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Review Article

A Review: Understanding the Impact of Cancer During the Search of Safe and Affordable Medicinal Plants. A Need for In Vivo Investigation for the Safety Aspect of *Asparagus Laricinus*?

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ABSTRACT

The understanding of the initiation, progression, and predictions about the burden of cancer are of importance during the scientific race for the discovery of much safer and cheap medicinal plants. The world population mostly relies on medicinal plants for the treatment of infections and diseases due to ongoing economic constraints and growing poverty. This review study seeks to establish the what the literature reported and the true extent to which *Asparagus laricinus* is being studied for safe use. Studies indicate how cancer spreads and affects the different organs in the body. Most studies on medicinal plants are performed invitro with few concentrating to in vivo due to ethical requirements during the use of animal rats. Literature does not reveal any previous toxicological studies for *Asparagus laricinus* per se in vivo, but several studies were performed on other medicinal plants used for the treatment of cancer. The safety aspects certain palnts were established for example *Moringa oleifera* and *Lithocarpus dealbata* were found to have no mortality or any visible signs of acute toxicity, while serum biochemistry tests did not reveal any noticeable changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol (CHOL) and protein levels in animals. While in vivo showed high dose of toxicological studies on *Moringa oleifera* have indicated to cause severe hepatotoxicity and organ damage. The acute lethality (LD50) test has been found to be relatively safe with subchronic toxicity studies, eliciting no significant difference in sperm quality, haematological and biochemical parameters in the treated rats, as compared to the controls . Both studies engaged the use of laboratory experimental animal models to evaluate the toxicology of plant extracts. With the growing interest in the use of *Asparagus laricinus* in Botswana, South Africa, Lesotho and Swaziland for the treatment of infections and diseases, there is a need to correlate the published data with the in vivo data which is very scares current.

Keywords: Impact of cancer, Asparagus laricinus, burden of cancer.

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OVERVIEW OF CANCER

One of the most prominent diseases in humans today is cancer. Cancer is a generic term used for a large group of diseases that can affect any part or organs of the body. It is also referred to as malignant tumours or neoplasms. It is a group of diseases characterized by uncontrolled cell growth beyond their usual boundaries; which can invade adjoining parts of the body and spread to other organs. The process of spreading to other organs is referred to as metastasis and is the major cause of death from cancer[1].

Cancer arises from a single cell. The transformation from normal to a tumour is a multistage process, typically from pre-cancerous to malignant tumours. The changes are the results of the interaction between an individual's genetic makeup and three categories of external or environmental factors, viz.:

- biological carcinogens, such as viral, bacterial or parasitic infections,
- chemical carcinogens, e.g. asbestos, aflatoxin, components of smoke or arsenic; and
- physical carcinogens such as ultraviolet and ionizing radiation.

Generally, cancer begins after a mutational episode in a single cell and then it progressively transforms to malignancy in multiple stages through sequential acquisition of additional mutations[2]. In view of the fact that these initial events are the underlying causes of the whole progression of carcinogenesis, their inhibition would therefore be an efficient preventive measure[3].

Phases in the development of cancer

Cancer develops in several phases, depending on the type of tissue affected. Typically, these phases are dysplasia, cancer *in situ*, localized invasive cancer, regional lymph node involvement, and distant metastases[4]. The first indication of abnormality is a change in the character of cells, known as dysplasia. The term "carcinoma *in situ*" is used when microscopic examination discloses cells with certain characteristics of cancer, that is, changes in the cell nuclei, but with no penetration of the underlying membrane that holds them in the tissue of origin. When the abnormal cell growth reaches areas underlying the tissue of origin, the cancer is regarded as invasive. With further growth, there is increasing invasion and destruction of adjacent tissues. Often, the cancer extends to the regional lymph nodes that drain the area. Cancer cells may also spread through the blood or lymphatic system to affect other organs (distant metastases).

