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Review on the anti-cancerous properties of *Oldenlandia diffusa* Roxb.

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Abstract
All cultures throughout history have used herbal medicine as a form of healthcare. From ancient medicinal plant have been use various source of medicine. Medicinal plants accumulate various secondary metabolites like saponin, alkaloids, terpenes, sterols, flavonoids, glycosides, cyanogenics, tannins, lactones, quinines, resins, phlobatannins, volatile oils. *Oldenlandia diffusa* Roxb. Most of the important plant for the treatment of Cancer, snake bites, ulcers, various skin disease. *Oldenlandia diffusa* Roxb. (*OD*) in English is called White Diamond Flower and in West Bengal's locally it is known as Khet Papra, in Bengali. Breast cancer is the most frequent tumor and a major cause of death among women and lung cancer major cause of death among human beings. *OD is* a well-known medicinal plant used to prevent and treat many disorders, especially cancers. The main objective of this review is to give an overview of anticancerous properties of *OD* and provide information for further research.

Keywords: Traditional medicinal plants, ethnobotany, anti-cancerous, *Oldenlandia diffusa*, *OD*

I. Introduction
A regular global cancer burden estimate is one of the responsibilities of the Cancer Surveillance Branch (CSU) at the International Agency for Research on Cancer (IARC). According to World Health Organization (WHO) 10 million deaths by cancer in the world and second leading cause of death globally. One of the major public health problems is cancer that leading in India cause of death. In 2020, the coronavirus disease 2019 (COVID-19) pandemic had a negative impact on cancer detection and therapy. The national anti-cancer 'Indian Cancer Society (ICS)' was established in 1951 and main aim of this society is provided routine cancer check-ups and public awareness of cancer. Over 80% of children with cancer are affected by low- and middle-income countries (LMICs), including India, which has a population of around 90% of paediatric patients. There are well-established traits that are common to cancerous cells. It is evident that neoplasia is organised by a combination of somatic and genetic variables, including cell-to-cell interactions, immunity, humoral factors, microenvironmental circumstances, metabolic changes, and others.
It implies that the foundation of traditional or folklore remedies is the use of medicinal herbs [1]. *Oldenlandia diffusa* Roxb. (*OD*) belongs to the Rubiaceae family, which has more than 12,000 species worldwide. The genus *Oldenlandia* contain 300 species, but mostly found *OD in* Africa and South Asia and is naturalized in tropical. Hooker (1882) reported 19 species have been found in India. It is an annual plant and found different country like India, Sri Lanka, Bangladesh, Pakistan.
Indian subcontinent residents have traditionally used *Oldenlandia* species to cure various forms of internal and external irritation. Plant decoctions have been used to treat inflammation in conditions such as tonsillitis, pneumonia, and cholecystitis. *Oldenlandia* species are believed to be a natural source of significant medicinal potential. Plant decoctions of *OD* have traditionally been used in various societies to treat internal and external inflammation and infection, such as tonsillitis, bronchitis, pneumonia, mumps, acute appendicitis, cholecystitis, pelvic infection, urinary tract infection, rheumatic fever, and gout [2]. The plant is used in African civilizations to cure hydrops and swelling, as well as a pain reliever, and the roots are utilized as a depressive. According to preliminary research, the plant may be a potential source of antibacterial, antimalarial, analgesic, and anticancer effects [2, 3, 4].

The plant's ethanolic and methylene chloride extracts, which exhibit potential anticancer properties against the YMB-1 cell line, and the main component asperluside were thought to be responsible for this characteristic [5].

Oldenlandia considered as medicinal plants, possess some secondary compound like sterols alkaloids, flavonoids, terpenes, glycosides and saponin, etc. [6]. For the treatment of sore throat, hepatitis, tonsillitis, appendicitis, arthritis, urethral infection, rheumatism, autoimmune illness, and malignant tumours of the liver, lung, and stomach, *OD* is used in Southern China. The plant's leaves are used to alleviate edoema and hydrops in African civilizations, while the roots are utilised as a depressive [7].

