International Journal of Pharmacology and Clinical Research

ISSN Print: 2664-7613
ISSN Online: 2664-7621
Impact Factor: RJIF 8
IJPCR 2024; 6(1): 49-54
www.pharmacologyjournal.in
Received: 10-09-2024
Accepted: 18-10-2024

Abhishek Konar
School of Life Sciences, Seacom Skills University, Santiniketan, Bolpur, Birbhum, West Bengal, India

Jasmine Kaur
Department of Applied Biology and Environmental Sciences, Centennial College, Toronto, Ontario, Canada

Shivaranjani DS
Department of Microbiology and bioinformatics, Molelixir informatics, New Delhi, Delhi, India

Sanjukta Chakraborty
Department of Computer Science and Engineering, Seacom Skills University, Santiniketan, Bolpur, Birbhum, West Bengal, India

Pranabesh Ghosh
School of Life Sciences, Seacom Skills University, Santiniketan, Bolpur, Birbhum, West Bengal, India

Corresponding Author:
Abhishek Konar
School of Life Sciences, Seacom Skills University, Santiniketan, Bolpur, Birbhum, West Bengal, India

Role of *Vernonia cinerea* in breast cancer: A review

Abhishek Konar, Jasmine Kaur, Shivaranjani DS, Sanjukta Chakraborty and Pranabesh Ghosh

DOI: https://doi.org/10.33545/26647613.2024.v6.i1a.37

Abstract
Vernonia cinerea Less. (VC) of the associated with Asteraceae family, which play significant ethnopharmacologically as anti-effects of breast cancer. Food and medicine use *Vernonia cinerea* plants widely, which are commonly used medicinally. Globally, Breast cancer (BCa) is the most common cause of women & men death. In this time various treatment available in the market, but they have other negative point. In this view *Vernonia cinerea* is an important plant. The herb is a priceless treasure that is commonly found everywhere but has significant medicinal benefits. In ancient times it was used in critical disorders, but in this time very few new generation know, its benefits.VC is an Angiosperms plant and generally found in tropical and subtropical region. This plant contains various chemical components, which can be regulating Cell cycle including G2 or M. In this study, we review the major and minor metabolite composition of *Vernonia cinerea* of vegetative and other important plant parts as well as their potential activity against Breast cancer cell (MCF-7) lines. This review was carried out on the anti-effects of breast cancer of *Vernonia cinerea* less.

Keywords: *Vernonia cinerea*, breast cancer, MCF-7, ethnnobotany

Introduction
Now a days Breast cancer is a prime health problem for women in the world [1, 2]. Not only does Breast Cancer develop in women, but it also develops in men. In 2018, 2.1 million new cases and 627,000 died by Breast cancer in Asian countries [1, 2, 3, 4]. But, the risk of breast cancer is higher for women than for men. There is a high rate of breast cancer among women between 50 and 69 years old [1, 2]. Globally, In 2020 Breast Cancer (BCa) is the Fifth mortality cause and has spread lung cancer as the leading cause of cancer incidence and in 2023 it increased 15.2%. [3]. Breast cancer develops various internal and external aspects such as genetic factors, obesity, menstruation, high-fat consume, smoking and drinking, whether lactation, ionizing radiation [1,2]. However, various modern treatments are available such as endocrine therapy, chemotherapy, targeted therapy, immunotherapy, and antibody drug, but this treatment create various another side effect weight gain, sexual and Cardiac dysfunction, neutropenia damage healthy cells, interstitial lung and liver disease swelling, function etc. It can also significantly reduce the quality of life and increase mortality and morbidity due to toxicity [5]. Due to their side effects and high cost, people are cautious about using synthetic drugs today, and traditional herbal treatments are becoming more popular. This has led to a prosperous research initiative for both existing and new pharmaceutical companies alike. From ancient time Plants have been versatile utilized for the well-being of mankind immemorial due to their therapeutic potential [6, 7]. Plants produce bioactive compounds in the form of secondary metabolites. According to WHO 80% medicines are produced from plant [8]. In this time day by day herbal medicinal plant demand due to low cost, and fewer side effects compare to synthetic drugs [7, 8, 9, 10, 11].
Vernonia cinerea know as a medicinal plant which belongs in Asteracee family. It is generally called little iron weed. It is widely found in Africa, India, Bangladesh, and Sri Lanka. Native to Africa including Benin, Cameroon, Nigeria, Ghana, Kenya, Liberia, etc., tropical and temperate Asia including Indonesia, China, Fujian, Bangladesh, Japan, Malaysia [9]. This genus was named after William Vernon, an English botanist. In an Ayurvedic medicine system, *V. Cinerea* has been widely used to treat various critical diseases including cancer.