With sufficient multiplication of abnormal cells, the cancer becomes apparent to the individual or to the

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physician. It commonly takes the form of a lump that may be seen or palpable in the organ involved, for example skin, breast, or prostate. Sometimes, even before detection, the cancer will have spread to lymph nodes or, if rapidly progressive, will have already caused detectable distant metastases. Figure 1 summarizes processes or stages in cancer development. The growth of the cancer can involve blood vessels and cause bleeding, which will be apparent if the cancer reaches part of an organ that is in direct or indirect contact with the exterior. For example, there may be blood in the sputum from lung cancer, blood in the stools from bowel cancer, or blood in the urine from bladder cancer. The growth of a cancer may also cause functional disturbances. For example, cancer of the brain may give rise to neurological symptoms and signs.

Burden of Cancer

According to the WHO, cancer is the leading cause of death worldwide and accounted for 8.2 million deaths (around 14% of all deaths) in 2012[5]. The major causes of death are cancer of the lung, liver, stomach, breast and colorectal cancer. The distribution in terms of causes of mortality differs between males and females and also varies between developing and developed countries. Table 1 indicates the global and regional patterns of death by cause, as captured by the World Health Organization (2001)[5].

Cancer remains a major obstacle to the overall public health in the more developed regions such as Europe and North America, as indicated in Table 1. More than 60% of the world's total new annual cases occur in Africa, Asia and Central and South America. These regions account for 70% of the world's cancer deaths[6]. Although cancer is not a major problem for Africa, medicinal plants found throughout Africa may be a solution to developed countries in terms of providing plants (as herbs) or in identifying novel chemotherapeutic agents in plants.

The following tables indicate the top 20 cancer deaths by cause for the population of South Africa for the year 2000. Table 2 clearly demonstrates that tracheal, bronchial and lung cancers are the major causes of death (16.5%) in the overall population, followed by oesophageal (13.3%) and cervical (8.3%) cancers respectively.

Tables 3 and 4 categorize the causes of death by gender, male and female respectively. In Table 3 the picture remains the same for the number one and two causes of death, i.e. tracheal, bronchial and lung cancers; and oesophageal cancers which represent 21.9% and 16.7% of the male population respectively. Prostate cancer moves from the seventh position to third in the male population.

In Table 4, breast cancer leaps from the fourth to the first position in the female category. This represents 17.2% of the female population, followed by breast cancer (15.5%) and tracheal, bronchial and lung cancers (10.9%) in the third position. As mentioned earlier, Mashele & Kolesnikova (2010) have demonstrated *in vitro* antimutagenicity of *Asparagus laricinus* extracts against breast cancer (MCF7), which is the second major cause of death within the female population[8].

Global cancer projections and the strategies to curb the growing numbers.

It was projected that the annual cancer burden would rise from 14 million in 2012, to 22 million within the next two decades. The World Health Organization (WHO, 2005) also projected an escalation in deaths from cancer, with an estimated 9 million deaths in the year 2015, and 11.4 million deaths by 2030[9].

Primary prevention measures, early detection mechanisms and cure are needed for Africa's cancer burden (715,000 new cases and 542, 000 deaths in 2008), a burden projected to double by 2030 due to demographic changes alone. Figure 2 illustrates the escalation in deaths caused by cancer in both developed and developing countries throughout the globe, as projected by the World Health Organization[10].

Currently, there is marked scientific and commercial interest in the continuing discovery of new anti-cancer agents from natural product

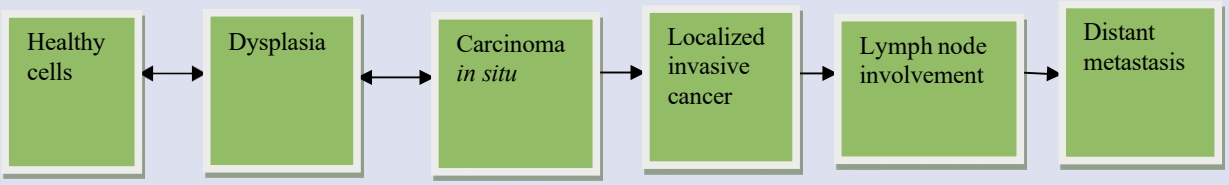

Figure 1. Typical phases or stages of cancer development.