Taxonomical classification
Domain: Eukaryota
Kingdom: Plantae
Subkingdom: Viridiplantae
Division: Tracheophyta
Subdivision: Spermatophytina
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Rubiales
Family: Rubiaceae
Genus: Oldenlandia
Species: *Oldenlandia diffusa*
Botanical Name: *Oldenlandia diffusa* Roxb.
Common Name: Snathikari, Khet Papra, ltci, White Diamond Flower, Vakhakhaparo, Punarnnava, Djambo, Komma, Ghetuli.

II. Geographical location
In West Bengal *Oldenlandia diffusa* plant is called Khet Papra. *OD* is widespread throughout the world's tropical and warm subtropical regions. It is found in Hooghly, Burdwan, North-24-Pargana, Bankura, Howrah, Birbhum, Midnapur, Kolkata in West Bengal, India. They grow in forests, along rivers and coasts, and on dry, sandy soil.

III. Morphology
Habitat
Oldenlandia diffusa Roxb. Is annual herb, an erect.

Height
It has a woody base and stands between 2-4 meters high throughout India.

Root
Roots are woody, hard, brown colour, diameter is 0.3 to 1.5m passing deep into the soil, very young condition Secondary growth formed.

Stem
The stem is square, erect, branched provide with nodes and internodes, dichotomously or trichotomous branched (Figure 1).

Leaves
Leaves are 23mm length and 5mm width, lanceolate shape, opposite decussate manner, showing prominent midribs, hairy margins, leaves are dark green or pale green coloured (Figure 2).

Flower
Flowers have 4 petals, lobes white, axillary Inflorescence, funnel shaped, Actinomorphic, complete, Bisexual, tetramerous, epigynous, 25 mm to 30 mm long.

Calyx
4 Sepals, gamosepalous, calyx present in the fruit, sub-globose, 2 mm length.

Corolla
White Corolla or pinkish to purple in colour corolla, tube is 0.5-1.1 mm.

Stigma and Anthers
0.3-0.5 mm long, Stigma liner.

Androecium
Stamen, filament short, stamens remain alternate with petals, anther are sagittate.

Gynoecium
Number of Carpel 2, syncarpous, ovary 2 chambered each contain one to many ovules, inferior ovary, axile placentation.

Fruit
Fruit is capsule shape, pyriform or globose, Calyx present in the capsule, 1.1-2.2 mm size.

Seed
Pale brown Seeds are, at high temperature seeds are germinate.

Fruiting and Flowering Time
August to October.

