloric and protein intake, and

malnutrition is a common consequence of the disease. Among the most studied nutritional approaches are:

- Omega-3 Fatty Acids: Polyunsaturated omega-3 fatty acids, notably docosahexaenoic acid and eicosapentaenoic acid, are recognized as potent anti-inflammatory mediators in SCD. Clinical studies have demonstrated their utility in controlling pain and reducing the frequency of VOC episodes, which are hallmark painful events in SCD
- Antioxidant-Rich Edible Mushrooms: Various edible mushrooms possess significant pharmacological effects and can contribute to improved health, lifespan, and quality of life for individuals with SCD. Specific examples include:
  - *Ganoderma lucidum*: Reported to reduce the rate of hemoglobin polymerization, a key pathological event in SCD
  - *Auricularia auricular*: Known for its ability to scavenge free radicals, addressing the oxidative stress prevalent in SCD
  - *Hericium erinaceus*: Plays a role in regulating heat shock proteins, which are involved in cellular stress responses
  - *Termitomyces*: Demonstrated to increase both hemoglobin levels and white blood cell counts, which can be beneficial in managing anemia and immune function in SCD patients.

Specific Medicinal Plants and Their Anti-Sickling Properties

A wide range of medicinal plants have been traditionally used and scientifically investigated for their anti-sickling properties, particularly in regions with a high prevalence of SCD.

African plants

Indigenous medicinal substances from Africa have been a primary focus of research for their potential in SCD management:

- Seed oils from plants such as *Ipomoea involucrate*, *Solenostemon monostachyus*, *C. cajan* (Pigeon pea), *Acacia senegal*, and *C. papaya* have been investigated for their nutritional advantages in individuals with SCD, particularly in Nigeria. *C. cajan* has a historical record of use to prevent or reduce RBC sickling and as a treatment for anemia. A 2017 study identified two specific molecules in its stem with anti-sickling properties, building on prior reports of anti-sickling effects from the whole plant and its seed extracts. *C. papaya* and *Terminalia catappa* are among the most frequently reported species demonstrating anti-sickling activities
- *Ceiba pentandra* and *Alchornea cordifolia* are used medicinally in the Democratic Republic of Congo to prepare "blood tonic" beverages, reflecting their traditional role in promoting blood health
- Conventionally, *M. oleifera*, which is abundant in phytochemicals with anti-urolithiasis properties, has been used to treat SCD
- *N. sativa* (black seed) is valued for its antioxidant qualities, which are crucial in mitigating the oxidative stress associated with SCD
- Other examples of herbal drugs used in SCD management include *Zanthoxylum chalybeum*, *Carissa edulis*, and *Ficus capensis*. Specifically, *Zanthoxylum zanthoxyloides* root is extensively used in home-based remedies among underprivileged communities for SCA
- Niprisan, a polyherbal anti-sickling medication, was developed from a combination of medicinal plants such as *Syzygium aromaticum*, *P. guineense*, *Aframomum melegueta*, *Sorghum bicolor*, and *Pterocarpus osun*. This product successfully passed Phase IIA and IIB clinical trials and is widely used in Nigeria, India, and the USA
- Ciklavit, another product based on *Cajanus cajan*, has also undergone randomized placebo-controlled single-blind intervention trials to assess its safety and efficacy in Nigeria.

Other Herbs: Several other herbs have been explored for their potential benefits in SCD:

- *Aloe vera* (*Aloe barbadensis*): A 2021 research review suggested that aloe vera extract might help prevent the sickling of cells and decrease vaso-occlusive and pain crisis episodes
- Lemongrass (*Cymbopogon citratus*): Identified as an herbal remedy with a long history of use in managing SCD in Eastern Uganda. A 2015 study found that daily consumption of lemongrass tea for one month increased RBC counts, although this study did not specifically focus on SCD patients
- Garlic: A 2021 review notes that garlic may be effective in treating SCD due to its antioxidant effects, which can prevent the growth of dense cells
- Turmeric (*C. longa*): *In vitro* studies have shown significant anti-sickling effects. Its rhizome extract demonstrated a 66.81% reversal effect on sickled RBCs, normalizing approximately two-thirds of sickled cells
- Fenugreek (*Trigonella foenum-graecum*): *In vitro* studies also revealed significant anti-sickling properties, with its seed extract showing a 61.28% reversal effect on sickled RBCs, correcting a substantial portion of sickled cells.