Table 1. Global and regional patterns of annual deaths, by cause, 2000.

Deaths from all causes(thousands)		Deaths from infectious and parasitic diseases (%)	Deaths from cancer (%)	Deaths from circulatory diseases (%)	Perinatal deaths (%)	Deaths from injury (%)	Deaths from other causes (%)
World total	55694	25.9	12.6	30	4.4	9.1	18
More developed countries	13594	6.1	21.6	47.9	0.7	7.9	15.9
Less developed countries	42100	32.3	9.8	24.2	5.6	9.5	18.7
Africa	10572	61.7	5.1	9.2	5.5	7.1	11.5
South and Central America	3097	14.6	14.1	28.5	4.3	12.3	26.2
North America	2778	6.3	23.8	41.1	0.6	6.4	21.9
Middle East	4036	32.1	6.1	26.9	7.5	8.4	19.1
South East Asia	14157	29.9	8.1	28.9	7.1	9.7	16.4
Western Pacific	11390	10.6	18.6	31.2	2.8	10.7	26.1
Europe	9664	5.4	19.8	51.5	0.8	8.5	14.1

Source: The World Health Report 2001[7].

Table 2. Number of deaths due to different cancers in the year 2000 for South Africa.

All persons		
Rank	**Cause of Death**	**Deaths**
1	Tracheal, Broncheal and Lung cancer	6885
2	Oesophageal cancer	5579
3	Cervical cancer	3498
4	Breast cancer	3206
5	Liver cancer	2651
6	Colorectal cancer	2567
7	Prostate cancer	2524
8	Stomach cancer	2348
9	Pancreatic cancer	1541
10	Leukaemia	1465
11	Mouth and Oropharyngeal cancer	1386
12	Lymphoma	1032
13	Laryngeal cancer	746
14	Bone and Connective tissue cancer	707
15	Ovarian cancer	691
16	Bladder cancer	673
17	Uterine cancer	638
18	Brain cancer	527
19	Melanoma	437
20	Kidney cancer	427
All cancers		41657

(Source: Cancer Association of South Africa)

Table 3. Number of deaths due to different cancers in the year 2000 for males.

Males		
Rank	**Cause of Death**	**Deaths**
1	Tracheal, Broncheal and Lung cancer	4669
2	Oesophageal cancer	3566
3	Prostate cancer	2524
4	Liver cancer	1666
5	Stomach cancer	1386
6	Colorectal cancer	1157
7	Mouth and Oropharyngeal cancer	985
8	Leukaemia	818
9	Pancreatic cancer	789
10	Laryngeal cancer	633
11	Lymphoma	601
12	Bladder cancer	469
13	Bone and Connective tissue cancer	360
14	Brain cancer	274
15	Kidney cancer	233
16	Melanoma	233
17	Non-Melanoma skin cancers	158
18	Breast cancer	50
All cancers		**21361**

(Source: Cancer Association of South Africa)

sources[11]. More than 50% of drugs used in clinical trials for anticancer activity, were isolated from natural sources or are related to them[12]. Hence, the search for natural products to be used in cancer therapy represents an area of great interest in which the plant kingdom is the most important source, providing many anti-tumour agents with novel structures and unique mechanisms of action[13].

Present chemotherapy cancer treatments have proved to be ineffective as a result of their toxicity and cells developing resistant[14]. Many conventional drugs also induce genetic damage that itself can be carcinogenic[15]. A segment of the research community is thus focusing on identifying novel chemotherapeutic agents in plants that do not induce the destructive effects of conventional cytotoxic therapeutic agents. Table 5 below illustrates examples of side effects of some conventional drugs:

Cancer and medicinal plants

Knowledge about the medicinal value of many plants that form part of the rich biodiversity in South Africa is largely contained in the oral traditions of the various ethnic groups that constitute the indigenous people of South Africa[16].