Traditional medicine uses *V. Cinerea* to treat a large-scale of diseases, including cancer. In chemical studies, phenolic resin, triterpenes, sterols, and sesquiterpene lactones have been identified as components of VC [12, 13]. This paper aims to determine the effect of Breast Cancer (BCa) of *V. Cinerea* and its bioactive component.

Taxonomical Features

Classification of *Vernonia cinerea* (L.) Less. [12, 13].

- **Kingdom:** Plantae
- **Subkingdom:** Tracheobionta
- **Super-division:** Spermatophyta
- **Division:** Magnoliophyta
- **Class:** Magnoliopsida
- **Subclass:** Asteridae
- **Order:** Asterales
- **Family:** Asteracee
- **Genus:** *Vernonia*
- **Species:** *Vernonia cinerea* (L.) Less.

Habitat: It is herbaceous, annual plant. This, species is typically found in sunny or partly sunny habitats, such as wasteland, roadsides, disturbed areas, agricultural land, and cultivated areas. VC is an autotrophic plant, they produced own food using inorganic compounds and light [9, 14].

Morphology

Stem: Stems are rigid, ribbed and grooved, somewhat pubescent, striate, and branching, growing up to 17 cm tall. Stems are flexible, and without woody structure [15].

Root: A main tap root measures between 5 and 11 cm long and 1 to 7 mm thick, tapering gently, obliquely, and bearing few rootlets [14].

Leaves: There are simple, alternate, petiolar (With smallest upper leaf). Leaves are various shape such as elliptic or lanceolate, acute or obtuse, multifidus, Inflorescences with shallow crenations, irregular toothing, and hairy leaves [14, 15].

Flower: Pinkish and purple, Violet coloured flowers appear during August-April [14, 15].

Fig 1: Whole Plant, Flower and Leaf

Vernacular Names

In the following list, we provide a list of different vernacular names mentioned in various books [16, 17, 18].

Bengali	Songa, Kalajira, Kukshim, Peetpushpi, Kukur.
English	Ash coloured fleabane, Ash-colour fleabane, purple fleabane, and purple fleabane.
Hindi	Sadodi, Dandotpala, kalgira, kaljiri, sadori, sandr.
Hindi	Daudotpal, Dandotpala, sahadevi, sahadei.
Urdu	Shehdevibuti
Punjabi	Sahadevi
Tamil	Cakatevi, cenkalunir, neycatti, puvamkurundal, sahadevi, sirashengalanir
Indochina	Bacdau

Overviews of Breast Cancer

Most women develop nonmelanoma skin cancer, followed by breast cancer. It is the primary cause of cancer-related deaths among women globally. Approximately 316,000 women die every year from breast cancer, making it the second most common cause of cancer-related deaths among women, after lung cancern [19, 20, 21]. A diverse group of experts in medical, surgical, and radiation oncology is needed to treat breast cancer. Medical professionals are generally the initial ones to see patients who get a breast cancer diagnosis because the majority of breast cancers are detected by mammography or physical examination. Primary care doctors must be knowledgeable about the first stages of breast cancer therapy as well as the diagnostic process [22].

Pathology, Risk Factors

Several risk factors are known, but the pathophysiology of breast cancer is complex and still poorly understood. Approximately 10% of breast cancer cases are caused by genetic abnormalities, namely BRCA 1 and 2. Ductal carcinoma in situ, high body mass index (BMI), early menarche (Before the age of thirteen), nulliparity (The first child born after the age of thirty), late menopause, a family history of breast or ovarian cancer, and postmenopausal hormone therapy are some of the recognized risk factors. The majority of women who utilize postmenopausal hormone treatment are Caucasian, have normal BMIs, and have thick breasts. A higher risk also applies to women who have previously had chest radiotherapy [23, 24].

