Am J Cancer Res 2021;11(5):1828-1844
www.ajcr.us /ISSN:2156-6976/ajcr0127404

Review Article

Anti-ovarian cancer potential of phytocompound and extract from South African medicinal plants and their role in the development of chemotherapeutic agents

Chella Perumal Palanisamy[1], Bo Cui[1], Hongxia Zhang[1], Mani Panagal[2], Sivagurunathan Paramasivam[3], Uma Chinnaiyan[3], Selvaraj Jeyaraman[4], Karthigeyan Murugesan[5], Mauricio Rostagno[6], Vijayakumar Sekar[7], Srinivasa Prabhu Natarajan[8]

[1]State Key Laboratory of Biobased Material and Green Papermaking, College of Food Science and Engineering, Qilu University of Technology, Shandong Academy of Science, Jinan 250353, China; [2]Department of Biotechnology, Annai College of Arts and Science, Kovilacheri, Tamil Nadu, India; [3]Department of Microbiology, Faculty of Science, Annamalai University, Tamil Nadu, India; [4]Department of Biochemistry, Saveetha University, Chennai, Tamil Nadu, India; [5]Department of Biotechnology, Arumugam Pillai SeethaiAmmal College, Tamil Nadu, India; [6]Laboratory of Functional Properties in Foods, School of Applied Sciences, University of Campinas, Limeria, Sao Paulo, Brazil; [7]Marine College, Shandong University, Weihai 264209, China; [8]Department of Biotechnology, Bharathidasan University, Tamil Nadu, India

Received December 1, 2020; Accepted February 26, 2021; Epub May 15, 2021; Published May 30, 2021

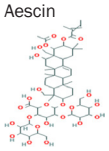
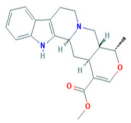
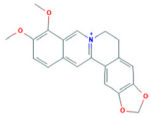
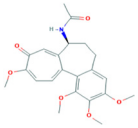
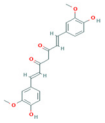
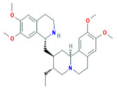
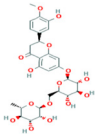
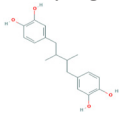
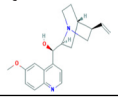
Abstract: Ovarian cancer (OC) accounts for the highest tumor-related mortality among the gynecologic malignancies. Most of the OC patients diagnosed with advanced-stage (III and IV) this situation creates panic and provokes an emergency to discover a new therapeutic strategy. Plants that possess medicinal properties are gaining attention as they are enriched with various chemical compounds that are potential to treat various diseases. It is a prolonged process to provide innovative and significant leads against a range of pharmacological targets for a human disease management system. Though challenges and difficulties are faced in the development of a new drug, the emergence of combinatorial chemistry is providing a new ray of hope and also, the executed effort in discovering the drug, and a chemical compound has been remarkably successful. This review discussed the role of medicinal plants that are native of South Africa in treating the Ovarian Cancer and in drug discovery.

Keywords: Ovarian cancer, south african medicinal plants, anti-ovarian cancer activity, drug development

Introduction

Plants with medicinal values have been a part of human culture and tradition [1]. It possesses significant nutrition and is prescribed for various therapeutic purposes [2]. World Health Organization (WHO) assessed that about 80% of the population primarily rely on plant medicines to stay healthy [3]. Also, 21,000 plant species are reported by WHO to possess to have therapeutic values to be used as medicines [4]. Plant chemicals are extracted and the compounds of interest are identified continuously till date and recently to standardize the herbal medicines (**Table 1**) and to elucidate analytical marker compounds drug discovery techniques are applied [5]. Discovering a drug is an interdisciplinary action where it includes various fields of science. Novel drug discovery is an extravagant, challenging process, it devours time as well. The important process (**Figure 1**) involved in identifying New Chemical Entities (NCEs) which possess characteristic features such as effective druggability and medicinal chemistry [6]. NCEs are synthesized synthetically using chemicals or obtained from a natural process by isolation, approximately it would take 12 years for a new drug to reach a clinic from its discovered stage, also the investment done for the drug discovery is 1 billion US$ [7]. Numerous examples have proven that natural sources (including semi-synthetic analogues) and its products have been the backbone of more than 80% of drug substances [8].

Table 1. Some of the natural compounds from the medicinal plants

S. No.	Plant-derived compound	Classification	Plant Name	Biological function	References
1	Aescin 	saponins	*Aesculus hippocastanum*	Anti-inflammatory, vasoconstrictor and vasoprotective effects	[113]
2	Ajmalicine 	alkaloid	*Rauwolfia spp., Catharanthus roseus, and Mitragyna speciosa*	Antihypertensive drug used in the treatment of high blood pressure	[114]
3	Berberine 	alkaloid	*Berberis vulgaris*	Treatment for bacillary dysentery	[115]
4	Colchicine 	alkaloid	*colchicum autumnale*	Antitumor agent	[116]
5	Curcumin 	phenols	*Zingiberaceae*	dietary supplement	[117]
6	Emetine 	alkaloid	*Cephaelis ipecacuanha*	Amoebicide, emetic	[118]
7	Hesperidin 	Flavonoid	*Citrus species*	Treatment for capillary fragility	[119]
8	Lapachol 	Phenols	*Handroanthus impetiginosus*	Anticancer activity	[120]
9	Nordihydroguaiaretic acid 	Phenols	*Larrea tridentata*	Antioxidant activity	[121]
10	Quinine 	Alkaloid	*Cinchona officinalis*	Antimalarial drug	[122]