Several medicinal plants are traditionally used in the treatment of a variety of ailments, including cancer in many communities of South Africa and neighbouring countries. Since ancient times, herbal medicine has always been one of the main components of the healthcare system. Despite the range of medicinal plants used and the rich biodiversity of South Africa, only a relatively small number of plant species have been scientifically validated for safety and efficacy[17].

Traditional medicine has been a fertile source for revealing novel lead molecules, which are then subjected to investigation using the techniques of modern drug discovery[18]. In fact, modern pharmaceutics have benefited from medicinal plants (Table 2.6). Although discovered through serendipitous laboratory observation, three of the major sources of anticancer drugs on the market, or completing clinical trials, were derived from North American plants used medicinally by Native Americans: the Papaw (Asimina spp), the Western Yew Tree (Taxus brevifolia), effective against ovarian cancer and the May-apple (Podophyllum peltatum) used to combat leukaemia, lymphoma, lung and testicular cancer[19].

Interestingly, of the 877 novel medicines that were developed in the period 1981-2002, 6% were natural products, 27% were derivatives of natural products and 16% were synthetics developed on the model of a natural product[20]. This demonstrates that nature is an important source

Table 4. Number of deaths due to different cancers in the year 2000 for Females.

Females		
Rank		**Deaths**
1	Cervical cancer	3498
2	Breast cancer	3156
3	Tracheal, Broncheal and Lung cancer	2216
4	Oesophageal cancer	2013
5	Colorectal cancer	1410
6	Liver cancer	986
7	Stomach cancer	962
8	Pancreatic cancer	752
9	Ovarian cancer	707
10	Leukaemia	647
11	Uterine cancer	638
12	Lymphoma	431
13	Mouth and Oropharyngeal cancer	401
14	Bone and Connective tissue cancer	331
15	Brain cancer	253
16	Bladder cancer	204
17	Melanoma	203
18	Kidney cancer	176
19	Laryngeal cancer	114
20	Non-Melanoma skin cancers	108
All cancers		**20296**

(Source: Cancer Association of South Africa)

Table 5. Excerpt of Table of Major Chemotherapy Drugs and Hormones (modified from Mora & Potts, 2003).