Breast cancer has four subtypes, each with its own histologists and prognoses. There are three subgroups of breast cancer, depending on their morphological origin (Lobular or ductal), their hormone responsiveness, and their expression of the human epidermal growth factor receptor 2 (HER-2). Hormone receptivity describes whether or not the cancer expresses progesterone and estro-gens receptors. Hormone receptor-positive Hormone-blocking therapy is an effective treatment for breast cancer, especially when it is nonmetastatic. HER-2-expressing cancers can be treated with monoclonal antibodies directed against HER-2. Breast cancer that expresses hormone receptors positively but lacks HER-2 is quite prevalent. Breast cancers classified as triple-negative indicate that they do not exhibit HER-2 or hormone receptivity. Triple-negative breast cancer affects about 12 per cent of female patients. In contrast to other subgroups, triple-negative illness tends to be diagnosed at an earlier age but is more frequent among non-Hispanic black women [23]. Furthermore, stage III or IV diagnoses are more common in later life for women with triple-negative illnesses. Triple-

negative basal subtype breast cancers also tend to be more aggressive and of a higher grade than hormone receptor-positive HER-2 negative tumours. Recently, the proliferation biomarker Ki-67 has been utilized to aid in the risk of recurrence stratification for breast cancer. Although it is no longer advised, new immuno-histologic indicators are being found that might aid in further stratifying the likelihood of recurrence [25].

Breast Cancer Stages and Classification

Tumour size, nodal involvement, the existence of metastases, and certain biomarkers like progesterone, estr-gens, and the ERBB2 (Previously HER2) receptor are used to define the stage of breast cancer [26]. All pathology samples should undergo testing for ERBB2 status, progesterone receptors, and estro-gens receptors following a histologic diagnosis of breast cancer [27, 28]. Triple-negative breast cancers are defined as those that express none of these markers. Stage 0 non-invasive breast cancer is called Ductal carcinoma in situ (DCIS). Stages I, IIa, and IIb correspond to early invasive cancer, while stages IIIa, IIIb, and IIIc correspond to locally progressed cancer. These are all nonmetastatic phases of breast cancer. Metastatic breast cancer is stage IV [26].

Stage 0, Ductal Carcinoma in Situ (DCIS)

DCIS is a kind of pure, non-invasive cancer that is often detected by microcalcifications limited to the breast ducts on mammography [29]. Invasive breast cancer develops in up to 40% of DCIS cases if treatment is not received **[30]**. Treatment options for DCIS include mastectomy or radiation therapy, with a 2-mm surgical margin as the ideal result **[30, 31]**. At the time of mastectomy, a sentinel lymph node (SLN) biopsy is performed to rule out the (very uncommon) chance of lymph node involvement. Technically, it might not be feasible to do an SLN biopsy following a mastectomy. Radiation therapy is a therapeutic option provided to patients having a lumpectomy; the combination of radiation plus lumpectomy is thought to preserve breast tissue. Patients deemed to have a minimal risk of recurrence due to tiny, low-grade lesions may be spared radiation treatment. Patients undergoing mastectomy should not get radiation therapy [28, 32].

Endocrine treatment should be administered for five years to patients with estro-gens receptor-positive DCIS and remaining breast tissue. If the patient is premenopausal, this treatment entails tamoxifen; if the patient is postmenopausal, tamoxifen or an aromatase inhibitor is used **[28]**. In the past, lobular carcinoma in situ was thought to be cancerous. Nevertheless, despite the name, it is a proliferative illness that raises the chance of developing breast cancer in the future rather than a carcinoma. The staging standards for breast cancer no longer take it into account [26].