Cancer is referred to as the uncontrolled growth of abnormal cells anywhere in a body that can infiltrate normal body tissue and it is one of the leading fatal disease which leads to death worldwide [9]. The different types of cancer existence with histopathologies, genetic-epigenetic variations, and clinical outcomes are the challenges that persist in apprehending the mechanism of action of chemotherapeutics and in the development of innovative rehabilitations [10, 11]. Ovarian cancer cruelly affects the human population when compared with other gynaecological malignancies in worldwide. There is an urgent need for novel therapies to treat and prevent this life-threatening disease. Innovative research interest is illus-

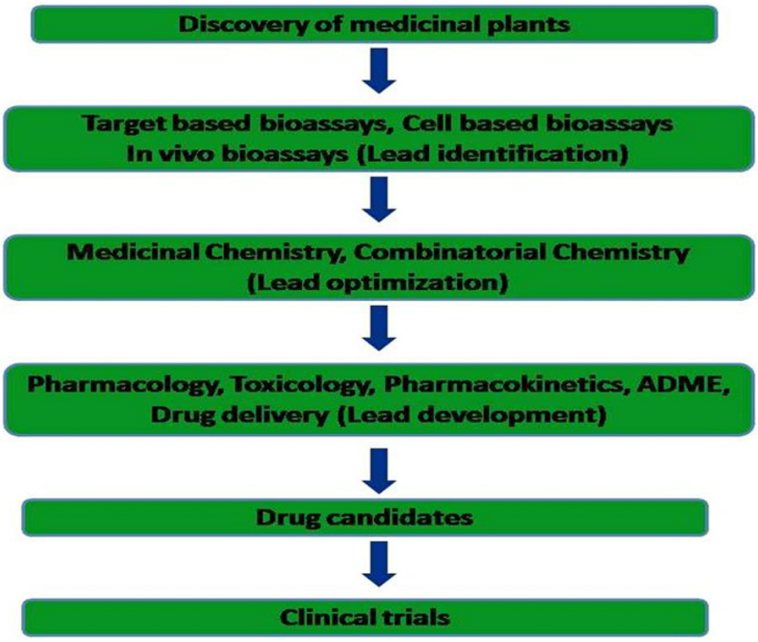


Figure 1. Modern drug discovery and development from the medicinal plant.

trating its attention towards naturally-derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy, laser therapy, radiotherapy, gene therapy, hyperthermia and surgery. Plants produce secondary metabolites which are being investigated for their anti-ovarian cancer activities leading to the development of new clinical drugs. Development anti-ovarian cancer compounds from the medicinal plants have been utilized as staple drugs for treatment and prevention, the new technologies are emerging to expand the area further. Increasing demand for plant-derived drugs is putting pressure on high-value medicinal plants and risking their biodiversity. Plant-derived anti-ovarian cancer agents are effective inhibitors of cancer cells lines, making them in high demand [12].

Ovarian cancer and medicinal plants

Ovarian cancer (OC) stands seventh worldwide among the most commonly occurring types of cancer. Roughly it is estimated that twenty four hundred thousand females are diagnosed with the disease every year, this report depicts that 2% of all cancer cases around the world [13]. According to the World Cancer Research Fund International 2017, the highest incidence of OC occurs in Fiji (with estimated fifteen cases per hundred thousand), surprisingly very few cases are recorded in China and some parts of Africa (four cases among a hundred thousand female individuals) [14]. 1 in 70 women are prone to ovarian cancer risk. 150,000 deaths are recorded globally every year due to OC and this is considered as the fatal disease that leads to death when compared to other gynaecological malignancies. Due to poor diagnosis attributed to lack of symptoms at the early stages, as the symptoms appear at advanced stages (III and IV) [15]. The mortality is high comparatively. Chemotherapy, laser therapy, radiotherapy, gene therapy, hyperthermia, and surgery are few interventions practised or in trials to intervene in the growth of the cancer cells [16]. The medical aid includes a combined effort of incision, chemical treatments, and therapies which involves the action radiations [17]. Though there are pros in the procedures mentioned earlier the scientific community recognized that the interventions have disadvantages and limitations. Consequently, a development of drug that is capable of overcoming the obstacles and treating the disease effectively [18].

For centuries our ancestors were using plants to treat various human diseases and cancer is one among them [19-21]. Many medicinal plants have been reported to exhibit a variety of pharmacological and actions related to life functions namely antioxidant, antimicrobial, anticancer, antidiabetic properties and so on. Since plants acts as a store house of various phytochemicals they are capable of treating various ailments. these properties exhibited by plants [22-24]. The biologically important phytochemicals play a pivotal role in drug discovery [25-27] and the plant-derived biomolecules are recognized as an attractive and promising approach; possess high value in biomedical research for the development of drugs against cancer [28]. Interestingly in the recent past decades, plant that are medicinally important are been used to prepare drugs and the numbers are increasing comparatively. Inthe last twenty years a successful investigations are

done on natural products especially to treat cancer much effectively in most parts of the world [29, 30].