Name and Use	Common Side Effects	Occasional Side Effects
Aminoglutethimide (Cytrdren, Elitpen). An aromatase inhibitor used in adrenal and prostate cancers. May be used as medical adrenalectomy in breast cancer. Given as a tablet.	Skin rash with fever, sluggishness and tiredness (usually goes away slowly within 4 to 6 weeks after treatment is finished).	Dizziness, swelling of face, weight gain, leg cramps, fever, chills and sore throat, loss of appetite, mild nausea and vomiting, leg cramps.
Cyclophosphamide(Cytoxan, Neosar, Endoxan) An alkylating agent used in lymphomas and Hodgkin's disease, myeloma, neuroblastoma, retinoblastoma, sarcomas, Wilms' tumor, cancers of the ovary, breast, prostate, head and neck, lung, bladder, cervix, stomach and uterus. Given IV or as a tablet.	Nausea, vomiting, loss of appetite, loss of hair. (The patient) needs to drink extra liquids to prevent bladder problems. If (the patient) misses a dose, they *should not* double the next dose, but should talk with one's doctor.	Blood in urine, pain when urinating, black tarry stools, fever, chills, nasal stuffiness and sore throat, cough and shortness of breath, dizziness, confusion, fast heartbeat, sterility (may be temporary), skin darkening, metallic taste during injection, blurred vision, cataract, second cancers (leukemia, bladder).
Doxorubicin (Adriamycin, Rubex, Adriamycin RDF, PFS or MDV) An antitumor antibiotic used in leukemias, lymphomas, Wilm'stumor, neuroblastoma, multiple myelomas, sarcomas, cancers of the breast, ovary, bladder, thyroid, stomach, cervix, endometrium, liver, esophagus, head and neck, pancreas, prostate, testes and lung. Given IV.	Nausea and vomiting, red urine (usually lasts one or two days after each dose), hair loss, loss of appetite, heart problems.	Mouth sores, darkening of soles, palms or nails, may reactivate skin reactions from past radiation, fever, chills and sore throat, diarrhea, eye problems, fast or irregular heartbeat, shortness of breath, pain in joint, side or stomach, burning pain at injection site.
Fluorouracil (Adrucil, 5-FU, 5-Fluorouracil, Efudex) An antimetabolite used in cancers of the stomach, colon, rectum, breast, pancreas, bladder, cervix, endometrium, esophagus, head and neck, liver, lung, ovary and skin. Usually given IV, except for skin, where a cream is used.	Nausea, mouth sores, diarrhea, skin darkening (sensitive to sun).	Mouth, tongue or lip sores, hair loss, skin rash or dryness, vomiting, poor muscle coordination, swelling of palms and soles, nail loss or brittle nails, eye irritation, increase of tears, blurred vision, headache, euphoria.
Methotrexate (Folex, Folex PFS, Mexate, Mexate-AQ, Abitrexate, Rheumatrex) An antimetabolite used in choriocarcinoma, hydatiform mole, multiple myeloma, leukemia, lymphomas, sarcomas, cancers of the breast, head and neck, lung, bladder, brain, cervix, esophagus, kidney, ovary, prostate, stomach and testes. Given IV most commonly, in the muscle, or as a tablet.	Mild nausea and vomiting, diarrhea, mouth sores. (The patient) should not take more or less than the amount prescribed by the doctor. If a dose is missed, the next dose should *not* be doubled and the physician should be consulted. (The patient) may need to drink extra liquids to prevent kidney problems. (The patient) should *not* take aspirin or other medicine for swelling or pain without first checking with the physician. When very high doses are given, it is followed by the drug leucovorincalcium to counteract life- threatening side effects (called leucovorin rescue).	Loss of appetite, stomach pain, yellowing of eyes or skin, fever, chills and sore throat, cough, shortness of breath, blood in urine or dark urine, hair thinning, headache, dizziness, blurred vision, drowsiness or confusion, joint pain, skin rash, reddening of skin (sensitive to sun) anemia, flank pain, blurred vision, confusion, seizures.
Tamoxifen (Nolvadex, taxomifen citrate) Anantiestrogen used in breast cancer. Given as a tablet.	Hot flashes, vaginal discharge. (The patient) should not take more or less than the amount prescribed by the physician. If (the patient) misses a dose, she should not take the missed dose at all and should not double the next dose; she should consult with her doctor. The patient should use birth control while taking tamoxifen, but she should not take birth control pills since they may change the effects of the tamoxifen. If she should become pregnant while taking tamoxifen, she should consult with her physician immediately	Vaginal bleeding, dryness or itching, nausea, and vomiting, loss of appetite, irregular menstrual periods, hot flashes, endometriosis, bone and tumor pain, visual changes skin rash and itchiness, dizziness, loss of hair, depression, light- headedness, confusion, fluid retention, headache, anemia, swelling of legs, loss of appetite, blood clots, increased risk of uterine cancer.
Vincristine (Oncovin, Vincasar PFS, leurocristine) A plant alkaloid used in leukemia, lymphomas, sarcomas, neuroblastoma, Wilms' tumor, melanoma, multiple myeloma, cancers of the colon, rectum, brain, breast, cervix, ovary, lung and thyroid. Given IV.	Hair loss, numbness or tingling in hands or feet.	Pain in arms, legs, jaw or stomach, pain in testicles, mouth sores, fever, chills and sore throat, severe constipation, metallic taste, hoarseness, agitation, confusion, light-headedness, dizziness, drooping eyelids, jaw or joint pain, blurred or double vision, anemia, stomach cramps.
Temodal Brain cancer **Vectibix** Colorectal cancer Cisplatin Ovarian, testicular and bladder cancer	Blood and bone marrow problems, hair loss, nausea vomiting, diarrhoea Metabolic problems, blurred vision, back pain, hair loss, coughing, breathing difficulties, difficulty in sleeping Neurotoxicity, deafness	

Table 6. Botanical drugs used in traditional medicine, and from which useful modern drugs were produced.