Stage I, Early Invasive and Locally Advanced, Nonmetastatic Cancer

Preoperative and postoperative systemic treatments for non-metastatic breast cancer include immunotherapy using monoclonal antibodies targeted at tumour receptors, endocrine medications, chemotherapy, and radiation. Molecular testing might be helpful when deciding whether to add chemotherapy to a patient's treatment plan. The optimal assay for disease prognostication and chemotherapy treatment decisions for patients with hormone receptor-positive, node-negative breast cancer, including males, is the 21-gene expression assay (Oncotype DX). When postoperative chemotherapy and hormone treatment are given, chemotherapy is always given before hormone therapy [28].

Stage 2, Metastatic Breast Cancer

Breast cancer medicines have advanced over the past few decades, improving the median survival rate for individuals with metastatic breast cancer. Although metastatic breast cancer is rarely cured, the current survival rate is 24 to 40 months. Reducing symptoms, extending life, and maintaining quality of life are the primary goals of therapy **[33, 34]**. To target the specific suitable subtypes of breast cancer, treatments such as immunotherapy, chemotherapy, and endocrine therapy may be provided. For individuals whose quality of life is affected by tumour burden, surgery or radiation therapy after systemic therapy may be recommended [35].

Treatment with bisphosphonates like pamidronate (Aredia) or zoledronic acid (Reclast) or denosumab (Prolia) should be made available to the 60% to 80% of patients with metastatic breast cancer who develop bone metastases **[28]**. These treatments have been demonstrated to lessen the impact of metastases on bone, including fractures and hypocalcaemia [28]. In stage IV breast cancer, metastases to the brain, liver, and lungs are frequent. Treatments for symptoms should be suggested as necessary to provide palliation [26].

Clinical Assessment

About 30% of breast cancer patients have a palpable breast mass **[25, 36]**. Breast cancer can be identified by outward manifestations such as orange peel look, edema, erythema, blistering, dimpling, excoriations, sanguineous nipple discharge, and nipple distraction. Breast cancer which is inflammatory and Paget disease are closely linked to skin abnormalities such as peaud' orange and blistering. Papillary breast neoplasia is linked to sanguineous nipple discharge. Advanced illness might show signs of ulcerations. Never neglect to do a cancer test on individuals undergoing therapy for mastitis or a breast abscess that is not clinically improving. When a woman has a palpable breast mass, benign disorders such as intraductal papilloma, breast cysts, fibroadenoma, and fibrocystic alterations are among the possibilities for a differential diagnosis. When a mass is felt, the patient is referred for diagnostic mammography and ultrasound [25].

Bioactive Components of *Vernonia cinerea*

V. cinerea leaves is important part of lant, which contain more than 40 Flavonoids, 13 Saponins, 36 Alkaloids, and 108 Terpenoids [16, 37]. Flavonoids, alkaloids, and terpenoids are secondary metabolites which used against various diseases **[14]**. Dichloromethane fraction of stem and leaves has been found to contain two sesquiterpene lactones (Vernolides C and D) [38]. The leaf extracts were also found to contain lupeol, Beta-amyrin benzoate, Alpha-spinasterol, hirsutinolide-13-O-acetate, and 24-hydroxytaraxer-14-ene. Youn *et al.,* isolated 8-alpha- (2' Z-tigloyloxy)-hirsutinolide, 8-alpha-hydroxy-13-O-tigloyl-hirsutinolide, and 8-alpha-(20 Z-tigloyloxy)-hirsutinolide-13-O-acetate using combining stems and leaves with chloroform fraction

of a methanol extracts. In this plant, vernolides are the primary terpenes sesquiterpenoids ($C_{15}H_{24}$) reported to be active [39, 40, 41].

Root extract contain 10 caffeoylquinic acid, Ethanolic, phenolic resin and dichloromethane [12, 42]. Another two studies detected more than 50 important chemical compounds of aerial vegetative parts in Methanolic Extract, such as Ethyl 2-butynoate, Dodecanoic acid, Methyl strearate, Pentadecanoic acid, Caryophyllene-oxide, ethyl ester, 2-Pentanone, 4-hydroxy-4-methyl-, Acetic acid, methyl ester, n-Nonadecanol-1, 2,4-Di-tert-butylphenol, Oxirane,2,2-dimethyl-3-, O-Xylene, Ethanol, 2-ethoxy-, 9-Octadecenoic acid (Z)-, methyl ester, 8-alpha –tigloyloxyhirsutinolide, Caryophyllene-oxide, Alpha spinasterol, Luteolin-7-mono Beta-D-glucoside, Caryolane-1, 9-Beta-diol, Hirsutinolide-13-O-acetate [7, 16].

