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Ethnomedicinal and phytochemical properties of sesquiterpene lactones from *Dicoma* (Asteraceae) and their anticancer pharmacological activities: A review

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ABSTRACT

Dicoma species belonging to the Asteraceae family are commonly utilized as traditional medicine in Southern Africa. *Dicoma anomala, Dicoma capensis, Dicoma schinzii* and *Dicoma zheyeri* are the most common ethnomedicinal plant species used in Southern Africa. The plant species of Dicoma genus are identified as the main source of sesquiterpene lactones. Dicoma species are associated with pharmacological properties such as antiviral, antibacterial, antihelminthic, antispasmodic antiplasmodial, as analgesic, antiinflammatory, , anticancer, , and wound healing properties. The plant species of Dicoma genus are identified as the main source of sesquiterpene lactones. In this review, the authors report the ethnomedicinal and phytochemical properties, and pharmacology of sesquiterpene lactones from the genus Dicoma from 1978 to 2020. There are over eighty (80) reported sesquiterpene lactones isolated from Dicoma species including, germacronolides, eudesmanolides, melampolides, guaianolides and pseudoguaianolides. Sesquiterpene lactones possess antimalarial, anticancer and antiinflammation activities due to their structural diversity. The diagnostic search on phytochemistry of sesquiterpene lactones from Dicoma carried out in the 70's has limited pharmacological screening activities; hence these may need to be revisited and explored. Furthermore, the literature search conducted in this review showed that out of the 35 *Dicoma* species, seven species were investigated, and their medicinal uses, pharmacology and photochemistry reported. The recommendation drawn is that Dicoma species that are not investigated and not fully exploited should be studied for their phytochemicals and efficacy. The information compiled in this review on the pharmacological, phytochemistry and ethnomedicinal activities of genus Dicoma was obtained from relevant literature sources, including books, book chapters, websites, theses, reviews and research articles from databases such as Web of Science, Scopus, Science Direct, BioMed Central, Springer link, PubMed, and Google Scholar.

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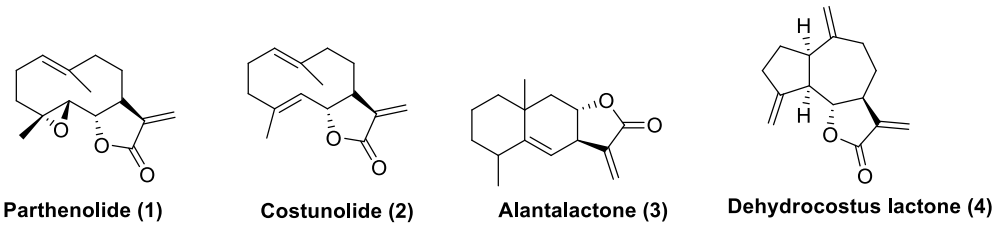

Fig. 1. Structures of anticancer active sesquiterpene lactones from Asteraceae species [43].

Introduction

Exploring medicinal plants is an established method for the discovery of leads and new drugs that contribute to the development of today's pharmaceutical industry [42]. Medicinal plants are of great importance to humans and society in general. Amri and Kisangau [4] and Steenkamp et al. [48] reported that the World Health Organisation (WHO) predicted almost 80% of people globally rely on locally available plant resources for primary health care, since western pharmaceutical products are costly, inaccessible, or unsuitable for local populations. Medicinal plants were reported to be effective due to the presence of bioactive secondary metabolites such as alkaloids, tannins, flavonoids and phenolic compounds, which have interesting pharmacophores [63].

The rich diversity of plant kingdom could be investigated in the search for effective and affordable medicine globally. In 1960, the National Cancer Institute (NCI) launched a large-scale screening program for antitumor agents, with 35000 plant samples evaluated. Taxol, the antibreast cancer drug, is a success that emerged from exploring traditional medicinal plants [6]. There are more than 200 plant-derived drugs in preclinical or clinical development [19]. Sesquiterpene lactones (SLs) are plant-derived secondary metabolites. SLs possess potential biological activities such as antiviral, anticancer, antifungal, antitumor, , , antibacterial and antiinflammation. About 1500 publications reported SLs antiinflammatory and anticancer properties [17]. Artemisinin and parthenolide isolated from *Artemisia Afra* and *Tanacetum parthenium* species of Asteraceae family are in clinical trials [17,52].

Sesquiterpene lactones are 15-carbon terpenoids, consisting of three isoprene units [14]. SLs are classified amongst the largest class of secondary metabolites in plants, with over 5500 structures reported between 1978 and 2020 ([41], , [3]) and the number continues to grow. Plant extracts that contain SLs were used in traditional medicine practice as antibacterial, antiinflammatory, anticancer and antiimmunomodulatory since ancient times [12]. Previous reports suggest that SLs display anticancer activities resulting from α-methylene-γ-lactone moiety, lipophilic, molecular geometry and electronic features [27,41,57]. Literature described the anticancer activity of some selected α-methylene-γ-lactones including costunolide, parthenolide, alantalacotone, dehydrococtus lactone and artemisinin [38,57].

SLs such as thapsigargin, artemisinin, parthenolide and their several synthetic derivatives were evaluated in cancer clinical trials [11,17,62]. These SLs were selective towards cancer stem cells and tumor through targeting signalling pathways, which resulted to lead compounds in cancer clinical trials [11,17,62].