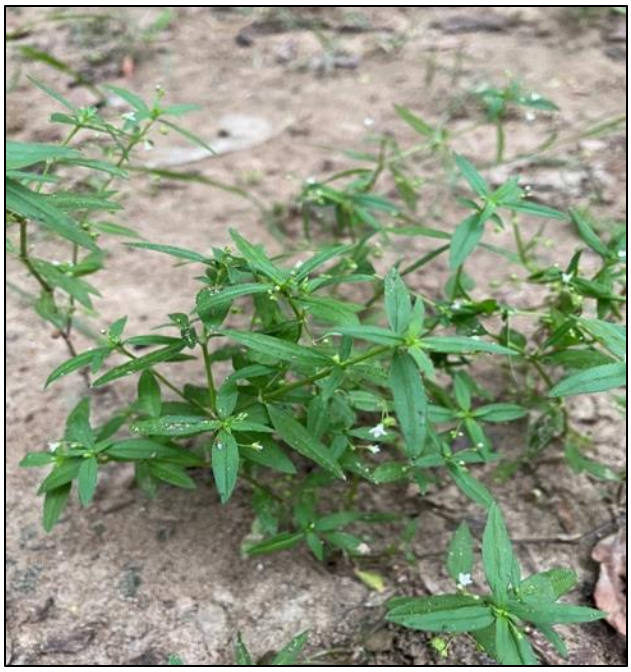

Fig 1: Whole plant part of *Oldenlandia diffusa*

Fig 2: Leaf of *Oldenlandia diffusa*

IV. Phytochemistry

Numerous *Oldenlandia* species are used to treat a variety of diseases in traditional medicine. *OD* plants contain various phytochemical, flavanoids, proteins, carbohydrates, phenols, terpenoids, tannins, saponins, steroids, coumarin and glycosides [6]. Because of the increasing incidences of antimicrobial resistance and cancer, there is an urgent need to discover active compounds that would prevent the development of germs while also acting as antioxidants. The study of methanolic extracts of *OD* revealed the presence of phenolic acids such as p-hydroxybenzoic, vanillic, p-coumaric, ferulic, syringic acid, melilotic acid and caffeic acids; anthocyanidins such as cyanidin and elargonidin; as well as irridoids and alkaloids [7]. Gamma sitosterol, urosilic acid, and oleanolic acid are all present in *OD*. It was discovered that the plant contains 0.12% of the alkaloids bifloron and biflorin (white crystalline powder). These two alkaloids can be converted into one another [6]. Numerous studies revealed the existence of a few substances such as iridoid glycosides, 6 alpha-hydroxygeniposide, and others from *OD* plants Geniposide, 10-o-benzoylscandoside methyl ester, scando side methyl ester (6 beta-hydroxygenipo side), rutin, 10-o-p-hydroxy benzoylscando side methyl ester, deacteyl asperuloside, asperuloside, and asperulosideidic acid as well as (+)-lyoniresinol-3-alpha -o-glucopyranoside [6]. Table 1 gives a brief account of chemical components present in *OD* [8].

Table 1: Summary of some chemical components present in *OD* [8]

Phytochemical	Petroleum ether	Aqueous	Ether Alcohol (95%)
Alkaloids	-	-	+
Tannins	-	-	+
Carbohydrate	-	+	+
Glycosides	-	-	+
Flavanoids	-	+	+
Sterols	+	-	-
Saponins	-	-	-

+ ve = Present -ve = absent

V. Cancer

Cancer is set of disorders, occur when cells divide uncontrollably and continually. In the trillions of cells that make up the human body, cancer can develop practically anywhere. The replication of genomic DNA and the subsequent segregation of daughter cells during different cell cycle phases in eukaryotic cells are the two fundamental events that are the focus of cell cycle control. In eukaryotic cells, two processes-the replication of genomic DNA and its subsequent segregation between daughter cells-occur during different cell cycle phases. These two processes are the core focus of cell cycle control. Cell cycle control pathways, such as cyclins and Cyclin Dependent Kinases (CDKs), G1–S transcriptional regulation, checkpoint signaling and the ubiquitin ligase regulatory pathways [9].

A brief history of exploring cancer

Rudolph Virchow conducted one of the earliest studies to examine interactions between tumours and their surroundings in 1863, noting that solid tumours are characterised by leukocyte infiltration [10]. A pioneering concept of tumour microenvironment (TME) was introduced by Paget in 1889. Up until the 1980s, cancer research was dominated by a tumour-centric view of carcinogenesis and cancer progression, based on mutations in oncogenes and tumour suppressor genes. Proliferating tumour cells, blood vessels, the tumour stroma, invading inflammatory cells, and a range of related tissue cells make up the tissue microenvironment of a developing tumour. As the tumour progresses, a distinct habitat develops as a result of its interactions with the host. The gene cancer regulated by tumour microenvironment (TME). Angiogenesis and the immunological environment of tumours were primarily investigated as separate topics when modern TME research first began in the 1970s.

Paul Ehrlich, a well-known German chemist, began working on creating antibiotics to treat infectious infections in the early 1900s. He was the one who first used the word "chemotherapy" which he described as the application of chemicals to the treatment of illness [11]. Additionally, he was the first to demonstrate that using animal models to test a variety of compounds for their ability to treat diseases offered significant benefits for the development of new cancer drugs. The "chemotherapist" at the hospital where Vince DeVita started his career was an endocrinologist named Louis K. Alpert. Alpert had written one of the earliest studies on the use of nitrogen mustard in treating lymphomas and performed chemotherapy as a side job [11].

The discovery that nitrogen mustards may have anticancer effects by Goodman and Gilman and subsequent research on antifolates resulted in the development of the first effective cancer medications [10, 12, 13].