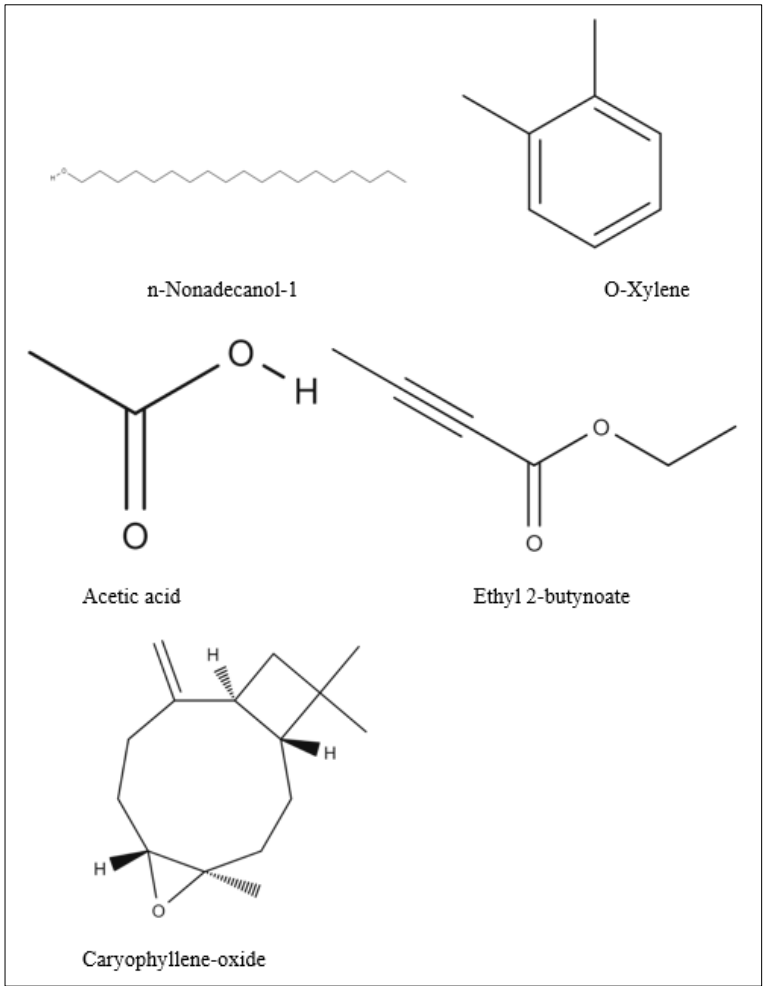

Fig 2: Structure of Chemical Compound [7].

Regulatory effect of human breast cancer cell line

The entire *VC* extract exhibited the highest level of activity against the human breast cancer (MCF-7) cell line. According to Miklossy *et al.*, when compared to normal NIH-3T3 mouse fibroblast cells, hirsutinolides and semisynthetic analogues suppressed aberrant Signal transducer and activator of transcription (STAT3) activity in MDA-MB-231 adenocarcinoma cells and U251MG glioblastoma cancer cells [41]. Vasincu *et al.* studied the viability of MCF-7 (Breast), A549, and PC3 cells using MTT assays and root extracts for 72 hours, and they reported Root extracts truly decrease the viability of MCF-7 cells. Ethanolic extract of root and its dichloromethane aqueous fractions strongly affect MCF-7 cell line viability [42]. Additionally, the dichloromethane fraction increased daunorubicin uptake, triggered both early and late stage apoptosis, and sensitized the cancer cells to the chemotherapeutic drug-mediated toxicity. Additionally, it prevented the multi-drug resistance transporters ABC-B1 and ABC-G-2 from functioning [12, 43]. In cancer cells, dichloromethane and ethanolic extract have dose-dependent cytotoxic effects with IC_{50} values of between 20 and 100 mg/mL. 8-alpha-tigloyloxyhirsutinolide-13-O-acetate (8-alpha-TGH) is a major sesquiterpene lactone bioactive compound of this plant. 8-alpha-TGH decrease cancer cell growth more effectively. As a result, G2/M cell cycle arrest was observed due to decreased CDK1/2 and Cyclin B1 expression [43]. According to sesquiterpene lactones (Vernolide A and B) regulate cytotoxicity effect in cancer cells. An Acetone extract of *Vernonia sp.* showed *in vitro* property ranging from IC_{50} of 4 to 26 mg/mL. Pharmaceutical agents are important to develop anti-cancer drugs that induce apoptosis in cancer cells. By using flow cytometry functional assays, Ram were able to assess the ability of the enriched fraction of *Vernonia cinerea* to supress MDR transporters (ABC-B1 and ABC-G2) and they suggest that 69% to 55% inhibition of MCF-7 [12, 44, 45, 46].