In recent years, the anticancer properties of SLs and molecular mechanisms of action were studied [23,25,57]. Zhang et al. [57] reported the SLs molecular mechanisms, chemotherapeutic and chemoprotective potential, anticancer mechanism of action through inhibition of the signaling pathway of nuclear factor kappa B (NF-kB). In cancer cells, NF-kB plays an important role in inhibiting apoptosis, induction of metastasis, resistance to chemotherapy and resistance to radiotherapy [20]. NF-kB regulates the immune system and plays a significant part in regulating inflammatory processes by controlling the expression of many mediators and effectors of inflammation [57].

Sesquiterpene lactone artemisinin revealed selective cytotoxicity towards human hepatoma cells, Hep G2 (P53 wild-type; IC_{50} =13.98 mM), Huh 7 (P53 mutant; IC_{50}= 8.9 mM), BEL-7404 (P53 mutant; IC_{50}= 9.9 mM) and Hep 3B (P53 null; IC_{50}= 10.4 mM) and a normal human liver cell lines 7702; IC_{50}= 60.9 mM [20]. Artemisinin suppresses prostate carcinoma cell line DU145; IC_{50}= 20 μM by apoptosis induction through the mitochondrial pathway, with intracellular heme serving as the molecular target [36].

Parthenolide (**1**) presented in Fig. 1 is a germacronolide isolated from a plant species named *fever few* of Asteraceae family. Parthenolide inhibited the growth of SiHa and MCF-7 cell lines in a concentration-dependent method at 24 and 48 h time intervals. The IC_{50} values of parthenolide against SiHa and MCF-7 cells were 8.42 $\pm$ 0.76 and 9.54 $\pm$ 0.82 lM, respectively. Cells treated with parthenolide inhibited up regulation of p53, Bax, caspase-3, and -6 genes and down regulation of Bcl-2 gene. At IC_{50}, the p53 gene was up regulated by 9.67- and 3.15-fold in SiHa and MCF-7 cells, respectively. The Bax to Bcl-2 ratio was 3.4 and 2.3 for SiHa and MCF-7 cells, respectively [2]. Parthenolide showed activity against multiple myeloma, (MM) cells , a chronic untreatable blood cancer that causes cancer-induced mortality. The mechanism by which

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parthenolide inhibits the growth of MM cell lines and primary cells was investigated[40], . The IC_{50} for all cell lines and primary cells ranged from 1-3 µM. Parthenolide was investigated on proliferation of three human cancer cell lines namely: human medulloblastoma (TE671), human colon adenocarcinoma (HT-29), human lung carcinoma (A549), and human umbilical vein endothelial cells (HUVEC) *in vitro*. Parthenolide inhibited proliferation of all three cancer cell lines (TE671, HT-29, A549,) and HUVEC with IC_{50} value of 6.5 mµM, 7.0 mµM, 4.3 mµM, and 2.8 mµM, respectively [40].

Costunolide (**2**) (Fig. 1) is a biological active SL that is found in many medicinally valued plants [43] from Astereace species. Choi et al. [13] reported that costunolide can suppress the growth of estrogen receptor-negative breast cancer cell lines MDA-MB-231 and MCF-7 estrogen positive at low concentration through receptor-mediated pathway with IC_{50} values of 20 and 10 μM, respectively. Costunolide revealed a slight effect on the viability of human hepatoma Hep3B cells when observed in Hep3B and HepA2 cell lines [59]. Costunolide slowed production rate of hepatitis B surface antigen (HBsAg) and hepatitis B antigen (HBeAg) in a dose-dependent method with IC_{50} value of 1.0 and 2.0 µM. Costunolide exhibits a strong inhibitory effect on the apoptosis and proliferation of various tumor cells at concentrations ranging between 2.5 and 40 µM [59]. Costunolide inhibited an anticancer effect against the H1299 human non-small-cell lung cancer (NSCLC) cell line with IC_{50} value of 23.93±1.67 µM and induced cellular apoptosis in a dose-dependent manner [54]. In addition, costunolide induced mitochondria-mediated apoptosis in human gastric adenocarcinoma BGC-823 cells with IC_{50} values of 32.80 μM [55] and also induced apoptosis in HL-60 human leukaemia cells by the reactive oxygen species (ROS)-mediated mitochondrial permeability transition and the resultant cytochrome release with IC_{50} value of 10 mM [26]. Furthermore, costunolide mediated cell cycle arrest at G2/M phase in two breast cancer cell lines, MCF-7 and MDA-MB-23, with IC_{50} value of 20, 40 μM respectively ([43], [13,29]).

Dehydrococtus lactone (**3**) (Fig. 1) induced cell cycle arrest in cancer breast cells ; MDA-MB-23 and MCF-7 cell lines both with IC_{50} of 8 μg/mL, leukaemia cells (K562); IC_{50} values of 12 μM and SW-480; IC_{50} of 5 μM (Penget, 2017, [15,28]). The SL dehydrococtus inhibited the NF-kB activation by stopping TNF-α-induced degradation and phosphorylation of its inhibitory protein $I_kB\alpha$ in human leukaemia HL-60 cells; IC_{50} of 5 μM [37].

Alantolactone (**4**) (Fig. 1) is an anticancer agent that inhibited the theoredoxin (Trx) reductase enzyme, and inhibited cell growth in the cervical cancer cells (HeLa) in a concentration-dependent manner with IC_{50} value of 10.0 μM [58].