Anti-ovarian cancer activity of other medicinal plants

Several indigenous medicinal plants of Africa which include *Aframomum arundinaceum, Aframomum. alboviolaceum, Aframomum kayserianum, Aframomum polyanthum* [31], *Echinops giganteus, Xylopia aethiopica, Piper capense, Imperata cylindrical* [32, 33]. *Gladiolus quartinianus, Vepris soyauxii* [34], *Polygonum limbatum, Polycias fulva, Beilschmiedia acuta, Crinum zeylanicum, Dioscorea bulbifera, Elaoephorbia drupifera* [35], *Solanum aculeastrum, Albizia schimperiana, Zanthoxylum giletii* and *Strychnos usambarensis* are used in the treatment and management of malignancies such as cancer, etc. these plants also showed significant cytotoxicity effect against the regions that have developed an immune against the drugs and that are endowed with sensation [36].

In vitro studies were performed using Korean medicinal plants to study the anti-cancer activity, Ethyl Acetate fraction from the *Lespedeza cuneata* methanolic extract proved to possess a cell-poisoning effect on A2780 human ovarian carcinoma cells with the IC_{50} value of 77.25 ± 2.05 μg/mL. The lignanosides compound of (-)-9'-*O*-(α-l-rhamnopyranosyl) lyoniresinol from this plant possess *in vitro* antiproliferative activity on A2780 with an IC_{50} value of 77.24 ± 2.05 μM [37]. The seeds of tea (*Camellia sinensis*) which contains saponins exhibited cancer chemopreventive effects, this was identified and reported when an athymic mice study was performed for Anti-tumor efficacy in human SKOV3 ovarian cancer xenografts [38]. Curcumin is a polyphenol that occurs naturally in a plant species called *Curcuma longa* which also holds another compound called curcuminoid has a potency to inhibit IL 6 and IL 8 secretion that was induced by lysophosphatidic acid (LPA) and STAT 3 phosphorylation, where LPA is a bilipid which is found to stimulate the invasion of cancer cells, and cells that carry the infection from the infected part to various other parts of the body and STAT 3 phosphorylation that inhibits the motility of OC cells, as portrayed in PA and OVCAR3 [39]. In the past in Kwara and Lagos state, *Pistia stratiotes* was cited frequently to treat ovarian cancer. But a recent study has thrown light on another species called *Securidaca longipedunculata* which is now considered to be the commonly used botanical source in aiding ovarian cancer [40]. Notably, the above study focused only on the Ijebus, an ethnic Yoruba group. Similarly, different plants namely *Kigelia africana, P. stratiotes, Chenopodium ambrosioides, Nymphaea lotus, Parquetina nigrescens, Nicotiana tabacum, Alstonia congensis, Elaeis guineensis, Piper guineense, Aframomum melegueta, Petiveria alliacea* were been in practicein Ogun state by the natives, southwest Nigeria to treat cancer [41].

Anti-ovarian cancer activity of South African medicinal plants

Africa is enriched with flora, and the phytochemicals in plants exhibit structure that draws interest also along with the diverse biological activities they serve as a starting point for a development of a new drug [42]. South Africa holds rich biodiversity where 22,600 indigenous medicinal plants are present. The flora contributes about ten percent of the higher botanical species on Earth. The traditional medicinal and healthcare history of Africa is very long [43]. Although there is limited information about the anticancer activity of South African plants available in the literature, there are several pieces of evidence suggesting that some of these plants could be used for the development of new therapeutic drugs. The most relevant candidates are discussed below providing information or insights to their pharmacological potential [44].

Aspalathus linearis (Burm.f) R. Dahlgren: Aspalathus linearis is a bush that has legumes or pods (Rooibos) belongs to the family Fabaceae and the presence of legume is a characterstic feature of the family Fabaceae. It is native (**Figure 2A**) to the Cedarberg Mountains in the Western Cape region of South Africa. They are cultivated widely within the region as they are commercially useful from which herbal tea or tisane are produced [45, 46]. This beverage has its History from South Africa and now it is profoundly known in other countries as well [47]. The compounds such as various types of polyphenols, flavonoids present in the plants

Figure 2. Anti-ovarian cancer activity of South African medicinal plants.

are filled with medicinal properties also an added advantage is that caffeine and theaflavins are absent and hence it is used medicinally [48].

Table 2. Reported South African medicinal plants with anti-ovarian activity

S.No	Plant name	Type of Cell line	Extract with anti-ovarian action	References
1	*Aspalathus linearis*	Chinese hamster	Whole plant (Aqueous)	[50-52]
2	*Brachylaena rotundata*	OVCAR-5	Leaf (Dichloromethane)	[55]
3	*Catha edulis*	Chinese hamster	Leaf (Aqueous)	[59, 60]
4	*Centella asiatica*	SKOV3 and OVCAR-3	Whole plant (Aqueous)	[66]
5	*Dicoma anomala*	Chinese hamster	Root (Ethyl acetate)	[71]
6	*Dodonaea viscosa*	A2780 human	Root (ethanol)	[75]
7	*Drimia robusta*	OVCAR-3	Whole plant (methanol)	[55]
8	*Gomphocarpus fruticosus*	OVCAR-3	Root (Ethanol)	[55]
9	*Leyssera gnaphaloides*	Chinese hamster	Whole plant (Hexane)	[83]
10	*Parinari curatellifolia*	SW626 human	13-Methoxy-15-oxozoapatlin compound from the plant	[87]
11	*Pelargonium acraeum*	PA1 and OVCAR-3	Whole plant (Aqueous and methanol)	[55]
12	*Plumbago auriculata*	PA1	Whole plant (methanol)	[92]
13	*Solanum acanthoideum*	IGROV1	Root (methanol)	[55]
14	*Solanum nigrum*	ES-2, SKOV-3 and OVCAR-3	Whole plant (Aqueous)	[99, 100]
15	*Xanthium strumarium*	SKOV-3	Leaf	[111, 112]

