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METABOLITES OF *ABRUS PRECATORIUS* TARGETING MULTIPLE ONCOGENIC AND ONCO-SUPPRESSIVE SIGNALING FOR CANCER PREVENTION AND INTERVENTION

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Review

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ABSTRACT

Cancer remains as the subsequent cause of death in the contemporary society trailing after heart disease. *Abrus precatorius*, a vine of the Fabaceae family, has proven to be immensely beneficial in cancer management. Its seeds, leaves androots are rich source of phytochemicals such as terpenoids, alkaloids, lectin proteins, flavonoids, tannins and phenolic compounds. These metabolites possess a plethora of properties such as anti-cancer, anti-angiogenic, antioxidant, anti-inflammatory *etc.* This review takes a comprehensive and critical look at the evidence on *Abrus*-derived metabolites in cancer therapy. It reviews the results of preclinical (*in-vitro* and *in-vivo*) investigations on the therapeutic potential of *A. precatorius* metabolites targeting a wide range of malignancies including those of the gastrointestinal tract, breast, gynaecological related, urogenital cancer *etc*. The review also explores the existing limitations and concerns in this field, as well as the post-analysis recommendation to guide future research.

Keywords: Abrin, *Abrus precatorius*, cancer, chemotherapeutic, chemopreventive, molecular targets, phytochemicals

INTRODUCTION

Cancer ranks among the top most causes of mortality as well as a significant and a key barrier to life expectancy across every nation around the globe. Cancer incidence and mortality data are only available for the years 2018 and 2019 whereas access to care has been hampered attributed to the health-care facility's closure. COVID-19 exposure concerns and closures hindered the screening and management, which could result in a temporary reduction in cancer rates, accompanied by an increase in advanced-stage disease and, ultimately, increased mortality. Statistics reveal that 19.3 million new cases of cancer were diagnosed and roughly 10.0 million deaths were reported due to cancer worldwide in 2020. Demographic changes may impact the global cancer burden causing it to reach about 28.4 million cases in 2040, indicating a staggering increase by 47 percent from 2020, with a significant increase in transitioning (64 percent) than transitioned (32 percent) countries, though this may be aggravated even more by increasing risk associated with globalisation and a growing economy **(Siegel *et al.*, 2020)**. Considering this burden, cancer mortality could be reduced with even better targeted cancer control strategies and investment in enhanced early diagnosis and treatment. Therefore, research oriented towards natural plant products or pharmaceuticals derived from natural resources has garnered considerable attention from all over the world in attempt to improve the effectiveness of cancer therapy.

Medicinal plants have long been recognised as an integral part of the human society to combat diseases, since time immemorial **(Biswas *et al.*, 2002)**. India ranks one of the leading producer and manufacturer of herbs and herbal products, respectively. Such plants are vital sources of therapeutic compounds enabling them for treating a wide range of ailments, including cancer **(Pandey *et al.*, 2013)**. According to the World Health Organization (WHO), plant-derived medications are used by over 88 percent of the world's population **(WHO, 2019)**. Purely synthetic compounds account for 24.6 percent of the 1881 novel chemical entities designated as drugs between 1981 and 2019, while the vast majority of modern drugs come from medicinal plants **(Newman & Cragg, 2020)**. Many of the leading chemical structures utilised as templates for medication production are derived from natural molecules, which aid in the development of novel compounds with improved biological capabilities against certain diseases **(Khazir *et al.*, 2013)**. Furthermore, there is a pressing need to address the threat of anti-cancer drug resistance **(Levy, 2002)**.There is a good chance of getting novel molecules by studying the mechanism of action of diverse crude extracts and plant-based chemicals **(Pan *et al.*, 2013)**.

Abrus precatorius, belonging to the Fabaceae family and nomenclature as ***Abrus precatorius* Linneaus., 1753,** is a well-known medicinal plant **(Chaudhari *et al.*, 2012)**. It has been proven to be a reservoir of many phytochemicals such as steroids, terpenoids **(Chang *et al.*, 1982; Gupta, Singh, & Bhakuni, 1969)**, saponins, alkaloids **(Ghosal & Dutta, 1971)**, lectin proteins, flavonoids **(Sujit *et al.*, 2012)**, tannins**(L.-C. Lin *et al.*, 2003; Reddy *et al.*, 2003)** and phenolic compounds **(Arora *et al.*, 2011).** *A. Precatorius'* phytochemicals have been shown to provide a variety of health benefits, including anticancer properties **(Lébri *et al.*, 2015; Patil *et al.*,2015)**, anti-angiogenic **(Sujit K. Bhutia *et al.*, 2016)**, anti-inflammatory **(Jeong *et al.*,2017)**, antioxidant **(Okoh *et al.*, 2014)**, and antidiabetic **(Boye *et al.*, 2020)** effects. Cancer researchers from all around the world have been drawn to *A. precatorius* to investigate its anticancer potential due to its plethora of metabolites (primary/secondary) and various biological and therapeutic properties, as well as its use in traditional medicine **(Attal *et al.*,2010)**. This fact, together with the high frequency of cancer and the numerous severe side effects of conventional first-line treatments, lays a strong platform for future research into non-dietary preventive and effective natural medicines. A number of interesting researches have been conducted on the anticancer properties of extracts and phytoconstituents of *A. precatorius* **(Gul *et al.*, 2013; Sofi *et al.*, 2013)**. Furthermore, numerous research concentrated solely on major *Abrus*-derived lectins *eg.*, Abrin and *Abrus agglutinin* **(Sujit K. Bhutia *et al.*, 2016; Sujit K. Bhutia *et al.*, 2008; Mukhopadhyay *et al.*, 2014; Panigrahi *et al.*, 2020; Niharika Sinha *et al.*, 2017)**. Furthermore, there has been limited research into the molecular targets of the different phytochemicals found in *A. precatorius*, and how this knowledge could be utilised in chemoprevention.