Botanical names	English names	Indigenous use	Origin	Uses in Biomedicine
Adhatodavasica	-	Antispasmodic, antiseptic, insecticide, fish poison	India, Sri Lanka	Antispasmodic, oxytocic, cough suppressant
Catharanthusroseus	Periwinkle	Diabetes, fever	Madagascar	Cancer chemotherapy
Condrodendrontomentosum	-	Arrow poisoning	Brazil, Peru	Muscular relaxation
Gingko biloba	Gingko	Asthma, anthelmintic (fruit)	Eastern China	Dementia, cerebral deficiencies
Harpagophytumprocumbens	Devil's claw	Fever, inflammatory conditions	Southern Africa	Pain, Rheumatism
Piper methysticum	Kava	Ritual stimulant, tonic	Polynesia	Anxiolytic, mild stimulant
Podophyllumpeltatum	May apple	Laxative, skin infections	North America	Cancer chemotherapy, warts
Prunusafricana	African plum	Laxative, 'Old man's disease'	Tropical Africa	Prostate hyperplasia

Source: A. Gurib-Fakim / Molecular aspects of medicine 27 (2006) 1-93[19]

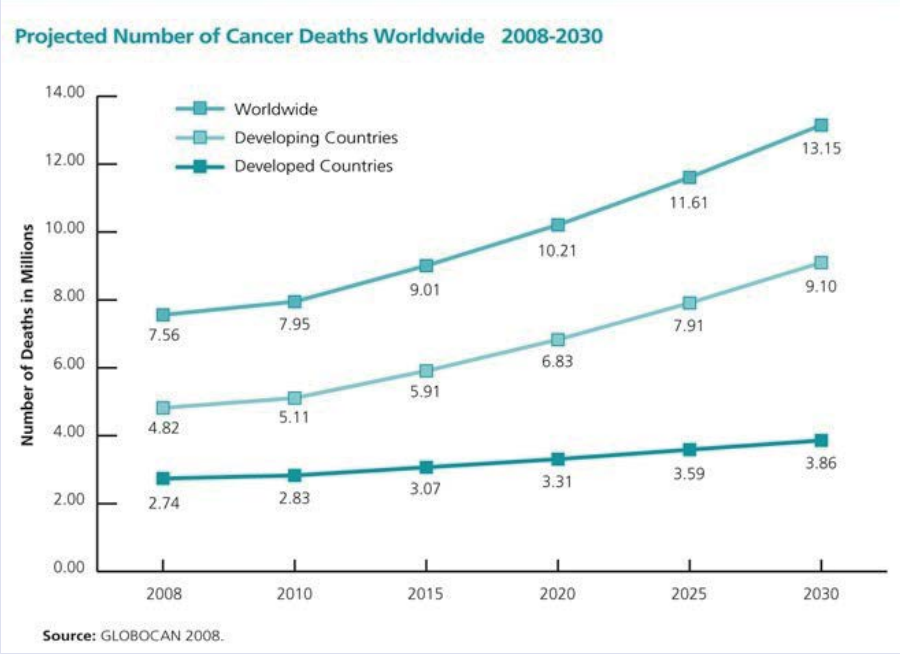

Figure 2. Global cancer death projections (2008 - 2030).[10]

for developing novel leads for medicines. Even when new chemical structures are not found during drug discovery from medicinal plants, known compounds with new biological activity can provide important drug leads.

Currently, over 85, or 48.6%, of drugs used in clinical trials for anticancer activity, are actually derived from natural products or are natural products[21]. This demonstrates the rationale for the search for novel drug molecules in medicinal plants, especially when literature shows that plant-derived compounds have provided attractive possibilities for treatment strategies[22].