Discussion

In this study evaluated the anti-breast cancer activity of *V. cinerea* plant. This study indicated that *VC* has a powerful activity against breast cancer (MCF-7) cell line.

Additionally, phytochemical analysis revealed many primary and secondary metabolites that might contribute to the anti-breast cancer properties of this plant. Therefore, Natural products and their bioactive compound an important potential sources for the development of new drug inventions, especially for Breast cancer treatment with little or no side effects and VC may prove effective in treating various drug-resistant breast cancers. Due to its easy availability, it can replace expensive medicines in the treatment of Breast cancer.

Acknowledgements
The authors of the article are grateful to the Honorable Chancellor Madam of Seacom Skills University for all kind of support to complete the research work.

Conflict of Interest
The author declares no conflict of interest.

References
1. Obeagu EI, Obeagu GU. Optimizing Blood Transfusion Protocols for Breast Cancer Patients Living with HIV: A Comprehensive Review. Elite Journal of Nursing and Health Science. 2024;2(2):1-7.
2. Obeagu EI, Obeagu GU. Breast cancer: A review of risk factors and diagnosis. Medicine. 2024 Jan 19;103(3):e36905.
3. Da Costa Nunes GG, De Freitas LM, Monte N, Gellen LP, Santos AP, De Moraes FC, *et al*. Genomic variants and worldwide epidemiology of breast cancer: A genome-wide association studies correlation analysis. Genes. 2024 Jan 23;15(2):145.
4. Zaib S, Masood N, Khan JS, Yasmin A. Breast Cancer: Epidemiology, Risk Factors and Survival Analysis in the Pakistani Population. Journal of University College of Medicine and Dentistry. 2024 Jan 4:18-23.
5. Boers-Doets CB, Wiseman T, Radia B, Hammond R. Early recognition and management of side effects related to systemic anticancer therapy for advanced breast cancer. InSeminars in Oncology Nursing. WB Saunders. 2024 Feb 1;40(1):151553.
6. Konar A, Kaur J, Chatterjee S, Roy A, Dalal DD, Ghosh P. A critical approach of medicinal plants to impede COVID-19. World J Pharm Res. 2023 Feb 6;12(5):753-765.
7. Singh L, Antil R, Ashmita P, Dahiya P. *In-vitro* biological activities of *Vernonia cinerea* (L.). Plant Arch. 2020;20(2):4889-4900.
8. Konar A, Ghosh P, Chatterjee S. Cassia fistula is a miraculous medicinal plant: A brief Review. Sarcouncil Journal of Plant and Agronomy. 2023;1(1):25-31.
9. Jisha KC, Sadiya EI. Heavy Metal Accumulation and Metabolic Changes Associated with Pollution in *Vernonia cinerea* (L.) Less. Growing Under Ecologically Different Habitats. Journal of Stress Physiology & Biochemistry. 2021;17(3):5-12.
10. Konar A, Chatterjee R. Solanum Xanthocarpum-A Critical Approach to the Lesser Known Aspects of the Herb. Int. J. Sci. Res. in Biological Sciences Vol. 2022 Oct, 9(5).