The focus of this article is to provide a complete and critical examination of the anticancer and cancer-prevention activities of A. Precatorius metabolites, with an emphasis on their numerous molecular targets. The main goal is to figure out specifically what role *Abrus* phytoconstituents play in cancer prevention and treatment. The article reviews preclinical research of *A. Precatorius*' chemopreventive and therapeutic applications in various types of cancers conducted *in-vitro* and *in-vivo*. This review also delves into the Current research constraints, problems, and future research directions.

Physical Attributes

A. precatorius, often referred to as the *crab's eye* or *rosary pea*, is a perennially climbing, slender, woody plant native to India. It grows by looping around trees, bushes, and fences. This plant is currently generally found in numerous tropical

and subtropical areas of the world, because of its intrusive limit. It is a slender herb with multiple branches possessing a wrinkled and cylindrical shaped stem and a smooth bark. The plant produces short brown colored pods, which open upon curling back to reveal seeds, red and black in color and are usually 4 to 6 in number per pod **(Chaudhari *et al.*, 2012)**.The seeds maintain a uniform weight of 0.1 gm, and are hence used as a weighing unit **(Tabasum *et al.*, 2018)**.The fruit is a 3 cm long pea shaped pod consisting of hard ovoid shaped seeds about a cm long **(Bhatia *et al.*, 2013).**

The various extracts derived from *A. precatorius* have been identified by utilizing a broad range of solvents like, hexane, ethyl acetic acid, ethanol, methanol, water and so forth. These extracts have shown innumerable pharmacological activities as mentioned in Table 1. The antioxidant activity of flavonoids and phenolic compounds in leaf extracts may be linked to anti-cancer properties of *A. Precatorius* **(Garaniya & Bapodra, 2014; Gul *et al.*, 2013; Sofi *et al.*, 2013).**

Table 1 Various types of *A. Precatorius* extracts showing different pharmacological activities

Plant part	Extract type	Biological function	Reference
Seed, root, and leaf	Petroleum ether and methanol	Anti-bacterial activity	**(Mistry*et al.*, 2010; Prabha*et al.*,)**
Seed	Methanol	Anti-bacterial, anti-fungal activity	**(T.R*et al.*, 2010)**
Seed	Petroleum ether and hydroalcoholic	Anti-cancer activity	**(Anbu *et al.*, 2011; Patil *et al.*, 2015)**
Seed	Chloroform – methanol	Anti-diabetic effect	**(Monago &Alumanah, 2005)**
Seed	Ethanolic and aqueous extract	Anti-fertility activity	**(Abu*et al.*, 2012; Attal *et al.*, 2010)**
Leaf	Water extract	Anti-inflammatory activity	**(Arora *et al.*, 2011; Gul *et al.*, 2013)**
Leaf	Water extract	Anti-cancer activity	**(Chaudhari *et al.*, 2012; Gul *et al.*, 2013; Lébri *et al.*, 2015)**
Seed	Methanol, chloroform, hexane and water	Anti-microbial activity	**(Bobbarala & Vadlapudi, 2009)**
Seed	Ethanol	Antioxidant activity	**(Sujit K Bhutia *et al.*, 2008; Pal*et al.*, 2009)**
Seed	Aqueous extract	Nephroprotective and immune-modulatory activity	**(Tilwari*et al.*, 2011)**
Seed	Ethanol	Anti-inflammatory activity	**(Arora *et al.*, 2011)**
Leaf	Ethanol, ethyl acetate extract and methanol	Anti-proliferative	**(Anbu *et al.*, 2011; Gul *et al.*, 2013; Lébri *et al.*, 2015),*(Wan-Ibrahim et al.*, 2019)**
Leaf	Chloroform and ethanol	Cytotoxic activity	**(Sofi *et al.*, 2013)**
Root	Methanol	Anti-proliferative and immune-modulatory activity	**(Okoro *et al.*, 2019)**