Studies carried out by Mhaidat et al. [30], Inayat-Hussain et al. [22] and Zhao and Li [60] showed that SLs exhibit anticancer effects in human cancer cells namely; i) colon cancer cells (HCT-15; IC_{50} of 0.818 mg/g) through activating apoptosis pathways that depend on or are independent of caspase; ii) prevent or palliate cervical cancer by reducing the expression of bcl-2 and increases the expression of p53, iii) leukaemia cells (HL-60 ; IC_{50} of 5 μM), activate and induces apoptosis through oxidative stress; iv) bladder cancer cells of (T24 ; IC_{50} of 25 μM)), activate MAP-K-P38 and inhibits the Akt pathway which causes a loss of balance in the mitochondrial membrane and breast cancer mutations in HER2 and its receptors ([30,22,60]).

This review provides a summary of the ethnomedicinal, phytochemicals and anticancer pharmalogical activities of sesquiterpene lactones from *Dicoma* species a from 1978 to 2020. This review further highlights previously successes in the discovery of the plant-derived anticancer sesquiterpene lactones isolated from other plant genera of Asteraceae family (i.e. costunolide, artemisinin and parthenolide). The information will be useful to the scientific community as a guide for focusing current research on scientific validation for uses of the *Dicoma* plant species widely claimed in traditional folklore and/or investigations to find new chemical entities or constituents that could contribute to new and improved cancer therapeutics.

Taxanomical profile of *Dicoma* species

Dicoma species are known for medicinal benefits and consist of secondary metabolites with a wide of biological properties against various diseases [21]. *Dicoma* belongs to the Asteraceae family or Compositae, which is classified as a family of flowering plants also known as the aster, daisy or sunflower family [1]. Asteraceae family plant species are among the chemically most diverse groups of flowering plants [1,39].

According to Panero and Funk [39] the name *Dicoma* was first derived by Cassini in 1817 in his first account of the tribe Carlineae. *Dicoma tomentosa* type species was described by Cassini in 1818. In 1819, Cassini published further description of the genus and species [39]. Genus *Dicoma* belongs to the tribe of Multiseae, the subtribe of Gochnatiinae and the subfamily of Cichoriodeae of the Asteraceae family [39]. The genus *Dicoma* is comprised of 35 species and 16 of these species are endemic in Southern Africa. Seven other species of *Dicoma* are recorded in Zimbabwe [61]. There are four main species that are widely used medicinally in Southern Africa namely, *Dicoma* zeyheri, *Dicoma anomala, Dicoma schinzii* and *Dicoma capensis. Dicoma tomentosa* grows in Asia and Tropical Africa. The name" Dicoma" arose from two Greek words "di" meaning "two" and "kome" meaning" tuft of hair", which refers to the double row of pappus bristles which are characteristic of species of the genus [32,39].

Other Dicoma plant species are endemic in Botswana, Namibia, the Democratic Republic of Congo, Zimbabwe, and in the North of Uganda [49,61]. In South Africa, it is distributed across KwaZulu-Natal, Eastern Cape, Gauteng, Limpopo, North-West Provinces and Free State and around the neighbouring inland kingdoms of Eswatini (formerly Swaziland) and Lesotho [7,61]. Panero and Funk [39] reported that some species of *Dicoma* are common in dry and very dry areas, grasslands, scrubland, sandy soils and sometimes in edges of pans. Zimudzi et al. [61] reported that other species such as *D. niccolifera* is near endemic to and mostly limited to serpentine soils of the Great Dyke Mountains of Zimbabwe,.*D. niccolifera* also occurs on

Table 1
Reported traditional medicinal uses of Dicoma species.

Dicoma species	Plant part used	Traditional uses	Country	References
D. anomala	Roots	Psychos, cataracts, respiratory complaints, sores and wounds, uterine pain, sedative, vertigo, fever, abdominal pains, dizziness and gonorrhoea. Circulation, colic, cardiovascular disorder, coughs and colds.	South Africa, Namibia	[49] [21],
		Blood disorder, ingested poisoned food, diabetes mellitus, gal sickness, wounds in horse.	South Africa, Zimbabwe, Lesotho, Burundi, Zimbabwe	[7,50]
		Intestinal worms, dysentery, toothache, pneumonia, purgative, sores and scabs, venereal diseases, varicose veins, ringworms, fever, diarrhoea, stomach pains, labour pains, and parasitic diseases. Dermatosis skin, eruption abscess, dermatosis, scabies, insanity, migraines and snakebites		
	Leaves	Constipation, coughs	Botswana, Rwanda, Zimbabwe	[49,50]
	Leaves and roots	Dysentery	Tanzania	[21]
	Roots mixed with *Berkheya setifera*	Biliousness, jaundice	Lesotho	[32]
D. capensis	Whole plant	Colds, back pains, haemorrhoids, bladder infections, kidney problems, influenza, nausea, liver problems, stomach problems, bitter tonic and rheumatism	South Africa	[31,47]
	Leaves	Asthma, diabetes, colds, cancer, febrile conditions, diaphoresis, expel retained placenta, flatulence, diuretic, fever and tuberculosis	South Africa	[31,47]
	Roots	Fever, gastrointestinal complaints	South Africa and Namibia	[47]
	Whole plant	Coughs and stomach problems	South Africa and Namibia	[31,47]
	Flowers and fruits	Sores and wounds	Botswana	[32]
D. Schinzii	Leaves and Roots	Measles, chicken pox, colds and flu, and blocked nose	Kalahari	[53]
	Unspecified plant part	Fever and stomach ailments, coughs, sore throat and febrile convulsions in babies	Kalahari	[53]
D. tomentosa	Leaves	Febrifuge drug during febrile attacks in the mother after child birth, Colds in the head, Pain in the testicle	Belgium, Africa	[24]
	Unspecified plant part	Tooth cleaner, sceptic wounds, fumigation to relieve skin itch	Africa	[24]
	Whole plant	Malaria	Burkina Faso	[24]

non-serpentine areas from one locality in Mature in the east of the country and another site near Lusaka in neighbouring Zambia [61]. Other two unidentified species of *Dicoma* occur in the Arabian Peninsula in India and Pakistan [44].