11. Konar A, Kaur J, Chatterjee S, Roy A, Dalal DD, Ghosh P. A critical approach of medicinal plants to impede COVID-19. World J Pharm Res. 2023 Feb 6;12(5):753-765.
12. Beeran AA, Maliyakkal N, Rao CM, Udupa N. The enriched fraction of *Vernonia cinerea* L. induces apoptosis and inhibits multi-drug resistance transporters in human epithelial cancer cells. Journal of Ethnopharmacology. 2014 Dec 2;158:33-42.
13. Rao MM, Raju AS, Ramana KV. Secondary pollen presentation and psychophily in Vernonia albicans & V. cinerea (Asteraceae). Phytologia Balcanica. 2017;23(2):171-186.
14. Trang NM, Vinh LB, Phong NV, Yang SY. Traditional Uses, Phytochemistry, and Pharmacological Activities of *Vernonia cinerea* (L.) Less.: An Updated Review. Nutrients. 2024 May 6;16(9):1396.
15. Fadhlina A, Abdul Majid FA, Zainol SN, Ismail HF. Bioprospecting of *Vernonia cinerea* for nutraceutical and homemade first aid remedies: A review update. Food Research. 2024;2:219-132
16. Zakir M, Khanam S, Kazmi MH. Ethno-pharmacology of Sahdevi (*Vernonia cinerea* Less.)-An important but lesser known drug of Unani System of Medicine. CellMed. 2020;10(4):26-1.
17. W. Dymock. Pharmacographia Indica. Byculla, India: Bombay Education Society's Press. 1890;2:224-299.
18. Ghani N. Khazeenatul advia. Lucknow, India. Matba Munshi Nawal Kishore; c1921. p. 241-242.
19. Ghosh P, Konar A, Dalal DD, Roy A, Chatterjee S. Phytoremediation technology: A review. International Journal of Agriculture and Plant Science. 2023;400:5-00.
20. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: A cancer journal for clinicians. 2019 Jan;69(1):7-34.
21. Viale PH. The American Cancer Society's facts & figures: 2020 edition. Journal of the advanced practitioner in oncology. 2020 Mar;11(2):135.
22. Ruddy KJ, Ganz PA. Treatment of nonmetastatic breast cancer. Jama. 2019 May 7;321(17):1716-7.
23. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, *et al*. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. Journal of the National Cancer Institute. 2014 May 1;106(5):dju055.
24. Hou N, Hong S, Wang W, Olopade OI, Dignam JJ, Huo D. Hormone replacement therapy and breast cancer: heterogeneous risks by race, weight, and breast density. Journal of the National Cancer Institute. 2013 Sep 18;105(18):1365-1372.
25. Watkins EJ. Overview of breast cancer. Jaapa. 2019 Oct 1;32(10):13-17.
26. Trayes KP, Cokenakes SE. Breast cancer treatment. American family physician. 2021 Aug;104(2):171-178.
27. Allison KH, Hammond ME, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, *et al*. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. Journal of Clinical Oncology. 2020 Apr 20;38(12):1346-66.
28. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, *et al*. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network. 2021 Mar 2;19(3):329-359.
29. Virnig BA, Shamliyan T, Tuttle TM, Kane RL, Wilt TJ. Diagnosis and management of ductal carcinoma in situ