Utility of *A. precatorius* in traditional and folk medicine

Different parts of *A. precatorius* including roots, leaves, and seeds are used for a wide range of medical purposes. It's found in Ayurveda, homoeopathy, folk medicine, Tibetan medicine, Sidha medicine, and Unani medicine. Its leaves are used as a nerve tonic and are used to treat swellings, wounds, and mouth ulcers. Traditionally, *A. precatorius* has been reported as beneficial in the treatment of tetanus and rabies, as well as wounds, scratches and sores produced by rabid dogs, cats, and mice **(Attal *et al.*, 2010)**.The herb is also used to treat leukoderma in combination with other substances. The roots have been used to treat jaundice, haemoglobinuric bile, stomach aches, tumours, bronchitis, hepatitis, and pregnancy termination, while the leaves have traditionally been used to treat tussis (cough), pyrexia (fever) and common cold **(Garaniya & Bapodra, 2014)**. Malaria and convulsions can be treated with a hot water extract of fresh root. Greying hair can be treated with a paste made from leaves and seeds. Dried seeds have been used in old times to cure worm infections. Moreover, veterinary professionals make efficient use of the plant in treating bone fractures. Evidence states that the seeds have insecticidal and anti-microbial activities. Various African folks have been using seed powder as birth control pills and to cure tuberculosis as well as swellings **(Attal *et al.*, 2010)**. During the Ayurvedic era, leaves of *A. precatorius* were being used as laxatives (relieve constipation), expectorants (aid in the clearance of mucus from the airways) and aphrodisiac (increases sexual pleasure) medicines and are used in hives (skin rash), dermatitis (patches of itchiness), conjunctivitis (pink eye), *etc.*, **(Garaniya & Bapodra, 2014)**. The seeds are also known for their nutritious value, since boiling seeds are consumed in several parts of India **(Rajaram & Janardhanan, 1992)**.

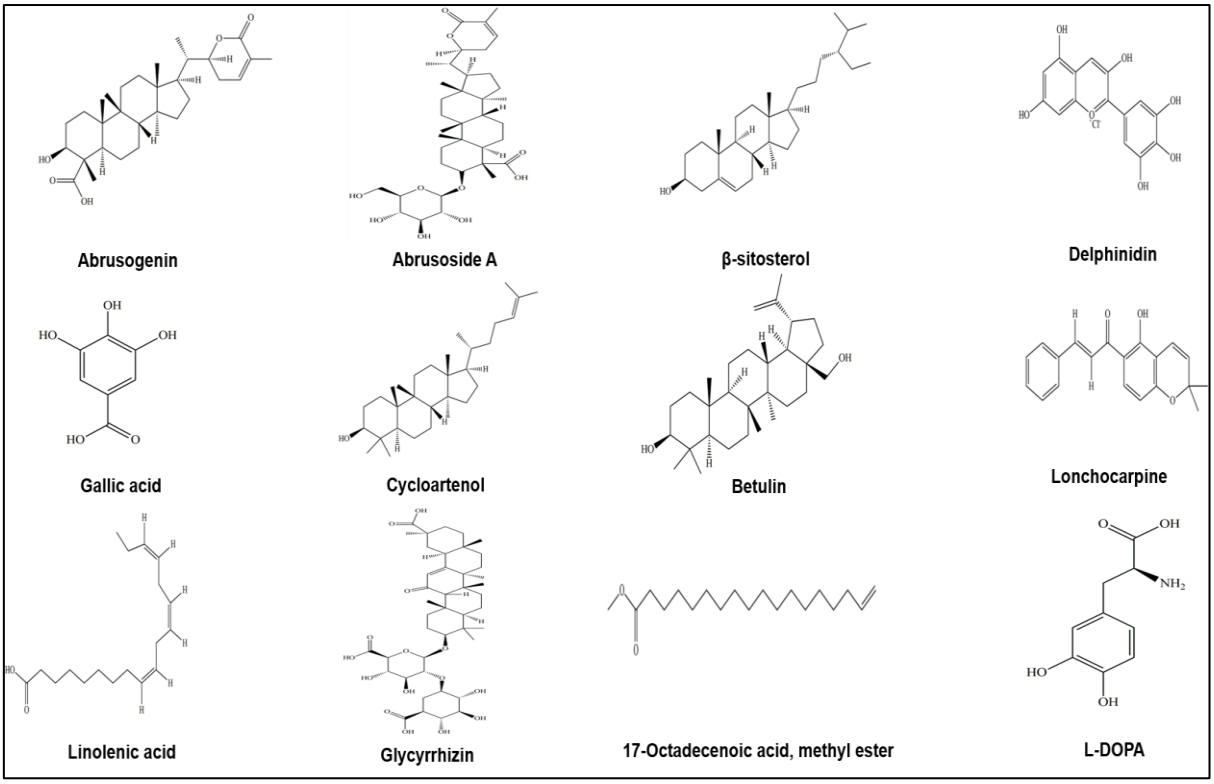

Figure 1 Chemical constituents derived from *A. precatorius*

Table 2 An overview of *in-vitro* studies demonstrating the role of *A. Precatorius* derived bioactive compounds and lectins in various cancers