The following table summarizes these key medicinal plants, their reported effects, and current research status.

Mechanisms of Anti-Sickling Action

The anti-sickling effects observed in various medicinal plants are primarily attributed to the presence of specific phytochemicals, notably anthocyanins and organic acids. These compounds are believed to interact directly with HbS, thereby competing with the polymerization process that leads to the characteristic sickling of RBCs.

Beyond direct interaction with HbS, many plants, including *N. sativa*, Garlic, and Turmeric, exert significant antioxidant qualities. This antioxidant activity is particularly crucial in SCD, where patients often experience increased gut damage, permeability, altered microbiota composition, and bacterial overgrowth, leading to dysbiosis that exacerbates inflammation and suffering. By scavenging free radicals, these plants can help mitigate the oxidative stress that contributes to RBC damage and VOC.

Other mechanisms include:

- Hemoglobin Polymerization Reduction: Certain compounds, such as those derived from *Ganoderma lucidum*, have been shown to directly reduce the rate of hemoglobin polymerization, a fundamental process in SCD pathology
- Free Radical Scavenging: Compounds from *Auricularia auricular* actively scavenge free radicals, directly addressing the heightened oxidative stress characteristic of SCD
- Increased RBC Count: Some plants like Lemongrass and *Termitomyces* have demonstrated the potential to increase RBC counts, which can help alleviate the chronic anemia experienced by SCD patients.

Despite the broad traditional use and promising *in vitro* results, only a limited number of plant-derived compounds have been pharmacologically validated for their anti-sickling activities through rigorous scientific assays. These include benzoic acid derivatives, butyl stearate, ellagic acid derivatives, and some pentacyclic triterpenoids. This highlights a significant gap between empirical traditional knowledge and the identification of specific bioactive molecules responsible for observed effects.

Safety and Efficacy Profile

The research into the effectiveness of herbal remedies for SCD is currently limited, and further comprehensive studies are still needed to fully understand their precise effects and determine their viability as mainstream treatment options. While traditional use is widespread, particularly in Africa, the scientific validation of these practices remains nascent.

A systematic review conducted in Africa, which examined the safety and efficacy of herbal remedies for SCD, found that approximately 38.5% of participants reported an improvement in their symptoms with the use of herbal remedies. However, the pooled efficacy of these herbal remedies for treating SCD was not statistically significant, despite appearing nearly 100% higher among users than controls. This situation presents what can be described as an "efficacy-safety paradox" in traditional medicine: while there is widespread traditional use and promising *in vitro* results for many plants, consistent and statistically significant clinical evidence supporting their efficacy is often lacking. This discrepancy arises partly because the primary studies included in the review often had small sample sizes and a high risk of publication bias, which can obscure the true benefit-risk profile. The absence of robust, statistically significant clinical data means that despite traditional acceptance, the overall benefit-risk assessment for widespread clinical integration remains unclear, underscoring the urgent need for well-designed, large-scale clinical trials to validate traditional practices and ensure patient safety.

In terms of safety, pertaining to 22.9% of participants who used herbal remedies reported experiencing headaches, fever, and common gastrointestinal symptoms involving vomiting, diarrhea, and distension in the abdomen. In animal studies, certain negative outcomes have been observed: When administered to laboratory rats, *Zanthoxylum chalybeum* bark extract resulted in noticeably increased squamous cell growths and total white blood cell counts in both the large and small intestines. Rats that received high dosages of *C. edulis* root and bark extracts also showed mild alterations in their hematological, hormonal, and renal systems. In human studies, Niprisan was linked to headaches, and *C. cajan* to gastrointestinal symptoms in some patients. Other commonly used remedies, such as *A. barbadensis*, *Zingiber officinale* (ginger), *Cymbopogon citratus* (lemongrass), Forever Living products, GNLD diet supplements, and ginseng products, were reported to cause fever and diarrhea. Conversely, some plants like *Petiveria alliacea*, *Chenopodium ambrosioides,* and *Entandrophragma utile* had no reported side effects.

The geographical focus of anti-sickling research is heavily concentrated in Africa, accounting for 86.58% of all publications, with over half of this research originating from Nigeria. This regional disparity highlights a significant imbalance in global research efforts, with limited studies from other continents. More extensive controlled studies with better-defined endpoints are critically required to provide definitive evidence for the safe and effective use of herbal medicines in managing SCD, especially for prolonged periods, as long-term safety data are largely unknown.