Cell Cycle phases and Checkpoints of Cell cycle

Interphase and M phase are the two separate phases of the mitotic cell cycle. The Cellular duplication occur during interphase and its separation into two genetically identical daughter cells in mitosis. DNA replication takes place in S phase of Interphase, S phase is also known as Synthesis phase. Gap phases have historically separated S phase and M phase. Due to the obvious gap between duplication and segregation of DNA, G1 precedes S phase and G2 follows S phase. Cell cycle regulation takes place during these phases, including the decision to enter the cell cycle during G1 and to initiate the process of chromosome segregation during G2 [7,9]. Cell cycle processes are regulated by Cyclin-Dependent-Kinase (CDK) and regulate mRNA processing, transcription, and the differentiation of nerve cells. CDK activity is regulated by cell cycle progression and completion and key role CDK activity is regulated by cell

cycle progression and completion and key role regulatory enzymes of CDK activity is in chromosome segregation of CDK activity is in chromosome segregation [8, 9, 10, 11, 12, 13].

VI. Anti-cancerous properties

Various studies have shown that the various *OD* fractions exhibit a variety of biological activities, such as anti-inflammatory, anticancer, anti-angiogenic, chemo preventive, anti-oxidant, and proapoptotic effects.

In Breast cancer

Breast cancer has been recognised since at least 1600 BC, when an ancient Egyptian medical text described eight cases of a tumour or ulcer of the breast that were treated by cauterisation [13]. Understanding of lymphatic circulation in the seventeenth century allowed for the connection to be made between the breast and the axillary lymph nodes, which resulted in the first lymph node surgery for breast cancer patients [47].

The Early Breast Cancer Trialists' Collaborative Group's Oxford review of their work, which includes information on over 250000 women randomly assigned to trials of poly chemotherapy for early-stage breast cancer, provides the most compelling support for this claim [11]. According to NICE Breast cancer with lymph node positivity that is locally advanced or early [12].

Breast cancer is the most prevalent malignancy among women in developed nations, and it is a substantial source of illness and mortality [15]. Many human breast cancers develop and advance due to estrogen interaction with certain estrogen receptors (ERs). Hormone binding to ERa promotes the receptor's "traditional" genomic actions and its direct contact with estrogen response elements (ERE) in target genes functions to either stimulate or inhibit gene expression. The use of a selective estrogen receptor modulator such as tamoxifen to suppress the function of ERa is an important therapeutic option in the treatment of all stages of breast cancer. Unfortunately, not all patients with ER-positive malignancies react to this treatment. Chemotherapy is still the preferred treatment for metastasis, although it is linked with serious side effects. As a result, novel antitumoral medicines with reduced toxicity are needed to approach breast cancer treatment [16].

Oldenlandia diffusa (Willd.) Roxb. (*OD*), a member of the Rubiaceae Family, is a well-known medicinal plant commonly used in Southern China for the treatment of hepatitis, tonsillitis, sore throat, appendicitis, urethral infection, rheumatism, arthritis, autoimmune disease, and malignant tumours of the liver, lung, and stomach. Several studies have illustrated fractions of *OD* exhibit multiple biological activities, including anticancer, chemopreventive, anti-angiogenic, anti-inflammatory, antioxidant, and proapoptotic properties [21, 22]. The aqueous extract of *OD* has been demonstrated to have an immunomodulatory effect in murine spleen cells and mouse peritoneal macrophages, and it may encourage the immune system to remove cancerous cells [21]. The aqueous extract has also been shown to suppress the proliferation of many cancer cell lines and to induce selective apoptosis in the leukemic cell line HL60 but not in human lymphocytes [20,17,25]. Furthermore, ursolic acid, a key component of the methanol extract that is not detected in the aqueous extract of *OD*, has anti-tumor actions in lung, ovarian, skin, brain, and colon cancer cells. Furthermore, ursolic acid extracted from Salvia officinalis induces apoptosis and decreases bcl-2 expression in MCF-7 breast cancer cells [16].

We found that *OD* extracts cause strong antiproliferative and apoptotic responses in ERa-positive MCF-7 breast cancer cells via increasing p53 gene expression [16]. *OD*, a traditional Chinese medicinal herb, is well-known for its anticancer properties. Indeed, the effects of *OD* therapy on tissue culture and animal models have long been studied, and it has been shown to produce cell cycle arrest in several cancer systems [17, 20, 21]. However, the molecular processes behind this herb's anticancer properties need to be further understood [16]. It has been revealed that one of the mechanisms for *OD*'s anticancer actions is the stimulation of apoptosis [17, 21]. Apoptosis occurs as a result of the activation of a proteolytic cascade process that results in irreversible DNA fragmentation [16].