Plant part	Bioactive Compounds	Nature	Cell type	Pathway/mode of action	Reference
Root	Lonchocarpine	Phenylpropanoid compound	Astrocytes, BV2 microglial cell	Modulation of AMPK, MAPKs signalling and NF-κB activity inhibition	**(Jeong *et al.*, 2017; Jeong*et al.*, 2016)**
Seed	Stigmasterol and β-sitosterol (4:1)	Phytosterols	-	-	**(Karawya*et al.*, 1981)**
Seed	L-DOPA	Non-protein amino acid	-	-	**(Fabricant & Farnsworth, 2001)**
Leaf	Stigmasterol and β-monolinolein	Phytosterols	Human breast tumour cells (MDA-MB-231)	↓ proliferation, ↑apoptosis	**(Sofi*et al.*, 2018)**
Leaf and root	Glycyrrhizin	Triterpenoid saponins	Promyelotic leukaemia (HL-60), human hepatoma (HLE), stomach cancer (KATO III), and herpes virus infected kaposi sarcoma cells	↑apoptosis, ↓ROS, ↑DNA fragmentation	**(Hibasami *et al.*, 2006; Sofi *et al.*, 2013)**
Seed	Abrin	Lectin	Human T lymphocyte cells (Jurkat)	↑apoptosis, ↑ROS, ↑DNA fragmentation	**(Narayanan*et al.*, 2004)**
Seed	Abrin	Peptide fraction (ABP)	Human cervical cancer cells (HeLa)	↑apoptosis, ↑DNA fragmentation, ↓mitochondrial transmembrane potential, ↑Bax, ↓Bcl-2, caspase-3 activation	**(Sujit K Bhutia*et al.*, 2009)**
Seed	Abrin	Lectin	Human cervical cancer cells (HeLa)	↑apoptosis, ⊥ AOP-1, ↑ ROS, activation of caspases 9 and 3	**(Shih*et al.*, 2001)**
Seed	Abrin	Lectin	Human B cells (U266B1)	↓mitochondrial transmembrane potential,↑ ROS, caspase-independent (necrotic cell death)	**(Bora*et al.*, 2010)**
Seed	Abrin	Lectin	Human T lymphocyte cells (Jurkat)	↑Fas/Fas ligand (Fas L)	**(Saxena*et al.*, 2013)**
Seed	*A. Agglutin* (apa-1)	Lectin	Human T lymphocyte cells (Jurkat) and human breast cancer cells (MCF-7)	Induces apoptosis by triggering intrinsic mitochondrial pathway	**(Bagaria*et al.*, 2006)**
Seed	*A. Agglutinin* (AGG)	Lectin	Endothelial cells of Human umbilical vein (huvecs) and human breast tumour cells (MDA-MB-231)	AKT- dependant pathway, intrinsic and extrinsic apoptosis	**(Sujit K. Bhutia *et al.*, 2016)**
Seed	*A. Agglutinin* (AGG)	Lectin	Hypopharyngeal carcinoma cells (Fadu)	ATM-p73 mediated apoptosis and Snail-degradation	**(Niharika Sinha *et al.*, 2019)**
Seed	*A. Agglutinin* (AGG)	Lectin	Hypopharyngeal carcinoma cells (Fadu)	↑DNA fragmentation, ↑ROS, ↑ATM-p73 mediated apoptosis	**(Niharika Sinha *et al.*, 2017)**
Seed	*A. Agglutinin* (AGG)	Lectin	Hypopharyngeal (Fadu) orospheres	Downregulation of Wnt/β-catenin signalling,	**(N. Sinha*et al.*, 2017)**
Seed	Permeate tryptic hydrolysate (10kdagp)	Peptide derived from *A. Agglutinin*	Human cervical cancer cells (HeLa)	↓mitochondrial potential; ↑ROS;JNK, p38, p53activation, autophagy and AKT deregulation	**(Behera, Mishra, *et al.*, 2014)**
Seed	*A. Agglutinin* (AGG)	Lectin	Human hepatocellular carcinoma cells (HepG2)	Induces caspase-mediated cell death.	**(Mukhopadhya y *et al.*, 2014)**
Seed	*A. Agglutinin* (AGG)	Lectin	Human oral cancer (CAL33) and human cervical cancer cells (hela)	Autophagy promoted NRF2 degradation, ROS-regulated caspase-dependent apoptosis, and ER stress via inhibiting the Akt/PH domain, resulting in autophagic cell death	**(P. K. Panda *et al.*, 2017; Panigrahi *et al.*, 2020)**
Seed	*A. Agglutinin* (AGG)	Lectin	Colon cancer stem cells (cscs)	Induces autophagy, which leads to β-catenin breakdown and differentiation	**(P. K. Panda, Naik, Praharaj, *et al.*, 2018)**
Seed	*A. Agglutinin* (AGG)	Lectin	Human glioblastoma cells (U87MG)	Mitophagy mediated by PUMA contributes to apoptosis by generating ceramide	**(P. K. Panda, Naik, Meher, *et al.*, 2018)**
Seed	*A. Agglutinin* (AGG)	Lectin	Prostate carcinoma cells (PC3)	Lipophagy-mediated accumulation of Fas, stimulate the production of ROS to accelerate senescence	**(Prashanta Kumar Panda *et al.*, 2020; Panigrahi *et al.*, 2020)**
Leaf and stem	Abruslactone A, abrusogenin	Triterpenoid saponin	Human breast cancer (MCF-7), human pancreaticadenocarcinoma (SW1990), Cervical (Hela), and prostate cancer cells (Du-145)	-	**(Xiao *et al.*, 2011)**