Dicoma species are erect, sub-erect, prostrate or perennial herbs, small shrubs or small trees [49]. Becker et al. [7] described the stems of *Dicoma* species as annual, branched, many from the root crown, sometimes woody at the base decumbent, and about 30 cm long. Some species of *Dicoma* have simple, narrow, linear leaves with bright green upper leaf surface and larger flower heads. Other species like *Dicoma zheyeri* have spine-tipped leaves, densely covered with hairs on the lower surface, long tubular purple to yellow-brown florets and thickened roots sticks [39]. According to Panero and Funk [39] the florets of *Dicoma* species are white to red bilabiate with the inner lips coiled, disc florets actinomorphic, with white corolla, yellow, cream to pink or mauve, glabrous to pubescent with different types of glandular.

Ethnobotany of *Dicoma* species

Steenkamp and Gouws [47] and Maness et al. [31] stated that the herbs of *D. capensis* are traditionally utilised as bitter tonic and diuretic and for treating bladder infections, kidneys, back pains, nausea, influenza, colds, cancer and diarrhoea (Table 1). *Dicoma tomentosa* is used to clean teeth (Table 1) [24]. *Dicoma anomala* is known as hloenya in Sotho, fever bush in English, Inyongwana in Xhosa, Koorsbossie in Afrikaans [49,50]. According to the report of Becker et al. [7], the roots and the leaves of *D. anomala* are widely used in treatment of various diseases such as constipation, cough, cardiovascular disorders, diarrhoea, infertility, fever, venereal diseases, tooth aches, sores, dizziness, wounds, dysentery, and diabetes mellitus (Table 1) [7,21].

Van der Merwe [49] reported that the roots of *D. zeyheri* are used to treat coughs and chest pains, to 'strengthen' blood for mothers after long and difficult births, strengthen limbs after long sickness, lumbago, back pains and stomach problems.

Dicoma schinzii also known as Kalahari fever bush is particularly known for treating fever and stomach ailments (Table 1) [53].

Pharmacological activities of *Dicoma* species

Shale et al. [46] stated that the leaf and root hexane extracts of *D. anomala* showed an *in vitro* antiinflammatory activity (>80% inhibition) (Table 2). Shale et al. [46] further suggested that activity may be due to the presence of sesquiterpene lactones soluble in methanol and hexane. Maroyi [32] and Hutchings and van Staden [21] reported that the traditional use of *D. anomala* could be connected to its numerous pharmacological properties which include, antibacterial, antiviral, antispasmodic, antihelminthic, wound healing, anticancer, antiinflammatory, antiparasitic and analgesic. *Dicoma schinzii* was found to possess antibiofilm properties (Table 2) [53]. Biofilm formation, inhibition and eradication were determined using microtiter plate assay. The leaves of the plant can be used in traditional setting for the treatment of biofilm infections related to the two strains tested (Table 2) [53].

Sesquiterpenes of *Dicoma* species

The genus *D*icoma species contain various bioactive compounds including sesquiterpenes known to possess cytotoxic, antitumor, anticancer and antimicrobial activities [24,48,49] and inhibitory activities against cytochrome P450 (CYP450) enzyme and p-glycoprotein (Pgp) [18].

Sesquiterpenes

Sesquiterpenes are natural compounds that are derived from three isoprene units (C15) [14,45]. Salminen et al. [45] stated that sesquiterpenes are effective in inhibiting cancer. Gemacrene D (**5**) shown in Fig. 2, was isolated from the aerial and root parts of *Dicoma anomala* [9,10]. The roots parts of *D. zeyheri* contain β-farnasene (**6**) and α-humulene (**7**) ([9], b, [49]). Van Der Merwe [49] reported that α-humulene exhibits antitumor properties.

Sesquiterpene lactones

According to Jansen et al. [24] and Chadwick et al. [11] sesquiterpenes are reported to have a wide range of biological activities ranging from phytotoxic, antiinflammatory, antifungal and antibacterial, to cytotoxic/anticancer. Jansen et al. [24] further added that several sesquiterpene lactones such as (pseudo) guaianolides, eudesmanolides, germacranolides and melampolides were previously isolated from Asteraceae family plant species and reported to exhibit antiplasmodial and cytotoxic activities.

Germacranolide and guainolide-type sesquiterpene lactones

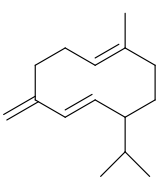
The phytochemical investigation of the aerial parts of *D. anomala* Sond. subsp. *anomala* afforded germacranolides **8, 9, 10** and **11** shown in Fig. 2. The aerial parts of *D. capensis* Less. afforded germacranolides **12-16**. Germacranolides **12, 14** and **17** were also isolated from *D. schinzii* O. Hoffm. Investigation of the aerial parts of *D. tomentosa* led to the isolation of compounds **14, 16** and **18**. Germacronolides **19-22** were isolated from the aerial parts of *D. tomentosa*. The germacran-8,12-olides **26-29** and guaianolides **23-24** were isolated from *D. anomala* subsp. *cirsioides* (Harv.) Wild. germacronolides **25-29** were isolated from *D. anomala* Sond. subsp. *anomala*. Guaianolide **25** was isolated from the roots of *D. zeyheri*. The aerial parts of *D. schinzii* O. Hoffm. afforded isobutyrates **30-32** and compound **33-34** were isolated from the roots of *D. macrocephala*. Compounds **35- 38** were isolated from the aerial parts of *D. anomala* Sond. subsp. *cirsioides* (Harv.) Wild. The aerial parts of *D. anomala* subsp. *cirsioides* (Harv.) Wild. yielded albicolide **39**, compounds **43-45, 47-52** and 14-acetoxydicomanolide **46**. Investigation of aerial parts of *D. schinzii* O. Hoffm. afforded isobutyrates with a germacrene skeleton compounds **53-57**. The investigation of the aerial parts of *D. anomala* subsp. *anomala* afforded germacronolides **40-43** and **51-56**. The investigation of the aerial parts of *D. anomala* Sond subsp. *cirsioides* (Harv) Wild. afforded the guaianolide artemisiifolin **58** [8–10,49,56].