(DCIS). Evidence report/technology assessment. 2009 Sep 1(185):1-549.
30. Cowell CF, Weigelt B, Sakr RA, Ng CK, Hicks J, King TA, *et al*. Progression from ductal carcinoma in situ to invasive breast cancer: revisited. Molecular oncology. 2013 Oct 1;7(5):859-869.
31. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, *et al*. Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. Journal of Clinical Oncology. 2016 Nov 20;34(33):4040-4046.
32. Das C, Dutta A, Muhuri A, Kothari S, Ghosh P, Roy A, *et al*. Biochemical analysis and evaluation of antimicrobial properties of theaflavins and flavonoids rich extract (TFE) and its silver nanoconjugates: A comparative study. International Journal of Pharmaceutical Sciences and Research. 2020;11(8):3690-701.
33. O'Sullivan CC, Loprinzi CL, Haddad TC. Updates in the evaluation and management of breast cancer. InMayo Clinic Proceedings 2018 Jun 1;93(6):794-807. Elsevier.
34. Caswell-Jin JL, Plevritis SK, Tian L, Cadham CJ, Xu C, Stout NK, *et al*. Change in survival in metastatic breast cancer with treatment advances: meta-analysis and systematic review. JNCI cancer spectrum. 2018 Oct;2(4):pky062.
35. Leung AM, Vu HN, Nguyen KA, Thacker LR, Bear HD. Effects of surgical excision on survival of patients with stage IV breast cancer. Journal of Surgical Research. 2010 Jun 1;161(1):83-88.
36. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: A cancer journal for clinicians. 2015 Mar;65(2):87-108.
37. Alara OR, Abdurahman NH, Ukaegbu CI, Azhari NH, Kabbashi NA. Metabolic profiling of flavonoids, saponins, alkaloids, and terpenoids in the extract from *Vernonia cinerea* leaf using LC-Q-TOF-MS. Journal of Liquid chromatography & related technologies. 2018 Jul 3;41(11):722-31.
38. Shelar D, Tikole S, Kakade T. *Vernonia cinerea*: A review. Journal of Current Pharma Research. 2014 Apr 1;4(3):1194.
39. Youn UJ, Miklossy G, Chai X, Wongwiwatthananukit S, Toyama O, Songsak T, *et al*. Bioactive sesquiterpene lactones and other compounds isolated from *Vernonia cinerea*. Fitoterapia. 2014 Mar 1;93:194-200.
40. Rajamurugan R, Selvaganabathy N, Kumaravel S, Ramamurthy CH, Sujatha V, Suresh Kumar M, *et al*. Identification, quantification of bioactive constituents, evaluation of antioxidant and *in vivo* acute toxicity property from the methanol extract of *Vernonia cinerea* leaf extract. Pharmaceutical biology. 2011 Dec 1;49(12):1311-20.
41. Jongrungruangchok S, Pradubyat N, Songsak T, Jarintanun F, Wall M, Chang LC, *et al*. Cytotoxicity and induction of the apoptotic activity of hirsutinolide series/sesquiterpene lactones from *Vernonia cinerea* on human colorectal cancer cells (COLO 205). Journal of Current Science and Technology. 2019;9(1):41-47.
42. Vasincu A, Luca SV, Charalambous C, Neophytou CM, Skalicka-Woźniak K, Miron A. LC-HRMS/MS phytochemical profiling of Vernonia kotschyana Sch. Bip. ex Walp.: Potential involvement of highly-oxygenated stigmastane-type saponins in cancer cell viability, apoptosis and intracellular ROS production. South African Journal of Botany. 2022 Jan 1;144:83-91.
43. Pouyfung P, Choonate S, Wongnoppavich A, Rongnoparut P, Chairatvit K. Anti-proliferative effect of 8α-tigloyloxyhirsutinolide-13-O-acetate (8αTGH) isolated from *Vernonia cinerea* on oral squamous cell carcinoma through inhibition of STAT3 and STAT2 phosphorylation. Phytomedicine. 2019 Jan 1;52:238-46.
44. Toyang NJ, Wabo HK, Ateh EN, Davis H, Tane P, Sondengam LB, *et al*. Cytotoxic sesquiterpene lactones from the leaves of Vernonia guineensis Benth.(Asteraceae). Journal of ethnopharmacology. 2013 Mar 27;146(2):552-6.
45. Kuo YH, Kuo YJ, Yu AS, Wu MD, Ong CW, Kuo LM, *et al*. Two novel sesquiterpene lactones, cytotoxic vernolide-A and-B, from *Vernonia cinerea*. Chemical and pharmaceutical bulletin. 2003;51(4):425-6.
46. Konar A, Pokhrel S, Halder S, Chatterjee R, Adhikari B. Dendrobium longicornu orchid has potential pharmaceutical properties in Nepal. Int. J. Sci. Res. in Biological Sciences Vol. 2023 Aug, 10(4).