Chemical Constituents

A. Precatorius already has garnered several groups of secondary metabolites (bioactive compounds) such as alkaloids**(Ghosal & Dutta, 1971)**, steroids, triterpenoids **(Chang *et al.*, 1982; Gupta *et al.*, 1969)**, starch, isoflavanoquinones, anthocyanins, tannin **(L.-C. Lin *et al.*, 2003; Reddy *et al.*, 2003)**, protein, flavonoids **(Sujit *et al.*, 2012)**, phenolic compounds, fixed oil, amino acid **(Arora *et al.*, 2011)**, luteolin, flavones, orientin, isoorientin, abrectorin, and desmethoxycentaureidin-7-0-rutinoside **(Bhardwaj*et al.*, 1980)**. Abrusoside-A, abrusogenin, β-sitosterol, gallic acid, delphinidin, cycloartenol, betulin, lonchocarpine, linolenic acid, glycyrrhizinare, 17-Octadecenoic acid, methyl ester, L-DOPA are few examples of bioactive compounds which have distinct chemical structures (Figure1).

A. PRECATORIUS DERIVED BIOACTIVE METABOLITES IN CANCER PREVENTION

Among the most fatal diseases is cancer, which is caused by the overgrowth of malignant cells. Cancer metastasizes (transport and spreads to the different locations in body) through the mechanism of angiogenesis, invasion, and metastasis, thereby taking a severe toll on people's lives all across the world. The keys to combating this deadly disease are prevention, early detection and immediate treatment **(Sharma *et al.*, 2014)**.
The most prevalent cancers worldwide are lung and breast cancers, which cause tremendous number of deaths in both men and women. Prostate cancer and lung cancer are leading causes of cancer-related mortalities in men and women in developed countries **(Ferlay J, 2020)**. Therefore, researchers all across the world are attempting to develop various methods aimed at cancer management. One such promising approach is the use of bioactive chemicals as a potential alternative of cancer prevention or treatment. The chemotherapeutic effects of different bioactive compounds extracted from *A. Precatorius* have shown significant efficacy in inhibition of cancer cells by modulating different signalling pathways when studied in different *in-vitro* models as discussed in the table below (Table 2.).

In-vitro Anticancer Effects

Several studies have shown that lonchocarpine, one of the plant's bioactive components, has antioxidant, anti-inflammatory, and anti-proliferative activities **(Georgewill & Georgewill, 2009; Gul *et al.*, 2013)**. In line with a study by **Jeong *et al.* (2017),** Lonchocarpine was observed to lower microglial activation and production of proinflammatory markers in LPS- or poly (I:C)-induced neuroinflammatory conditions.Similarly, another study demonstrated the antioxidant potential of lonchocarpine by deciphering its ability to enhance antioxidant enzyme expression through modulation of AMPK, MAPKs, and Nrf2 signalling pathways **(Jeong *et al.*, 2016)**.
Stigmasterol was isolated from a variety of medicinal plants, including *A. precatorius, Akebia quinata, Croton sublyratus,* and many others, and was found to have anti-cancer activity *in-vitro.* Similarly, a long-chain polyunsaturated fatty acid- β-monolinolein exhibits cytotoxicity in cancer cells. Stigmasterol hemihydrate and β-monolinolein, two key cytotoxic biomolecules from *A. precatorius* leaf extract, were found to have IC_{50} values of 74.2 and 13.2 µg/ml, respectively, *in-vitro* using MDA-MB-231 cells **(Sofi *et al.*, 2018)**.
Similarly, Glycyrrhizin is a triterpenoid saponin isolated from roots and leaves and of *A. precatorius,* which was found to induce apoptosis in a variety of cell types (Table 2.) including human hepatoma (HLE), stomach cancer (KATO III), promyelotic leukaemia (HL-60), and herpes virus infected kaposi sarcoma cells **(Hibasami *et al.*, 2006)**. *A. precatorius* extract suppressed the cell growth of MDA-MB-231 by inducing apoptosis rather than inhibiting cell proliferation (**Sofi *et* al., 2013).**

THE ABRIN STORY

Origin

Another major protein derived from *A. precatorius* is Abrin, a water-soluble plant toxin, derived from the seeds,and is structurally and chemically similar to ricin. *Ricinus communis* (Castor beans) is the primary source of ricin, a ribosome-inactivating protein from where it is produced, and is widely utilised in traditional medicine for treatment of a wide range of health conditions, however it is infamous due to its toxicity. Stillmark initially proposed that the chief reason for the toxicity of castor beans was the presence of a plant protein that he named 'Ricin' **(Sjur Olsnes, 2004)**. Ricin was isolated from castor bean seeds and found that ricin's toxicity comes from its capability to agglutinate erythrocytes. Another toxin, known as RCA (*R. communis agglutinin*), was later determined to be the source of the agglutination, not ricin. Ricin has a lot of potential as an anti-cancer drug, and it works by triggering apoptosis in tumour cells **(Tyagi *et al.*, 2015)**.
In addition to Abrin numerous strategies devoted to extraction of pure abrin have been well elucidated by scientists **(S Olsnes, 1976; Sjur Olsnes, 1978)**. Separation of abrin from *A. agglutinin* can be accomplished using ion exchange chromatography or sucrose gradient centrifugation. After purification, abrin can be generated as a powder with a yield of about 0.075 percent by weight **(Tahirov *et al.*, 1995)**.