Melampolide-type sesquiterpene lactones

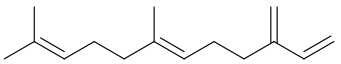
Investigation of aerial parts of *D. anomala* Sond. subsp. *anomala* yielded compounds **59-60** and **63** presented in Fig. 2. Compounds **60-62, 64** and **73** were isolated from the aerial parts of *D. capensis* Less. Compounds **59** and **60** were also isolated from aerial parts of *D. tomentosa*; compounds **65-69** and **70** were isolated from the same plants. The roots of *D. anomala* subsp. *cirsioides* (Harv.) Wild. afforded compounds **71-72**. Compound **75** was isolated from unspecified species of *Dicoma* [8,9,49,56]. Compound **74** was isolated from the aerial parts of *D. anomala* subsp. *anomala*. Jansen et al. [24] and Bohlmann et al. [9] reported the isolation of a melampolide-type sesquiterpene urospermal, A-15-*O*-acetate **76**. The compound **72** was isolated from *D. temantosa* through bioassay guided fractionation [24].

Table 2
Reported pharmacological activities of Dicoma species.

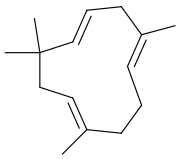
Plant species	Plant part	Extract	Activity tested	Effect	Reference
D. anomala	Roots	Methanol and water	Antibacterial	Exhibit activity at MIC>4 mg/mL against selected bacteria	[49]
		Ethanol, hydro-ethanol and methanol	Antidiabetic	Exhibited activity against α-amylase with the IC_{50} value of 34.16, 9.00 and 20.70 µg/mLrespectively and α-glucosidase with the IC_{50} value of 29.37, 29.37 and 39.62 µg/mL respectively.	[5]
		Water		Revealed the most effective inhibition with IC_{50} value of 51.90 and 27.4 µg/mL against α-amylase and α-glucosidase	[5]
	Leaves	Hexane	Anti-inflammatory	Showed anti-inflammatory activity above 85% inhibition	[46]
	Roots	Hexane	Anti-inflammatory	Showed activity of 79% inhibition	[46]
		Unspecified	Antimicrobial	Exhibited activities against Staphylococcus aureus, *Microsporum canis*, and *Trichophyton mentagrophtes* with IC_{50} value of 0.77 µg/ml.	[51]
		Aqueous and methanol	Antibacterial	Revealed the minimum inhibition concentration (MIC) value>4 mg/mL against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Streptococcus pyogenes*	[48]
		Methanol	Antimicrobial	Showed activity against *S. aureus* and *Staphylococcus* Group A with 3.25 mm and 4.25 mm inhibition respectively; MIC value of > 10.0 mg/mL for *S. aureus* and 2.25 mg/mL for *Staphylococcus* Group A. The extracts further showed activity against *Candida albicans* with MIC value of 1.25 mg/mL	[35]
		Dichloromethane: Methanol (50:50)	Antidiabetic	Exhibited potent dipetidyl peptidase IV (DPP-IV) with IC_{50} value of 169.96 µg/mL and glycation at 70.3% with IC_{50} value of 5 µg/mL inhibitory effects	[33]
		Dichloromethane: Methanol (50:50) and methanol	Antidiabetic	Showed potent modulatory effects on glucose utilization in Chang liver cells (IC50 of 1235.2 and 1495.2 µg/mL)	[33]
		Dichloromethane: Methanol (50:50)	Antidiabetic	Exhibited potent adipocyte differentiation (AD_{50}: extract concentration causing 50% adipocyte differentiation value of 68.55 µg/mL) in 3T3- l1 adipocytes	[33]
	Roots	Ethyl acetate	Anticancer	Screened against the preliminary 3-cell lines panel of cancer cells and exhibited activity with GI_{50} of 12.5 ppm	[49]
	Whole plant	Aqueous	Cardioprotective	Showed evidence of oedema and myocardial necrosis at 125 and 250 mg/kg doses, the alterations were ameliorated or cleared at 500 mg/kg dose suggesting that the maximum amelioration of the plant against isoproterenol (ISP) induced cardiotoxicity.	[5]
	Roots	Water	Hepatoprotective and antioxidant	Showed the activity IC_{50} values of 15.20, 11.20 and 0.84 µg/mL *in vitro* in 1.1-diphenylpicryl hydrazyl (DPPH), hydroxyl and superoxide anion radicals, respectively. Pre-treatment and treatment with different concentrations of *D. anomala* aqueous roots extracts significantly (P>0.05) reduced the elevated serum activities of aspartate transaminase, alanine transaminase levels while increasing the activities of superoxidase.	[5]
	Roots	Ethanol	Antioxidant	Showed IC_{50} value of 0.77 µg/mL for nitric oxide scavenging activities	[64]
	Roots	Methanol	Antioxidant	Exhibited an IC_{50}= 3.50 µg/mL metal chelating activity	[64]
D. capensis	Leaves	Ethanol	Antibacterial	Showed inhibitory activities against *Bacillus subtilis* with zone of inhibition value of 1.0 +/- 0.0 mm.	[34]
	Fibre and leaves	Ethanol	Antifungal	Inhibitory against *Candida albicans* and *Candida mycoderma* with zone of inhibition ranging from 1.0 +/- 0.0 mm to 2.5 +\- 0.0 mm was observed.	[34]
	Fruits	Ethanol	Antifungal	Exhibited activity against the *Candida albicans* with MIC value of 1.25 mg/mL	[34]
	Roots	Dichloromethane	Anticancer	Showed cytotoxic effects against a prostate carcinoma cell (DU-145), breast cancer cell lines MCF-7 and non-malignant breast cancer line MCF-12A. Revealed to inhibit the proliferation of DU-145, MCF-7 and MCF-12A cells. Low IC_{50} values were reported, 30 µg/mL and 31 µg/mL, when tested against MCF-7 and MCF-12A cancer cells, respectively.	[31,47].
D. schinzii	Leaves	Methanol	anti-biofilm	Inhibited *Pseudomonas aeruginosa* biofilm by 67.3% and is expected to help fight biofilm infections involving this bacterium and moderately eradicated *Streptococcus mutans* ATCC 25175 by 44.2%.	[53]
D. tomentosa	Whole plant	methanol and dichloromethane extract	Antiplasmodial	Showed promising antiplasmodial activity of $IC_{50} < 50\ \mu g/mL$	[24]