The following table provides an overview of the safety and efficacy findings for herbal remedies in SCD, particularly in the African context.

WOMEN'S HEALTH CONSIDERATIONS IN SCA

Impact on Female Reproductive Health

SCD significantly impacts female reproductive health, leading to a heightened risk of infertility, severe pregnancy complications, and increased rates of maternal and perinatal mortality. This burden is particularly pronounced in regions

like Sub-Saharan Africa, where SCD prevalence is high, and access to comprehensive healthcare is often limited.

The systemic effects of SCD extend far beyond hematological issues, directly compromising female reproductive organs and function. The ovaries, which are essential for preserving female reproductive potential and endocrine stability, are significantly impacted by the illness. This can lead in increased ovarian sickling, decreased reproductive lifespan, and altered ovarian follicular dynamics. Chronic hypoxic injury to ovarian tissues can quickly deplete ovarian reserve, impairing both the quality and quantity of oocytes and raising the risk of infertility. Ovarian sickling causes ischemia and reperfusion injury. In extreme situations, long-term blood transfusions and the ensuing hemochromatosis (iron overload) can worsen ovarian reserve and follicle quantity and quality, which may lead to infertility and difficulties using assisted reproductive technologies. Premature ovarian failure and ovarian dysgenesis are also caused by inflammation, vascular occlusion, and frequent ovarian sickling. Reduced ovarian reserve makes women more vulnerable to conditions like osteoporosis, elevated cardiovascular morbidity and mortality, depression, and decreased sexual well-being that are linked to lower estrogen levels. This reveals a complex interplay where the primary disease pathology and its conventional treatments converge to create a multifaceted challenge for female fertility and reproductive health. It highlights that managing SCD in women is not just about addressing acute crises but also about preserving long-term reproductive potential.

Pregnancy in women with SCD introduces additional physiological stress, significantly raising the risk of complications for both the mother and the developing baby. These complications include:

- A higher incidence of pre-eclampsia (a 2–3-fold increased risk), pre-term labor, intrauterine growth restriction (a 3–4-fold increased risk), and stillbirth (a 4-fold increased risk)
- Aggravation of pre-existing anemia, often necessitating increased blood transfusions
- Increased cardiopulmonary demands, which are particularly challenging for women with pre-existing pulmonary hypertension
- A higher risk of thromboembolic complications, acute chest syndrome, osteonecrosis, hepatic necrosis, and VOC due to pregnancy-related increases in blood viscosity, metabolic demand, and hypercoagulability
- Vaso-occlusion within the placenta, which can compromise uteroplacental circulation, leading to chronic fetal hypoxia and adverse fetal outcomes
- An increased risk of serious infections, including pneumonia and sepsis.

A thorough summary of the effects of SCD on female reproductive health and related complications can be found in the following table 4.

Role of Nutritional Support in Reproductive Health

Since SCD has a significant effect on female reproductive health, nutritional support evolves into a vital, less harmful, and frequently affordable intervention to improve reproductive outcomes and improve the broadly well-being of women with SCD. Vitamin B12, also known as cobalamin, is a crucial area of attention because people with SCD are especially vulnerable to deficiencies in this vitamin. This deficiency carries significant hematological and, importantly, reproductive consequences.

Vitamin B12 is indispensable for the normal functioning of the nervous and reproductive systems, DNA synthesis, and cellular energy metabolism. It is critical for preserving healthy folate metabolism, which essential for the rapidly replication of cells needed for the development of placental and fetal tissues. Furthermore, B12 facilitates a variety of methylation reactions that are essential for embryonic development and the control of fetal growth by taking part in the one-carbon metabolism cycle.

One of the critical functions of B12 is its role as a coenzyme in the process that turns homocysteine into methionine, known as methionine synthase. Homocysteine, a substance that impairs oocyte maturation, fertilization, and embryo quality, can build up as a result of a B12 deficiency. It can also harm the endometrium, which can end in deprived implantation.

Optimal B12 levels, therefore, help mitigate homocysteine accumulation, thereby supporting reproductive processes.