A substantial amount of data has revealed the simple significance of p53 signalling in the apoptotic cascades [24, 25]. With other cellular proteins, such as certain nuclear receptors, which in turn have an inhibitory effect on p53 biological consequences, p53 functions as a tumor suppressor. Activation of p53 by UV damage or other agents/signals results in p53-mediated transcription or upregulation of genes such as the cyclin-dependent kinase inhibitor p21WAF1/Cip1 to cause apoptosis, preventing the proliferation of cells with damaged DNA or cancer cells [16].

Previous phytochemical investigations of *OD* have revealed that Herba oldenlandiae includes a high concentration of iridoid glucosides, triterpenoids, flavonoids, and polysaccharides [26]. In the present investigation, we have extracted and identified from the most efficient chloroformic extract of *OD* two bioactive chemicals able to specifically inhibit breast cancer cell development. These substances are ursolic (UA) and oleanolic (OA) acids, as determined by 1H and 13C NMR [16].

UA and OA, found in *OD* in great quantity, are pentacyclic triterpenoids that appear abundantly in plants [27, 28]. The main variation between OA and UA is the location of the methyl group; UA is methylated on C19, whereas OA is methylation on C20 of the E loop. It has been noted that these two pentacyclic triterpenoids have varied potencies in terms of anticancer and chemopreventive properties [29, 30, 31, 32]. Both pentacyclic triterpenoids were shown to reduce cell viability in MCF-7 breast cancer cells while increasing p53 and p21WAF1/Cip1 expression. Furthermore, OA and UA have a strong inhibitory impact in tamoxifenresistant cells, indicating that these chemicals may play a role in breast tumours that develop hormone resistance [16].

Glucocorticoids (GCs) limit lymphocyte proliferation and induce apoptosis; nevertheless, they have variable effects on the development and chemo sensitivity of diverse kinds of cancer cells [33, 34, 35]. Dexamethasone treatment and glucocorticoid receptor (GR) activation in breast cancer cells resulted in the regulation of specific genes known to play key roles in cellular functions, such as growth, apoptosis, differentiation, metastasis, and survival genes associated with inhibition of chemotherapy-induced apoptosis [36, 37].

Although GCs are unsuccessful as chemotherapy adjuncts in breast cancer, the development of novel drugs is very desirable. Ursolic acid (UA), a pentacyclic triterpenoid acid with a structure similar to dexamethasone, has demonstrated antitumorigenic and chemo preventive effects by modulating cancer-related pathways such as apoptosis,

invasion, and metastasis [29, 33]. However, its impact on breast cancer is still entirely unclear.

New anticancer techniques target apoptosis, with the antiapoptotic Bcl-2 protein being an appealing molecular target [33, 38]. Poly (ADP-ribose) polymerase (PARP) cleavage is also a prominent hallmark and sensitive measure of apoptosis, with caspase-3 and caspase-7 acting as the principal effectors of apoptotic PARP cleavage [33, 39]. More importantly, the DNA fragmentation factor plays a role in the last phases of apoptosis (DFF). DFF occurs in its inactive state as a heterodimer, DFF45/40. DFF40 is activated after proteolysis of DFF45 by active caspase-3 and, to a lesser extent, activated caspase-7 [40, 41].

Many regulatory circuits are disturbed in cancerous cells, with errors in cell proliferation and/or apoptosis among the primary modifications that govern malignant progression in nearly all forms of cancer, including breast cancer [32]. GCs are currently used in conjunction with chemotherapy in the treatment of breast cancer; nevertheless, evidence suggests that their usage may be ineffectual or even harmful to the patient's result. As a result, creating new agents is a complex job [33].

In Lung cancer

Hedyotis diffusa, also known as *Oldenlandia diffusa* (Willd.) Roxb. (Abbreviated as HDW), is the dried entire herb of *Hedyotis diffusa* Willd. (Rubiaceae), which was originally discovered in Guangxi. Traditional Chinese Medicine Journal lists several effective treatments, such as those that remove heat, detoxify, eliminate moisture, reduce oedema, and activate blood analgesia. Modern medicine has also demonstrated that HDW has a therapeutic impact on illnesses connected to inflammation and cancer by demonstrating that the main active component extracts from HDW had mostly antitumor effects on a variety of human tumours [42].