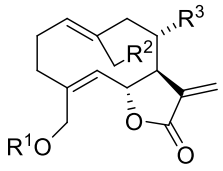
Germacrene D (5)



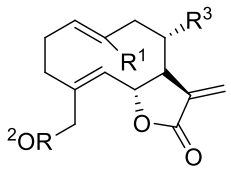
β-farnasene (6)

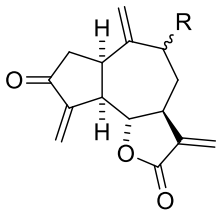


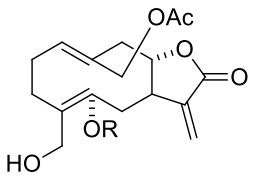
α-humulene (7)



	8	9	10	11	12	13	14	15	16	17	18
R^1	H	Ac	Ac	H	Ac	H	Ac	H	Ac	Ac	Ac
R^2	OH	OH	OAc	OAc	H	OH	OH	OAc	OAc	H	OAc
R	OAc	OAc	OAc	OAc	H	H	H	H	H	OH	OH





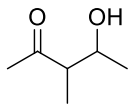


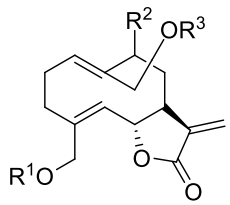
	19	20	21	22
R^1	CHO	CH_2OAc	CH_2OAc	CH_2OAc
R^2	Ac	Ac	H	Ac
R^3	H	OH	H	H

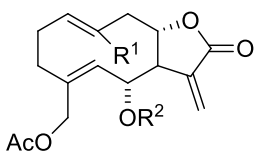
23 R= H
24 R= a-OH
25 R= B-OH

26 R= Ac
27 R= Tigl
28 R= Mebu

29 R=



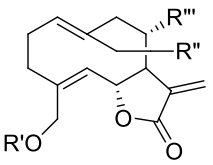




	30	31	32	33	34
R^1	H	/Bu	H	Ac	H
R^2	OH	OH	OAc	OAc	H
R^3	/Bu	/Bu	/Bu	/Bu	/Bu

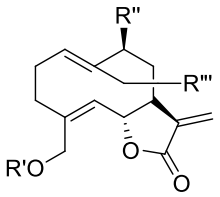
	35	36	37	38
R^1	CH_2OAc	CH_2OAc	CHO	CHO
R^2	CH_2OAc	CH_2OAc	CHO	CHO

Fig. 2. Structures of common sesquiterpenes, germacranolide-type, melampolide-type, eudesmanolide-type sesquiterpene lactones isolated from *Dicoma* species ([9], b, [8,24,49,56]).



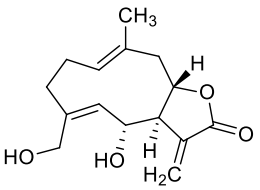
	39	40	41	42	43	44	45	46	47	48	49	50	51	52
R'	H	H	Ac	Ac	H	Ac	Ac	H	Ac	Ac	Ac	H	H	H
R''	OH	OH	OH	OAc	OR^1	H	OH	OAc	OAc	H	OAc	OAc	OAc	OAc
R'''	H	OAc	OAc	OAc	OAc	H	H	H	H	OH	OH	OAc	OR^2	OR^3

OR^1 = OCOCH(Me)CH(OH)Me $OR^2 = OCOC(CH_3)CHCH_3$ $OR^3 = OCOCH(CH_3)CH_2CH_3$



	53	54	55	56	57
R'	H	i-Bu	H	Ac	H
R''	OH	OH	OAc	OAc	H
R'''	i-Bu	i-Bu	i-Bu	i-Bu	R'