Toxicity

According to *in-vitro* studies, abrin is a toxin that is more lethal than ricin **(Griffiths *et al.*, 1994)**. The estimated concentration of abrin that is potentially lethal for human life is about 0.1–1 µg/kg of body weight. There is currently no antidote for abrin toxicity. Accidental and purposeful abrin poisoning have resulted in the death of humans as reported in previous case studies **(Dickers *et al.*, 2003; Wooten *et al.*, 2014)**. Abrin intoxication results from endothelial cell death brought on by abrin, which raises capillary permeability and causes fluid and protein leakage as well as tissue edoema. This is another characteristic of ricin poisoning when used in conjunction with ricin A chain chemotherapeutic treatments **(Baluna *et al.*, 1999)**. Differences in toxicity potential of abrin and volkensin have been observed, with abrin and volkensin being more harmful to mice than ricin **(Barbieri *et al.*, 1993)**. Furthermore, all harmful type 2 RIPs move retrograde via peripheral nerves **(R. G. Wiley *et al.*, 1995)**, when injected into the central nervous system, only modeccin and volkensin are carried retrogradely **(Ronald G Wiley *et al.*, 1988)**. The reasons for these discrepancies are currently unknown, but they could be related to B chain features.
Abrin and ricin have similar biological activities; they both elicit similar toxic symptoms and have no effect on mitochondrial respiration **(J.-Y. Lin *et al.*, 1970)**. It also discovered that abrin and ricin had a strong protective effect against Ehrlich ascites tumour cells in mice **(J.-Y. Lin *et al.*, 1970)**. Abrin and ricin were also discovered to prevent the growth of Ehrlich ascites tumour and Yoshida sarcoma **(Fodstad *et al.* ,1977; V. S. Reddy & M. Sirsi, 1969)**, but the activity was much smaller than that found by **Lin *et al.* (1970)**. There was also evidence of a protective effect against experimental leukaemia. Furthermore, these toxins have also been utilised to treat specific types of human cancers in preliminary investigations. In the few cases that have been documented so far, the results have been promising, and there have been few side effects.

Structure of Abrin

Most ribosome inactivating proteins (RIPs) have highly conserved active site residues, as well as their design. Ricin's structure was one of the first in the family of RIPs to be deciphered, whereas Abrin-crystal A's structure was deciphered with a resolution of 2.14 Å **(Tahirov *et al.*, 1995)** (Figure2).

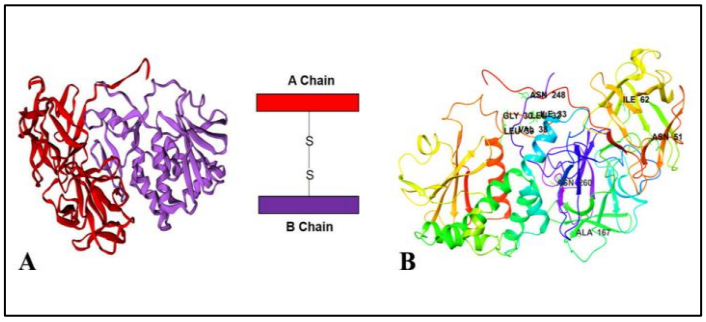

Figure 2 Pictorial representation of abrin molecule where (A); A chain has been shown in red and the B chain in purple colour and (B); crystal structure of abrin showing the active site residues of the A chain such as -Leu 30, Val 38, Gly 30, Leu 32, Ile 83 and Asn 248 as well as the B-chain residues such as- Ile 62, Asn 51, Asn 260, Ala 167.The Figure was generated using Maestro Suite 11 software (PDB ID for abrin: 1ABR)
Abrin, like ricin, is a type 2 RIP with a disulphide linkage between A and B chains. A-chain of abrin has a molecular weight of 30 kDa with 251 amino acid residues vs 267 in the ricin A-chain, both of which have a three-fold structural domain. 60% of the amino acid residues in the abrin B chain, which weighs 35 kDa, are identical to those in the ricin B chain **(Sjur Olsnes, 2004)**. Both B chains consist of two highly conserved saccharide binding sites **(Griffiths *et al.*, 1994)**. The Cys-247 residue of the A chain and Cys-8 of the B chain form a disulphide linkage between the two subunits of abrin. Unlike the A chain, the B chain of abrin is glycosylated twice **(Tahirov *et al.*, 1995)**.