Asparagus laricinus

Asparagus laricinus, belonging to Asparagaceae family, is a monogeneric family, which was previously included within the Liliaceae family[23]. It belongs to the family of Asparagaceae, a monocot and a member of the order Asparagales, and possesses great diversity throughout Africa, especially in South Africa. This plant is commonly known as Lesitwane among the Batswana clans in South Africa.

Asparagus (Asparagaceae) is highly diverse with hermaphroditic and unisexual taxa, a variety of growth forms (herbs, shrubs, and vines), and vegetative morphology (phylloclade morphology, presence or absence of spines)[24]. The genus *Asparagus* comprises approximately 100 species and consists of herbs, shrubs and vines.

Asparagus laricinus is part of the traditional medicine used in many parts of South Africa for the treatment of several ailments. Examples of its use include its roots for the treatment of tuberculosis, and its use as a diuretic in the Khoi-San and Cape Dutch ethnobotany[25]. In the North West province, the roots are used for treatment of sores, redwater, urinary infections, umblical cord inflammation and general ailments by Setswana-speaking people[16]. The leaves and stem are medicinally used in South West parts of Gauteng[26].

Many of these herbs, including *Asparagus laricinus,* have not yet been scientifically assessed for their efficacy or safety to tissue or organs of recipients *in vivo*. Several studies showed that *Asparagus laricinus* polyphenol extract exhibited a dose- dependent antimutagenic ability in vitro[15]. The plant extract showed no mutagenic effect on all tested *Salmonella typhimurium* bacteria strains *in vitro*. Previous *in vitro* studies on *Asparagus laricinus* extracts have demonstrated anticancer activity against three human cell lines namely, breast MCF7, renal TK10 and melanoma UACC62[8,27].

These cell lines were selected because of their high sensitivity to detect anticancer activity. Thus, investigation of traditionally used medicinal plants is valuable as a source of potential chemotherapeutic agents, and also to assess the safety of the continuous use of medicinal plants. As a result, most studies are being directed at popular medicine, with the aim of identifying natural products which exhibit therapeutic properties[28].

As some of the active ingredients are potentially toxic, there is a need to evaluate the safety of plant preparations. These necessitate further studies on *Asparagus laricinus* extracts, such as toxicity, adverse effects investigations, as well as *in vivo* biological studies using animal models.

Previous toxicology studies on medicinal plants

Although plant extracts have been used in the treatment of diseases according to knowledge accumulated over centuries, scientific research has shown some substances present in these medicinal plants to be potentially toxic and carcinogenic[29]. Investigation of traditionally used medicinal plants is thus valuable on two levels: firstly, as a source of potential chemotherapeutic drugs, and secondly, as a measure of safety for the continued use of medicinal plants[30]. The latter is the area of concern for the researcher, since *Asparagus laricinus* has been used in folk medicine for the treatment of cancer for years.

Literature does not reveal any previous in vivo toxicological studies for *Asparagus laricinus* per se, but several studies were performed on other medicinal plants used for the treatment of cancer. Arun & Tangpu demonstrated that *Lithocarpus dealbata* showed no mortality or any visible signs of acute toxicity, while serum biochemistry tests did not reveal any noticeable changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol (CHOL) and protein levels in animals[31]. Toxicological studies on *Moringa oleifera* have indicated an absence of severe hepatotoxicity and organ damage, except in very high doses. The acute lethality (LD50) test has been found to be relatively safe with subchronic toxicity studies, eliciting no significant difference in sperm quality, haematological and biochemical parameters in the treated rats, as compared to the controls[32-34]. Both studies engaged the use of laboratory experimental animal models to evaluate the toxicology of plant extracts.

Asparagus laricinus being native in Botswana, South Africa, Lesotho and Swaziland and mostly used for the treatment tuberculosis, sores, uterine infections and many more, makes the in vivo studying of this plants more important to ascertain its safety during its usage.

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ETHICAL CONSIDERATION

No ethical consideration is needed for this paper because there is no intervention in humans or animals in this paper.

DATA AVAILABILITY

The article contains all the necessary material to support this paper, no supplementary data needed.

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