R' = $COC(CH_3)CH_2$



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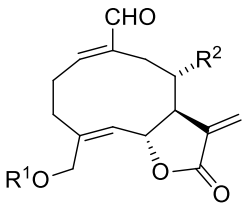
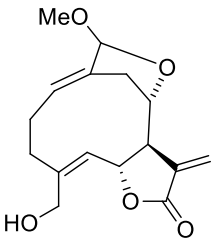
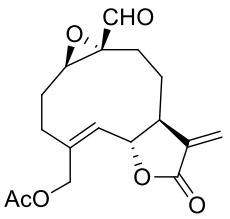


	59	60	61	62
R^1	H	Ac	Ac	Ac
R^2	OH	OH	H	H



63



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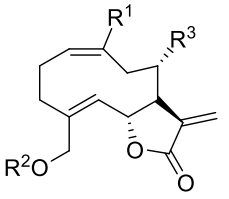
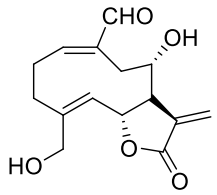


	65	66	67	68	69
R^1	CHO	CHO	CH_2OAc	CHO	CHO
R^2	H	Ac	H	Ac	H
R^3	H	OH	H	Ac	H



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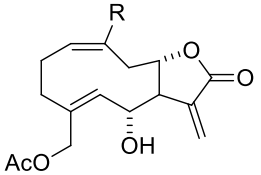
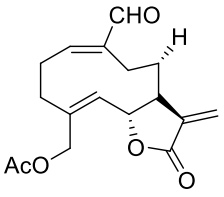
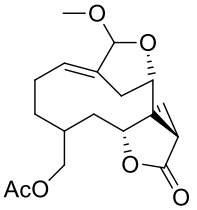


71 R= CH_2OAc

72 R= CHO

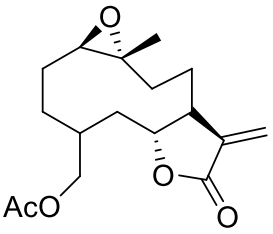


73



74

Fig. 2. Continued



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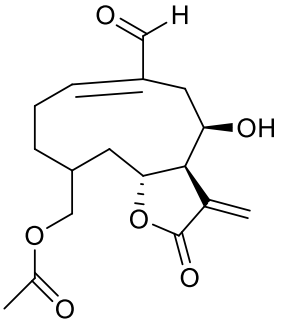
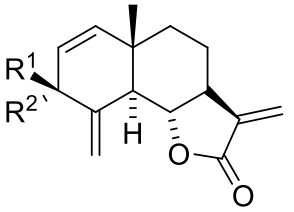
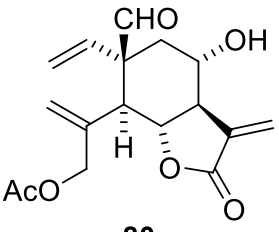


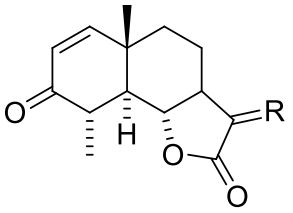
76



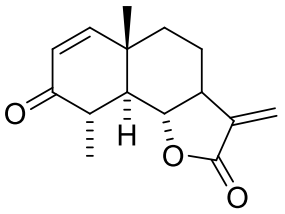
	77	78	79
R^1	H	H	=O
R^2	H	H	=O



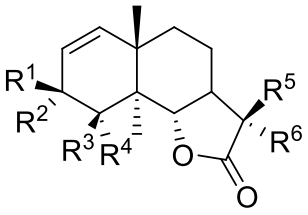
80

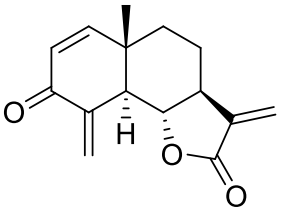


81 R= CH_2
82 R= a-Me, H
83 R= B-Me, H



84





91

	85	86	87	88	89	90
R^1	=O	=O	=O	=O	H	H
R^2	-	-	-	-	OH	OAc
R^3	H	H	H	-	-	-
R^4	Me	Me	Me	$=CH_2$	$=CH_2$	$=CH_2$
R^5	Me	H	-	-	-	-
R^6	H	Me	$=CH_2$	$=CH_2$	$=CH_2$	$=CH_2$

Fig. 2. Continued

Table 3
Pharmacological activity compounds isolated from *Dicoma* species.

Plant species	Compound	Activity tested	Effect	Reference
D. anomala	23	Antiprotozoal	Showed 75% inhibition at 33 μM of human recombinant GSTP1-1	Mukunganyama et al., 2011 [34]
		Antifungal	Possess antifungal properties at GI50= 30 μM	[16]
		Leishmanicidal	Inhibited, *in vitro*, the growth of 12 strains of *Leishmania* and 15 strains of *T. cruzi* at concentrations between 50 and 2.5 μg/mL	[16]
D. temantosa	76	Anti-plasmodial	Exhibited anti-plasmodial activity (IC_{50}) <1 μg/mL) against both 3D7 and W2 strains, and to be toxic with a selective index (SI) of 3.3	[24]
D. schinzii O. Hoffm. and *D. anomala* Sond. subsp. *cirsioides* (Harv.) Wild.	91	Anti-cancer	Showed anticancer activity (growth inhibitory 50% (GI_{50}) = 17,9 μM) in a 60-cell line panel comparable to parthenolide,	[49]
		Antiplasmodial	Showed in vitro inhibitory activity against P. falciparum, IC_{50} (D_{10}) = 0.38 μg/mL, IC_{50} (Ki)= 0.06 μg/mL)	[49]