Fantoukh et al. isolated 11 phytocompounds from methanolic extract of *Aspalathus linearis* such as Aspalathin (521 mg), Nothofagin (306 mg), Thermopsoside (23 mg), Isoorientin (90 mg), Vitexin (73 mg), Isovitexin (8 mg), Isoquercitrin (76 mg), Rutin (59 mg), Bioquercetin (136 mg), (R)/(S)-eriodictyol-6-C-β-D-glucopyranoside (68 mg) and Syringin (68 mg) which possess antioxidant, antimicrobial, anti-inflammatory, antidiabetic and anticancer activities [49, 50]. Rooibos extracts targe the premalignant cells present in the skin and inhibits the cell proliferation and thus intervenes in the growth of cancerous cells in the skin, it also induces apoptosis of tumor cells [51]. The efficacy of the extract has been revealed through various studies and it had shown significant anti-cancer effects against other types of cancer as well. An oral dose of this extract suppresses the activity of methylbenzlnitrosamine which induces the oesophageal squamous cell carcinogenesis in male F344rats [52]. B1 rats were given a dose of the Rooibos and this repressed the development of the fumonisin induced hepatocellular carcinoma [53].

Brachylaena rotundata (S.Moore): Brachylaena rotundata (Asteraceae) is a shrub or a small tree that grows up to 8 meters (**Figure 2B**). It also occurs in most Southern nations, particularly eastern Botswana, Transvaal, Mozambique, Zambia, and Zimbabwe, with presence in open woodland, on rocky koppies, and slopes, and on stream banks [54]. The dichloromethane extract of *Brachylaena rotundata* leaves (**Table 2**) has been found to reveal anti-ovarian cancer activity in OVCAR-5 ovarian cancer cell line with an IC_{50} value of 19.95 µg/ml [55].

Catha edulis (Vahl.) Endl.: Catha edulis (**Figure 2C**) is the South African medicinal plant belonging to the Celastraceae family. *Catha edulis* leaves contain phytochemicals and an indicative amount of vitamin C [56]. The worth of the foliage depends on the presence of cathinone contents [57]. Getasetegn (2016) reported the chemical composition of khat which possess 81 phytocompounds are classified into 7 major classes such as Phenylalkyl-amines ((+)-Cathine, (-)-Cathinone, 3,6-Dimethyl-2,5-diphenyl pyrazine, Merucathine, Merucathinone, (-)-Norephedrine, (-)-Norephedrine N-formyl, 1-Phenylpropane-1,2-dione and Pseudomerucathine), Cathedulins (Cathedulin E1-E6, Cathedulin K1, 2, 6, 12, 15, 17, 19 and 20, Cathedulin Y7-Y10, Cathidine A, B, D and Euonyminol), Flavonoids (Dihydromyricetin, Dihydromyricetin-3-O-rhamnoside, Kaempferol, Myricetin, Myricetin-3-O-b-D-galactoside, Myricetin-3-O-rhamnoside, Quercetin and Quercetin-3-O-b-D-galactoside), Sterol and Triterpenes (Celastrol, Friedeline, Iguesterin, Pristimerin, b-Sitosterol Tingenin A, B and b-Sitosterol glycoside), Volatiles (Fenchone, Linalool, Nerol, Ocimene, β-Phellandrene, α-Pinene, β-pinene, α–Terpineol, Terpinolene, α-Thujone and b-thujone), Amino acids and Vitamins (Vitamin C, B3, B2 and B1.) which hold unique biological activities in human disease management system [58].

The fresh leaf extract of *Catha edulis* exhibited the anti-ovarian cancer activity in the Chinese

hamster ovary cell line at the concentration of 50 µg/ml [59]. Alsanosy et al., (2020) examined the anti-ovarian cancer activity of Six different fractions from the extract of *Catha edulis* which exhibited the anti-ovarian cancer activity on A2780 with the significant IC_{50} values raging from 20.97 ± 5.03 to 53.78 ± 7.45 [60]. Elhag et al., (1999) isolated the phytocompound of 22b-hydroxytingenone from methanolic extract of *Catha edulis* and demonstrated their ovarian cancer activity in National Cancer Institute (USA) which showed the significant ED_{50} value of 2.35 µg/ml [61].