Mechanisms of Action

The Abrin B-chain plays an important function in abrin's toxicity at the cellular level, a class of lectins that facilitates its binding to cell membranes recognize a highly conserved region, a “GAGA” sequence (Figure3)

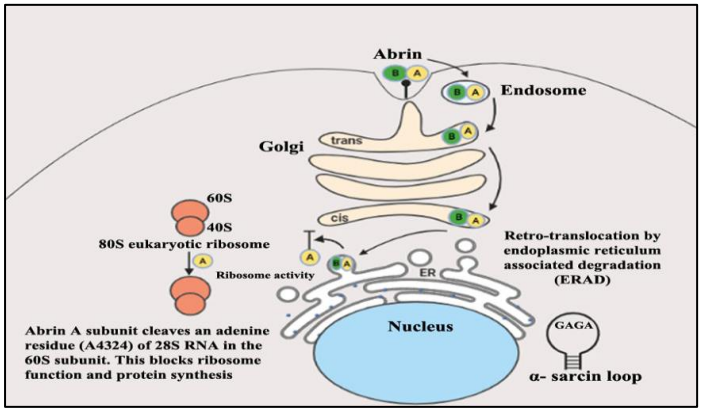

Figure 3 Schematic representation of intracellular uptake of abrin and ribosome inactivation-abrin can be internalized *via* clathrin-dependent and clathrin-independent endocytosis. Upon internalization, abrin moves from the early

endosome through the trans-Golgi network, then through retrograde trafficking from the Golgi body to the endoplasmic reticulum (ER). Its catalytic A-chain comprises of a highly active N-glycosidase which functions by depurinating adenine (A4324) in a "GAGA" sequence (α-sarcin loop) of 28S rRNA resulting in inhibition of EF-2 binding and ultimately impairing protein synthesis.
Several poisons target the 14-nucleotide long α-sarcin loop called as the ribosomal "Achilles' heel" **(Griffiths *et al.*, 1987; S Olsnes, 1976; Sjur Olsnes *et al.*, 1974)**. Abrin's B chain attaches to the surface of numerous different cell types especially those in the reticuloendothelial system that have mannose receptors that abrin readily binds to, enables the transportation of toxic A chain to the cytosol **(Gadadhar & Karande, 2013)**. Upon internalisation, the abrin A-chain moves from the cell membrane to the ribosomes, where it participates in the inactivation of the 60S ribosomal subunit (Figure3) by separating the adenine from the 4th and 324th (α-sarcin loop) positions of 28S rRNA, inhibiting the synthesis of proteins and ultimately leading to cell destruction **(Endo *et al.*, 1987)**.

Effect of Abrin on Cancer Cells

Abrin has two key effects on cells: inhibition of protein synthesis and programmed cell death.

a. Inhibition of Protein Synthesis by Abrin in Cells

It is reported that a single molecule of abrin is capable of inactivating nearly 1500 ribosomes per second, revealing its incredible inhibitory impact on protein synthesis. This property of abrin can stop malignant cells from proliferating if they have a faster metabolic turnover than healthy ones**(Dickers *et al.*, 2003)**. **Vinita *et al.* (2019)** found that the link between abrin-mediated protein synthesis inhibition and cell specific apoptosis, and that abrin can activate multiple pathways leading to cell death **(Tiwari & Karande, 2019)**. However, the correlation between the two biological processes, is still under study.

b. Abrin-Induced Programmed Cell Death

In Jurkat cells, **Narayanan *et al.*(2004)** found that abrin targets both caspase 3-dependent and caspase 8-independent apoptotic pathways, and promotes the formation of ROS by disrupting the mitochondrial membrane potential **(Narayanan *et al.*, 2004)**. The mechanism of cell death triggered by the abrin peptide fraction (ABP) in HeLa cells was reported. The apoptosis was indicated by DNA fragmentation and the onset of the sub G0/G1 peak in cell cycle study (**Bhutia *et al.*, 2009)**. Various biochemical apoptotic measures revealed the generation of ROS, a decrease in mitochondrial membrane potential, overexpression of Bax, decreased expression of Bcl-2, and caspase-3 activation. This peptide fraction contains mitochondria-penetrating peptides that could be leveraged to induce apoptosis in cancer cells **(Sujit K Bhutia *et al.*, 2009)**.
In addition to inhibiting translation process, abrin has been shown to cause apoptosis in cells. **Shih *et al.* (2001)** demonstrated that abrin acts by inactivating a thiol-specific anti-oxidant protein, resulting in ROS that can participate in a variety of cellular activities such as apoptosis **(Shih *et al.*, 2001)**. Typical apoptosis markers such as DNA fragmentation, chromatin condensation and membrane blebbing have been observed in abrin treated cells as the characteristic of apoptosis **(Hughes *et al.*, 1996)**.
Numerous cancer cell lines were effectively suppressed by protein-rich extracts or peptide components from *A. precatorius* seed and leaf extracts **(Sofi *et al.*, 2013; Sujit *et al.*, 2012)** without influencing the growth of normal murine peritoneal macrophages **(Gul *et al.*, 2013)**. p21 and p53 upregulation **(Gul *et al.*, 2013),** as well as clear evidence of apoptosis via the mitochondrial pathway, accompanied the cytotoxic effects **(Sujit K Bhutia *et al.*, 2008)**.
Another piece of data showed that abrin causes apoptosis in U266B1 cells without the use of caspases **(Bora *et al.*, 2010)**. The role of the Fas pathway in abrin-induced apoptosis was recently discovered in Jurkat cells **(Saxena *et al.*, 2013)**. While abrin suppresses the process of translation in all cell types, it can also activate various signalling pathways, resulting in cell death.