Beyond its metabolic roles, B12 plays a major role in lowering proinflammatory cytokines and oxidative stress. To reduce the harmful effects of lipid peroxidation on the ovaries and control the production of ROS, this antioxidant and anti-inflammatory activity is essential. This can help women with SCD maintain better reproductive health overall. B12 also contributes to the bioavailability of nitric oxide (NO). Numerous ovarian processes, such as ovulation, folliculogenesis, oocyte quality, and implantation, are modulated by NO, a critical paracrine mediator. Unfavorable reproductive outcomes may result from inadequate NO synthesis, which is frequently caused by high homocysteine levels.

Consequently, optimal B12 levels at preconception are correlated with favorable reproductive outcomes in both natural and assisted pregnancies; B12 supplementation has been linked to a higher likelihood of obtaining a clinical pregnancy and live birth. The present advised dietary allowance of 2.4 µg/day for adults may be inadequate given the higher demand for B12 in SCD patients resulting from increased hematopoiesis. Thus, routine assessment of B12 status and customized dietary intake are advised for reproductive-age women with SCD, especially those who are pregnant or lactating, representing a practical and actionable strategy to improve their reproductive health outcomes.

Pregnancy Management and Safety of Interventions

Managing pregnancy in women with SCD requires careful consideration of both the disease's complications and the safety of various interventions, including conventional medications and, where applicable, herbal remedies.

Conventional medications in pregnancy

Several conventional medications commonly used for SCD management carry specific considerations during pregnancy:

- Hydroxyurea: This medication is generally not advised during pregnancy due to potential risks to the developing fetus, though lower doses might be considered in specific circumstances after careful evaluation. Furthermore, research suggests that hydroxyurea might damage the ovaries, potentially affecting fertility
- Newer Medications: L-glutamine, voxelotor, and crizanlizumab are newer therapeutic options for SCD. However, their safety during pregnancy requires careful consideration and thorough discussion with healthcare providers, as comprehensive data in this specific population may still be emerging
- Opioids: While often necessary for pain management during sickle cell crises, regular opioid use may lower hormone levels, making it more challenging to conceive. In addition, infants whose mothers received regular opioid treatment during pregnancy should be monitored for withdrawal symptoms after birth
- Non-steroidal anti-inflammatory drugs (NSAIDs): Some research indicates that regular use of NSAIDs, commonly available over-the-counter for pain relief, may reduce the likelihood of ovulation in women
- Blood Transfusions: Although vital for managing severe anemia and complications in SCD, frequent blood transfusions can lead to high iron levels in the body, which may impair ovarian function and fertility.

Herbal remedies and pregnancy safety

A critical research void exists regarding the safety and efficacy of specific medicinal plants for reproductive health in women with SCD, particularly during pregnancy. The available research material explicitly states that the article on SCD and female reproductive health does not mention any specific medicinal plants for reproductive health in SCD, focusing instead on Vitamin B12. More broadly, data on the safety and efficacy of herbal remedies for SCD in Africa are limited, and the effects of prolonged use are largely unknown. This creates a significant "known unknown" in clinical practice: despite the widespread traditional use of herbs for SCD, there is a concerning lack of rigorous scientific data regarding their safety and efficacy specifically for pregnant women with SCD. This poses a major clinical dilemma, as potential benefits must be carefully weighed against unknown risks to both the mother and the developing fetus. This highlights an urgent and pressing need for dedicated research in this vulnerable population.

General pregnancy recommendations for SCD women

To mitigate risks and optimize outcomes, comprehensive preconception and prenatal care are paramount for women with SCD. Key recommendations include:

- Confirming the sickle cell status of both parents and considering genetic counseling to assess risks for future children
- Developing a proactive pain management plan tailored for pregnancy and breastfeeding
- Taking prenatal vitamins, including folic acid, which is crucial for new cell formation and fetal development
- Carefully managing all medications and avoiding alcohol and tobacco products
- Undergoing regular monitoring of heart health (e.g., echocardiogram) and fetal growth (e.g., ultrasound scans)
- Discussing birth control options with a healthcare provider, as some hormone-based methods may not be safe for women with SCD.