Centella asiatica (Linn.) Urb: Centella asiatica (Apiaceae), commonly called pennywort (**Figure 2D**) is a perennial creeper and the propagation is through stolons, they are commonly found in moist places. This plant has reported to have many medicinal values and the plant chemicals exhibit mitoprotective, antioxidant, anti-inflammatory, antioxidant, and anticancer properties [62-64]. It holds a very good healing property and this quality of the plant is assumed due to the presence of three active triterpenes such as Asiatic acid, madecassic acid and asiaticoside [65]. A triterpenoid compound of Asiatic acid was extracted from *Centella asiatica* and found to possess anti-ovarian cancer activity in SKOV3 and OVCAR-3 ovarian cancer cell lines (**Table 2**). At an intensity of 40 µg/mL of asiatic acid the practicability of the ovarian cancer cells was reduced to 50% and the colonization of the OC cells were also reduced by 25-30% at the concentration of 10 µg/mL of asiatic acid. Apoptosis of the tumor cells increased to 7-10 folds when the cells were treated with Asiatic acid and this also curbed the cell cycle at G_0/G_1 phase. Several molecular pathways were examined to study the asiatic-acid effect against ovarian cancer cells. The phosphorylation levels of P13, Akt, and mTOR were lowered in the asiatic-acid treated cells. The tumor cell cells are viable and constitutive overexpression of Akt reverses the cytotoxic effect of asiatic acid partially. The growth-suppressive activity of the acid was examined. The downregulation of Akt mimicked the activity of Asiatic acid in the repression of growth against tumor cells [66].

Dicoma anomala (Sond.): Dicoma anomala (**Figure 2E**) a member of Asteraceae Family and a resident of the South Africa known well for its medicinal values. It is an upright, partially bent, or an incumbent herb that bears a partially woody tuber which has a distinctive aroma at the base of a woody subterranean stem. This grassland species is widely distributed in sub-Saharan Africa [67]. There are many ethnomedical uses of *Dicoma anomala*. It is used in the treatment of cough and cold, fever, ulcer, dermatosis, venereal disease, labor pain, looseness of bowel, enternal parasite, abdominal pain, odontalgia and internal worm [68]. Its extracts also possess several pharmacological properties including anti-bacterial, anti-helminthic, anti-viral, anti-plasmodial, anti-spasmodic, wound healing, analgesic, anti-cancer, antioxidant, hepatoprotective, antidiabetic, cardioprotective, and anti-inflammatory activities [69]. Phytochemical investigations were done to identify various secondary metabolites and it revealed the presence of compounds such as acetylenic compounds, phenolic acids, flavonoids, sesquiterpene lactones, triterpenes, and phytosterols [70]. The compounds, Dehydrobrachylaenolide, and Chloroquine from Ethyl acetate extract of *Dicoma anomala* root have enormous cytotoxicity effects at the concentration (IC_{50} value) of 17.199 µM/ml and 35.800 µM/ml respectively on Chinese hamster ovary cell line [43].

Maroyi (2018) reported that different solvent extracts of (from non-polar to polar hexane, petroleum ether, chloroform, ethyl acetate, methanol and aqueous) leaf, root and twig of *Dicoma anomala* holds cytotoxicity activity on Chinese hamster ovary (CHO) cell line with moderate IC_{50} values from 0.44 µg/ml to 31.33 µg/ml. the isolated compound of (3aS, 5aS,9aR,9bS)-5amethyl3,9-dimethylidene-4,5,9a,9b-tetrahydro-3aHnaphtho[7,8-d]furan-2,8-dione from methanolic extract of *Dicoma anomala* showed the cytotoxicity against CHO cell line using the MTT assay with potential IC_{50} value of 4.2 µg/ml. The phytocompound of 3-oxoeudesma-1,4(15),11(13)-triene-12,6a-lide from *Dicoma anomala* showed the significant cytotoxicity against (CHO cell line using the MTT assay with an IC_{50} value of 17.2 µM [71].

Dodonaea viscosa (Jacq.) var. augustifolia (L.f) Benth: Dodonaea viscosa (Sapindaceae) is a blossoming plant (**Figure 2F**) in the soapberry family and it has a cosmopolitan distribution in tropical, subtropical, and warm temperate regions of South Africa. This shrub is extensive-

ly grown around the world. The roots bind the soil and thus are useful in sustaining stability in dunes and also curb the soil from getting eroded [72]. A variety of phytocompounds have been recorded with *Dodonaea viscosa,* such as flavonoids, fatty acids, and cyanolipids. A decoction was prepared from the leaf tips emerged newly to treat fever by the Cape settlers. In rural areas, *Dodonaea viscosa* var. *angustifolia* is still commonly used to treat colds, influenza, stomach trouble, and measles. Patients with a strep throat and oral infections caused by fungus gargle the decoction prepared using the leaves. The Khoi-Khoi used a concoction prepared from the roots and is used to treat colds and influenza [73]. Moreover, in Namaqualand, the extract prepared by boiling the leaves, this is then filtered, this extract is used for treating influenza, colds, and it also induces sweating. It is also used to relieve coughs and congested feeling typical of influenza, croup, and diphtheria. The same extract is considered to alleviate stomach ailments and fever [74]. The ethanolic root extract of *Dodonaea viscosa* exhibited a reproducible cell-perniciousness to A2780 ovarian cancer cell line (**Table 2**) with an IC_{50} value of 6.0 µg/ml. Cao et al., (2009) secluded the phytocompounds of two novel triterpenoid saponins from the root of *Dodonaea viscosa* (ethanolic extract) namely Dodonaeaside A and Dodonaeaside B which possess considerable antiproliferative activity on the ovarian cancer cell line of A2780 with IC_{50} values of 0.79 and 0.70 µM correspondingly [75].