Iridoids, flavonoids, flavonol glycosides, anthraquinones, phenolic acids and their derivatives, sterols, and volatile oils make up the 58 different types of antitumor components from HDW. Their anticancer actions include tumour cell growth suppression, induction of tumour cell death and tumour angiogenesis, host immune response modulation, anti-inflammatory, antioxidant, and protective autophagy [42]. The drug-likeness (DL) index, a thorough reflection of the physical, chemical, and structural qualities of the medication is a quality of an ideal medicine [42, 43].

Su *et al*. Found that treatment with kaempferol at the IC50 values of 40 M and 50 M dramatically decreased the levels of Bcl-2, p-Akt, and cyclin-dependent kinase-2 (CDK2) in lung cancer cell line H1975 and a murine macrophage cell line RAW264.7. Kaempferol was able to increase tumour cell death following irradiation *in vitro* and *in vivo* by inhibiting the AKT/PI3K/ERK pathway and activating the mitochondria apoptosis pathway [43]. Furthermore, in a dose-dependent manner, 2-hydroxy-3-methylanthraquinone (HMA) could effectively enhance apoptosis of IL-6-treated lung cancer A549 cells by partially upregulating the levels of pro-apoptotic proteins such as Bax, cleaved caspase-3, and cleaved caspase-9 while downregulating the expression of anti-apoptotic protein Bcl-2 [42].

The epithelial-mesenchymal transition (EMT) is a morphological and epithelial process. Epithelial cells lose cell polarity and cell-cell adhesion while gaining migratory and invasive abilities (the property of mesenchymal stem cells). Molecularly, EMT cells upregulate the expression of the EMT marker Vimentin while decreasing the expression of the epithelial marker E-cadherin. E-cadherin is a Ca2+-dependent adhesion molecule in epithelial cells that functions as a transmembrane glycoprotein to mediate intercellular adhesion and preserve the structural integrity and polarity of epithelial cells, which is vital in cell differentiation and tissue creation [36]. Hu *et al*. hypothesised that cyclotides with positive charges had more cytotoxicity to tumour cells by attaching to the outer membrane of cancer cells with 3%-9% anionic phosphatidylserine, hence inducing tumour cell membrane integrity and inhibiting tumour cell invasion and migration [44].

Angiogenesis is the formation of new blood vessels from pre-existing vessels, and tumour angiogenesis is a key event for tumour cell development and metastasis; hence, inhibiting tumour angiogenesis might help to prevent cancer progression [42]. Su *et al*. revealed that kaempferol, quercetin, and isoscutellarein, which were all isolated from HDW, have the capacity to inhibit proliferation and angiogenesis of non-small cell lung cancer cells by decreasing the VEGF, PI3K/Akt, and mitogen-activated protein kinase (MAPK) pathways. Furthermore, 4-vinylphenol from HDW aqueous extract was found as a styrene metabolite that could be changed from p-coumaric acid by enzymatic reaction and had pulmonary and hepatotoxicity at high dosages [43, 45, 46].

Future studies should explore new and better solutions, such as combining with other vectors to act on certain signalling pathways via targeted drug delivery systems and combining with other anticancer medications to boost the susceptibility of cancer cells to chemotherapy [42].

Conclusion

Oldenlandia diffusa plants are potential sources of anti-cancer agents that may be effective in treating human diseases, according to this study. *Herba oldenlandiae* has been identified as a source of iridoid glucosides, triterpenoids, flavonoids, and polysaccharides in previous phytochemical studies The present study demonstrated that *OD* extracts induced p53 gene expression in ERa-positive MCF-7 breast cancer cells and exerted significant antiproliferative effects. There has long been research on the effects of *OD* on tissue culture and animal models, and it has been shown to induce cell cycle arrest in various cancer models. Accordingly, we found that *OD* treatment inhibited the growth of ERa-positive and tamoxifen-resistant breast cancer cell lines, while having no effects on normal epithelial breast cells or ERa-negative SKBR3 cells. Therefore, these anticancerous properties of *OD* would be a potential area of research for exploring their various chemical compounds which possess strong biological properties.

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