CONCLUSION AND FUTURE DIRECTIONS

Synthesis of Key Findings

This thorough study emphasizes how rich and varied a source of bioactive compounds medicinal plants provide for both SCA and breast cancer treatment potential. Phytochemicals, including curcumin, resveratrol, and EGCG, show encouraging antitumor mechanisms for breast cancer, including induction of death, inhibition of proliferation, and suppression of metastases. While many of these compounds are still in preclinical stages, some are progressing to clinical studies, often explored as adjunctive therapies to enhance conventional treatments. A significant evolution in understanding pertains to phytoestrogens, where new research suggests potential benefits through selective modulation of ERβ, challenging previous cautionary advice and opening new avenues for personalized therapy. Furthermore, adaptogenic herbs like Ashwagandha and Rhodiola provide valuable supportive care, helping women manage the physiological and emotional stress associated with cancer treatment.

For SCA, a wide array of traditional African plants, alongside globally recognized herbs such as turmeric and fenugreek, has shown promising anti-sickling properties *in vitro*. Their mechanisms often involve directly reducing hemoglobin polymerization, scavenging harmful free radicals, and

increasing RBC counts, addressing core pathological features of the disease. However, the impact of SCD on women's reproductive health is profound and multifaceted, affecting fertility, ovarian function, and significantly increasing risks during pregnancy. In this context, nutritional support, particularly Vitamin B12, shows considerable promise in mitigating some of these complex reproductive complications by addressing underlying deficiencies and oxidative stress.

Critical Assessment of Current Evidence and Research Gaps

Despite the compelling potential, a significant gap persists between the extensive traditional knowledge and rigorous clinical validation of medicinal plants for both conditions. For SCD remedies, in particular, while *in vitro* and preclinical studies are abundant, large-scale, statistically significant clinical trials demonstrating consistent safety and efficacy are often lacking. This creates a disjunction where widespread traditional use is not yet consistently supported by robust modern scientific evidence.

Challenges such as the low bioavailability of some active compounds (e.g., curcumin, resveratrol) and the inherent variability in herbal formulations hinder their consistent integration into mainstream medicine. Furthermore, while some herbs show no reported side effects, others are associated with gastrointestinal issues, fever, or even more severe adverse events identified in animal studies, underscoring the critical need for comprehensive toxicological assessments.

A particularly critical research void exists regarding the safety and efficacy of herbal remedies for pregnant women with SCD, a highly vulnerable population. This contrasts sharply with the known risks of some conventional SCD medications during pregnancy, leaving a significant clinical dilemma for healthcare providers and patients. The nuanced and evolving understanding of phytoestrogens in breast cancer highlights the inherent complexity of hormonal interactions and the necessity for personalized recommendations based on individual receptor status and concurrent treatment regimens.

Recommendations for Future Directions

To advance the therapeutic application of medicinal plants in breast cancer and SCA, particularly for women, several key recommendations are proposed:

- Rigorous Clinical Trials: Prioritize the design and execution of well-designed, adequately powered, randomized controlled clinical trials. These trials are essential to definitively validate the safety and efficacy of promising medicinal plants for both breast cancer and SCD, with a specific focus on female patients
- Standardization and Quality Control: Develop standardized extracts and formulations with precisely defined phytochemical compositions. This will ensure reproducibility of therapeutic outcomes, improve quality control, and facilitate consistent dosing, which are critical for clinical integration
- Mechanistic Studies: Continue to elucidate the precise molecular mechanisms of action of active compounds. A deeper understanding of these mechanisms will inform rational drug development, optimize combination therapies with conventional treatments, and identify potential targets for novel drug discovery
- Pharmacokinetic and Pharmacodynamic Studies: Conduct comprehensive studies on the bioavailability, metabolism, and potential drug-herb interactions of these plant-derived compounds. This is crucial for optimizing dosing regimens, predicting efficacy, and minimizing negative consequences or interactions with conventional medications
- Targeted Research for Women's Health: Established specific research programs dedicated to investigate the impact of medicinal plants on female reproductive health in SCD, including fertility and pregnancy outcomes, to address the current data void. For breast cancer, further research on phytoestrogens should focus on cancer subtype-specific responses, long-term effects, and their potential role in personalized medicine
- Integration of Traditional and Modern Medicine: Foster collaborative research efforts that thoughtfully integrate traditional knowledge and practices with modern scientific methodologies. This approach can ensure cultural relevance while upholding scientific rigor, potentially leading to the discovery of novel therapeutic agents from understudied traditional remedies
- Patient-Provider Communication: Encourage open, informed, and non-judgmental communication among patients and medical professionals with use of herbal medicines. Patients should be empowered to disclose all treatments they are using to prevent potential adverse interactions and ensure a holistic, safe, and effective care plan.

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