Drimia robusta (Hyacinthaceae) is an important medicinal plant (**Figure 2G**) in South Africa because of its extensive usage [76]. The hot water infusions prepared using the pounded bulbs and leaves are used as enema by the Zulus as the leaves are diuretic in action which helps in cleaning the bladder and treat uterus related disease. It also exhibits anticancer, antimicrobial and antimicrobial activities due to the presence of aromatic compounds such as 4-hydroxy-3-methoxybenzoic acid, 3,4-dihydroxybenzoic acid and trans-3-(40-hydroxyphenyl)-2-propenoic acid, these compounds were isolated using ethyl acetate extraction of macerated bulbs [77]. Dichloromethane-methanol extract of *Drimia robusta* (Whole plant) possesses anti-ovarian cancer activity at the IC_{50} value of 1.05 µg/ml in OVCAR-3 cell line (**Table 2**) [55].

Gomphocarpus fruticosus (Linn.) Aiton f. (Apocynaceae), they have other few common names such as swan plant (**Figure 2H**), milkweed, or white cotton, is a perennial herb, spindly shrub, often with watery or milky sap. It is native to South Africa with a wide distribution in most Provinces, including Free State, Gauteng, KwaZulu-Natal, Mpumalanga, Cape (Eastern, Western, Northern), and North West [78]. *Gomphocarpus fruticosus* is used medicinally to treat headaches, stomach pain, tuberculosis, and as an emetic [79]. The acetone extract of *Gomphocarpus fruticosus* root possessed antigonoccol activity [80]. Similarly, the ethanolic extract of the root is reported to have anti-ovarian cancer activity with an IC_{50} value of 3.72 µg/ml in OVCAR-3 cell line (**Table 2**) [55].

Leyssera gnaphaloides (Linn.) L. (Fabaceae) is one of the South African medicinal plants (**Figure 2I**). It is used as a folk medicine medicine to treat various ailments including bronchitis, cough, diarrhoea, fever, and even tuberculosis [81, 82]. An extract was obtained using Hexane, bioactive fractions obtained from the extracts reveal that it possesses cytotoxic effects, however, more than 50% of the ovarian cells of Chinese hamster sustained even at a very high concentration. This result implies that the extract seems to be harmless to the Chinese hamster ovarian cells [83].

Parinari curatellifolia (Planch) ex. Benth. (Chrysobalanaceae) is a tree and is semi-circular in shape almost resembles a mushroom in its canopy and the hues are in blue-green and grey colour (**Figure 3A**). It is an evergreen, medium to large tree, that grows up to thirteen meters, but a height of twenty three-twenty six m also been recorded in certain areas [84]. The leaf extracts and bark are used for treating the symptoms of pneumonia, and eye/ear ailments. Many traditional healers incorporate the bark of *Parinari curatellifolia* in the formulation of their mixture or medicine [85]. The roots are soaked in water for about an hour or six in gelid water, it is used to aid cataract and earache respectively. This roots soaked water are used as eye and ear drops [86]. The bioactive compound, 13-Methoxy-15-oxozoapatlin from the plant, has significant cytotoxic activity against SW626 human ovarian adenocarcinoma cell line (**Table 2**) with the IC_{50} value of 0.6 µM/ml [87].