Eudesmanolide-type sesquiterpene lactones

Phytochemical investigation of the roots part and the aerial parts of *D. capensis* afforded three eudesmanolides **77-79**, which are presented in Fig. 2. Compound **80** was isolated from the aerial parts of *D. tomentosa*. Sesquiterpene lactones **81-82,** 11β,3-dihydrotubiferin **83** and **84** were isolated from *D. anomala* Sond. subsp. *cirsioides* (Harv.) Wild. Investigation of the roots of *D. schinzii* O. Hoffm. afforded compounds **81, 82** and **84**. The roots of aerial parts of *D. anomala* Sond subsp. *cirsioides* (Harv.) Wild. yielded compounds **85-88**. Compounds **89-90** were isolated from the aerial pats of *D. capensis*. Compounds **85-88** were also isolated from the roots *D. schinzii* O. Hoffm. Dehydrobrachylaenolide **91** was isolated from the roots of *D. schinzii* O. Hoffm. and *D. anomala* Sond. subsp. *cirsioides* (Harv.) Wild. [9,10,49,56].

Pharmacological activity of compounds isolated from *Dicoma* species

The sesquiterpene lactones dehydrobrachylaenolide and guaianolide dimer from *D anomala* were identified [49]. However, dehydrobrachylaenolide exhibited highest activity (IC_{50} (D_{10}) = 0.38 μg/mL, IC_{50} (Ki)= 0.06 μg/mL) and i*n vitro* IC_{50} of 1.865 μM against a chloroquine-sensitive strain (D_{10}) of *P. falciparum* [49]. Dehydrobrachylaenolide **91** (Table 3) showed anticancer activity (growth inhibitory 50% (GI_{50}) = 17,9 μM) in a 60-cell line panel comparable to parthenolide, a sesquiterpene lactone currently used in the clinical development as amino derivative [49]. a sesquiterpene lactone that is currently in clinical trials.

Conclusion

The aim of this review was to draw attention to the genus *Dicoma* focusing on phytochemicals, ethnomedicinal and pharmacology of sesquiterpene lactones (SLs) and anticancer activities due to the functional moiety, α-methylene-γ-lactone. The review summarised the SLs in general and the importance of SLs in terms of the biological activities, specifically on cancer activities. Some of the SLs currently in clinical trials were isolated from genera that are not *Dicoma* genus but from the same family, Astereaceae. This review highlights information on SLs mechanism or mode of action and the therapeutic abilities of such compounds including anticancer activities.

Findings analysed and reported in this review were based on medicinal traditional uses, phytochemical investigation and modern pharmacological methods. The results revealed that *Dicoma* genus is of considerable importance due to its traditional medicinal benefits and the diverse species of this genus possess secondary metabolites that exhibit ability to treat various diseases.

The plant species of genus *Dicoma* are used traditionally for treating bladder infections, kidneys, back pains, nausea, influenza, colds, cancer, diarrhoea, constipation, cough, cardiovascular disorders, infertility, fever, venereal diseases, tooth aches, sores, dizziness, wounds, dysentery, and diabetes mellitus [7,21,49,50].

Modern pharmacological studies revealed that *Dicoma* species exhibits a variety of activities such as antibacterial, anti-helminthic, antiviral, antiplasmodial, antispasmodic, anticancer, analgesic, antiinflammatory and wound healing [21,24,46]. In particular, the anticancer activities of genus *Dicoma* were of much attention in recent years.

The results revealed that there are more than eighty sesquiterpene lactones isolated from *Dicoma* species. After evaluation of the publications, some gaps were identified in the literature from a pharmacological perspective, which need to be taken into consideration for further research on the genus *Dicoma*. The review of literature found that some compounds including sesquiterpene lactones were isolated without bio-guided fractionation methods and screening. This may be attributed to the fact that some sesquiterpene lactones were isolated in the 80's and in that period screening of extracts and compounds was not exceptional, or due to high cost of screening the compounds and extracts, or toxicological and pharmacological studies were scarce.

The studies reported to date showed that when the screening was carried out, it was mainly focused on the crude extracts and fractions and there were few reports on the results of pure compounds. There are a few sesquiterpene lactones that were tested for their anticancer activity from *Dicoma* species and other therapeutic areas. Furthermore, it was observed that there is only one patent so far from genus *Dicoma*, the invention includes antiplasmodial activities for both human and animals [65].

A broader look at sesquiterpenes revealed that sesquiterpene lactones are important due to their biological activities. Some SLs including parthenolide that was isolated from a plant species of Asteraceae family was tested in clinical trials. It was further discovered that SLs are amongst the largely studied cytotoxic sesquiterpenoids. The structure-activity relationships showed that the α-methylene-γ-lactone moiety is often, though not always, necessary for cytotoxicity. It was reported that the important target protein for SLs cytotoxic activity is NF-kB.

Reviewing SLs revealed promising candidates for drug discovery and whether the SLs are selective towards tumours needs further investigation. SLs remain lead compounds of great interest despite limited exploration on those that are in clinical trials such as parthenolide. The pharmacological test of SLs supports the knowledge that says SLs-containing plants are known to induce contact dermatitis in exposed farm workers and can cause several toxic syndromes in farm animals. This information makes it necessary to synthesize more bioavailable and safe SLs and conduct pharmacological tests on the improved SLs analogues. Therefore, further studies of screening extracts, isolation and identification of compounds, performing pharmacological studies on isolated compounds, synthesis, and development of suitable delivery systems followed with clinical and toxicological efficacy trials remain to be explored. The studies will be helpful for modern drug development and may serve the purpose of drug formulation development in treating disease such as cancer and to improve clinical safety reliability and efficacy. The plant species of *Dicoma* can be utilised as affordable sources of active therapeutics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

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