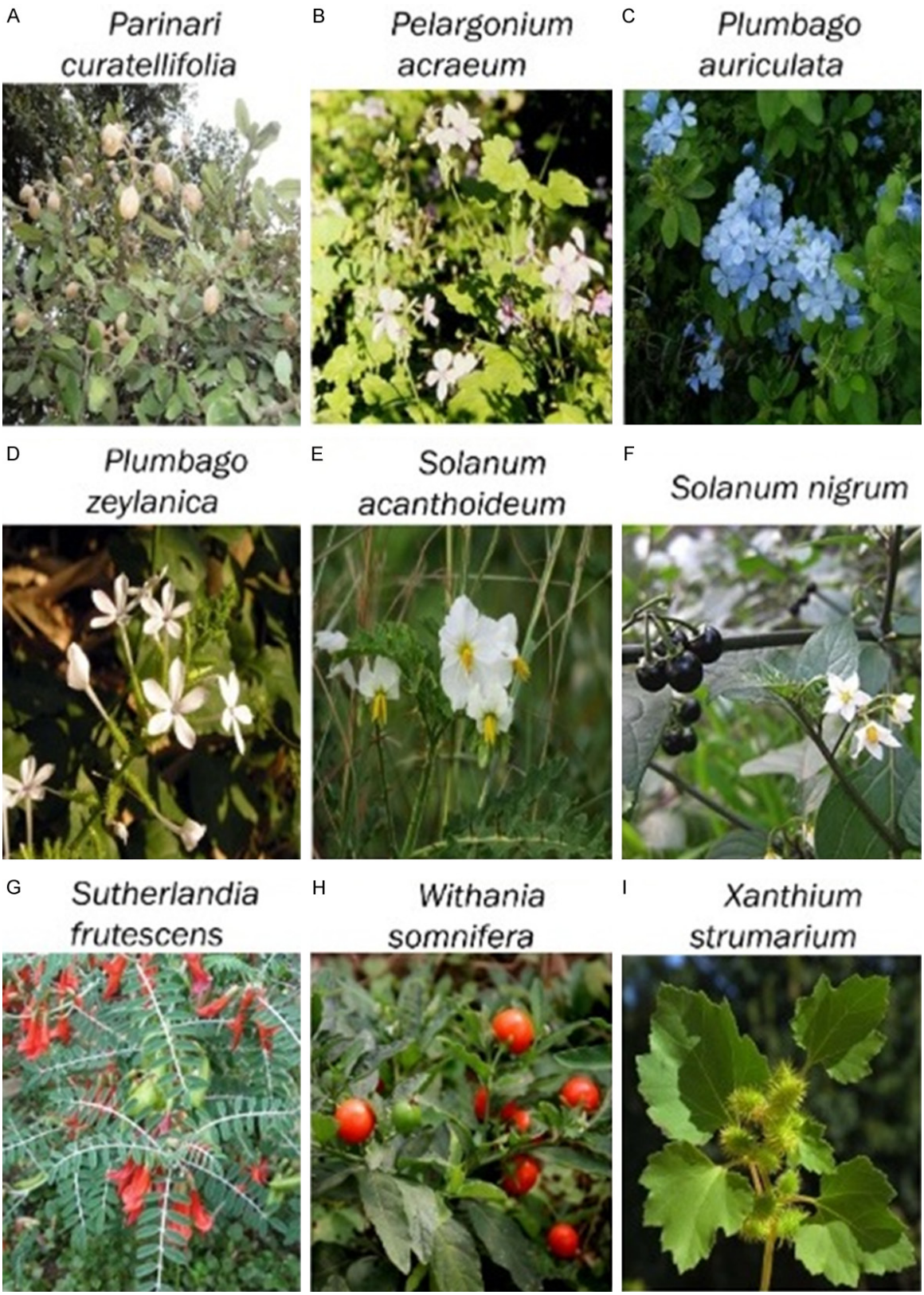


Figure 3. Anti-ovarian cancer potential of South African medicinal plants.

Pelargonium acraeum R.A.Dyer (Geraniaceae) is a small shrub (**Figure 3B**) of South African origin that grows up to 1 m, or occasionally 2 m high. The whole plant extract of *Pelargonium acraeum* has been reported to have anticancer activity. The genus *Pelargonium* is endowed with varieties of flavonoids and alkaloids characterized by antioxidant, antimicrobial, anti-inflammatory, and anticancer activities [88]. The methanolic extract of *Pelargonium acraeum* showed minimum cytotoxic activity with the IC_{50} value of 10 µg/ml and 60 µg/ml in PA1 ovarian cancer cell line after 24 hr and 48 hr respectively of exposure. Additionally, the aqueous extract of this plant showed better anti-ovarian cancer activity with the lowest IC_{50} value of 6.92 µg/ml on OVCAR-3 cell line (**Table 2**) [55].

Plumbago auriculata (Lam.) (Plumbaginaceae) is a medicinal plant and an ornamental shrub with clusters of light blue flowers (**Figure 3C**). it is commonly found in South Africa [89]. It is a rich source of alkaloids such as plumagain (2-methyl-5-hydroxyl, 4-naphthoquinone which could be used as an anti-cancer agent while also exhibiting antibacterial, antioxidant, antifungal, anti-inflammatory and anticoagulant potentials against various diseases such as rheumatism, piles, diarrhoea and skin diseases [90, 91]. The methanolic extract had a minimal cytotoxic activity at 10 µg/ml (24 hr) and 60 µg/ml (48 hr) on PA1 cell lines of human ovarian cancer. Consequently, of note is the significant morphological changes also observed in PA1 cancer cells (**Table 2**) by nuclear staining (4',6-diamidino-2-phenylindole) method [92].

Plumbago zeylanica (Linn.) (Plumbaginaceae) is a perennial herb (**Figure 3D**) commonly distributed across South Africa [93]. The entire plant is used to prepare a variety of folk medicines in Africa, but the roots hold an effective bioactive compound called Plumbagin, it had shown to have anti-malarial, anti-obese, anti-ulcer, antimicrobial, anticancer, anti-inflammatory, antioxidant properties etc. [94]. The chemotherapeutic potential of Plumbagin acts as an anticancer agent in BRCA1-mutated ovarian cancer patients. The mitochondrial membrane is lost, the nucleus gets condensed, DNA gets fragmented and other morphological changes are induced by Plumbagin in ovarian cancer cells. Moreover, it binds to the active site of ER-α and inhibits the classical ER-α signaling pathway in ovarian cancer [95].

Solanum acanthoideum Drege ex Dunal (Solanaceae) is also a medicinal plant (**Figure 3E**) of South African origin traditionally used to treat fever, intestinal infections, asthma, and to heal sores. It is similarly used to stimulate milk production in cows and treat cattle that are affected by gall sickness [79]. The root extract is reported to have anticancer activity in cancer cell lines. Intriguingly, the methanolic root extract of the plant has been reported in a study to possess anti-ovarian cancer activity with the IC_{50} value at 18.62 µg/ml using IGROV1 ovarian cancer cell line (**Table 2**) [55].

Solanum nigrum (Linn.) (Solanaceae) is one of the prominent species (**Figure 3F**) in the genus Solanum regarded as a common, important and one of the largest genera, that comprises about 84 families and 3000 species [96]. South Africa, Eurasia are its native and introduced to America, Australia and Asia. It is also known as black nightshade [97]. The ripe berries are used as food by the natives, while other plant parts are used as traditional medicine. Traditionally, it is used as an analgesic, antispasmodic, antiseptic, antibacterial, antibiofilm, anti dysenteric, antinarcotic, emollient, diuretic, tonic, soporific, laxative, anticancer, antiulcer and also to treat the disarrays of the neuro-vegetative system, etc. All these curative dispositions exhibited by the plant attributed to the alkaloid contents in them [98]. Aqueous extract of *Solanum nigrum* possess an anti-ovarian cancer activity in ovarian cancer cell lines of ES-2, SKOV-3 and OVCAR-3 (**Table 2**) with the significant IC_{50} values of 1.052, 1.779 and 2.000 mg/ml respectively [99, 100].

Sutherlandia frutescens (Linn.) Goldblath & J.C. Manning

Sutherlandia frutescens (**Figure 3G**) were newly referred to as *Lessertia frutescens* subsp. *frutescens* belong to the Fabaceae family, it is the third-largest family of flowering plants. These plants are the habitat of dry areas and are commonly found in South Western and Northern Provinces of Cape [101]. The plant can also be found in other areas of Southern Africa, especially Botswana, Zimbabwe, and Namibia [102]. *Sutherlandia frutescens* enhancing well-being, provide immune support for tuberculosis (TB),

and acquired immune deficiency syndrome (AIDS) as well as in the treatment of cancer; hence, the name cancer bush [103]. Pharmacologically, it is established to have antioxidant, anti-inflammatory, anti-ovarian cancer, and anti-diabetic activities [104].

Withania somnifera (L.) Dunal (Solanaceae) is widespread but not common in all (**Figure 3H**) the Provinces of South Africa but also distributed in Namibia, Botswana, Swaziland, and Lesotho. It grows in a large number of vegetation types from dry areas to areas with reasonably high rainfall, such as coastal vegetation and or grassland [105]. It possesses chemical compounds that exceeds 80 notably alkaloids and steroids (withanolides) are present in *W.somnifera*. Many studies have been performed and the studies disclose the truth about the pivotal deeds namely antibiotic, anti-inflammatory, cytotoxic, anti-tumor, and cholesterol-lowering deeds of these compounds, which are predominantly acquired from leaves and roots [106]. In a study, the supplementation of plant extract reduces the progression of ovarian cancer in the animal model. Moreover, Withaferin A, is a bioactive compound that has been isolated from this plant inhibits the activity of ovarian epithelial cancer cell line (A2780) by 70-80%, also the tumor growth is reduced and metastasis inhibition is also a part of the function of the isolated compound when compared to untreated controls in nude mice [107, 108].

Xanthium strumarium (Linn.) (Asteraceae) is a South African medicinal plant (**Figure 3I**) with global distribution found in abundance in Eurasia and America [109]. The entire plant has been used in the traditional medicine to treat the infections caused by bacteria, high-sugar, itching of the skin, and inflammatory diseases like coryza and rheumatoid arthritis. It has been used included in traditional Chinese medicine for anti-cancer treatment [110]. The fruit extract of the plant contains 3, 4-dihydroxybenzaldehyde investigated to inhibit malignant tumors in human. Two xanthanolide sesquiterpene lactones, 8-epi-xanthatin, and 8-epi-xanthatin-5b-epoxide have been isolated from leaves to inhibit ovarian cancer cell line of SK-0V-3 (**Table 2**) [111, 112].

Conclusion

The role of Medicinal plants in treating Ovarian Cancer is inevitable. Only a very few numbers of plants were been explored and phytochemical studies have been performed among 270,000 plant species. Though there many synthetic medicines are involved to treat various diseases about 3/4th community of the population adhere to the traditional medicines for their primary healthcare needs; however, only a few indigenous medicinal plants of South African have been investigated to their full potential in terms of commercialization. The opportunity for bioprospecting of the medicinal plants and their compounds for novel pharmaceuticals remain largely untapped. This paper addressed the anti-ovarian cancer activity of some of these South African medicinal plants and their bioactive compounds with a view that these medicinal plants are the real sources with less or no side-effect in treating a disease, especially they would create a revolution in combating against the Disease Ovarian Cancer by developing novel leads. This would help an individual to sustain their life.

Acknowledgements

The financial supports received from National Key Research & Development Program in China (Grant No. 2019YFD1002704), Shandong major projects of independent innovation (Grant No. 2019JZZY010722), the Key Research and Development Program of Shandong Province (Grant No. 2017YYSP024), Funds for Innovation Team of Jinan (Grant No. 2018GXRC004), and Special Funds for Taishan Scholars project are acknowledged. Authors also express our thankful to the Department of Plant Sciences, Faculty of Natural and Agricultural Sciences, University of the Free State, QwaQwa, South Africa for completion of this work in fine fulfillment.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bo Cui, State Key Laboratory of Biobased Material and Green Papermaking, College of Food Science and Engineering, Qilu University of Technology, Shandong Academy of Science, Jinan 250353, China. Tel: +86-186-60811718; E-mail: cuibopaper@163.com

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