Effect of *A. Agglutinin* on Cancer Cells

Abrus agglutinin (AGG) is a type II heterotetrameric ribosome inactivating protein (RIP) isolated from *A. precatorius* seeds. It is also effective at inducing various signalling cascades causing cell death in different cancer models**(Bagaria *et al.*, 2006; Sujit K. Bhutia *et al.*, 2016; Mukhopadhyay *et al.*, 2014; P. K. Panda *et al.*, 2017; P. K. Panda, Naik, Meher, *et al.*, 2018; P. K. Panda, Naik, Praharaj, *et al.*, 2018; Prashanta Kumar Panda *et al.*, 2020; Panigrahi *et al.*, 2020; Niharika Sinha *et al.*, 2019; Niharika Sinha *et al.*, 2017; N. Sinha *et al.*, 2017**). Similarly, **Behera *et al.* (2014)**, demonstrated that different pro-apoptotic pathways are modulated by agglutinin-derived peptides, including a decrease in mitochondrial membrane potential; activation of JNK, p38, MAPK and p53; generation of ROS; and dysregulation of AKT. It promotes the apoptosis as well as autophagy, which adds to the induction of total cell death **(Behera, Mishra, *et al.*, 2014)**.

Table 3 An overview of *in-vivo* studies demonstrating the role of *A. precatorius*

Plant part	Bioactive Compounds	Nature	Type of cells	Murine model	Dosage	Route of drug administration	Mechanism of action	Reference
Seed	*Abrus agglutinin* (AGG)	Lectin	Hypopharyngeal (FaDu) cell xenografts in athymic nude male mice	Xenograft mouse model of Head and Neck Squamous-Cell Carcinoma (HNSCC)	50 µg/kg body weight	subcutaneous (s.c)	↓PCNA expressions, ↑ caspase-3 activation	**(Niharika Sinha *et al.*, 2017)**
Seed	*Abrus agglutinin* (AGG)	Lectin	Xenografts athymic nude mice model of human breast cancer (MDA-MB-231)	Xenograft mouse model of Human breast cancer	500 mg/kg body weight	intraperitoneal (i.p)	↓ Ki-67, ↓CD-31, and ↑TUNEL expression	**(Sujit K. Bhutia *et al.*, 2016)**
Seed	Permeate tryptic hydrolysate (10kdagp)	Peptide derived from *A. Agglutinin*	Injection of Ehrlich's ascites carcinoma (EAC) cells in Swiss albino mice and injection of B16 melanoma in (B16M) C57 BL 6J mice	Solid tumour models of Ehrlich's ascites carcinoma (EAC) and B16 melanoma (B16M)	2 mg/kg body weight	intraperitoneal (i.p)	↓tumour volume for B16M by 58.8% and for EAC by ~82%	(**Behera *et al.*,2014)**
Seed	Permeate tryptic hydrolysate (10kdagp)	Peptide derived from *A. Agglutinin*	Hollow fiber encapsulated HeLa cells in Swiss Albino mice	Hollow Fiber Assay	2 mg/kg body weight	Intraperitoneal (i.p)	inhibiting cervical cancer cells	**(Behera*et al.*, 2014)**
Seed	Abrin	Lectin	Splenocytes	Balb/c mice	1 µg/kg body weight	Intraperitoneal (i.p)	↑Fas/Fas ligand (Fas L)	**(Saxena *et al.*, 2013)**
Leaf	Stigmasterol and β-monolinolein	Phytosterols	Sprague Dawley rats (virgin)	DMBA-induced mammary tumor model	20 mg/kg body weight	oral	↓ Ki-67 and ↑TUNEL expression	**(Sofi *et al.*, 2018)**

In-Vivo Anticancer Effects

RIPs induces the apoptosis in rat **(Griffiths *et al.*, 1987)**. The seed preparations were effective in inhibiting the growth of several tumour types in murine models **(Anbu *et al.*, 2011; V. V. Reddy & M. Sirsi, 1969)**. Abrin-treated Meth-A tumour cells were administered to animal models, which resulted in potent anti-tumor immunity **(Shionoya *et al.*, 1982)** demonstrating that abrin's anti-tumour actions were mediated through the immune system. The immune-potentiating and immune-stimulatory capabilities of abrin **(Sujit K Bhutia *et al.*, 2009; Ramnath *et al.*, 2002),** as well as *A. Agglutinin*'s behaviour as a stimulator of B-cell and T-cell was identified **(Ghosh *et al.*, 2009)**. **Sinha *et al.* (2017)** reported that AGG inhibited the growth of a FaDu tumour xenograft in a nude mouse model, with an increase in caspase-3 activation and decrease in the expression of PCNA compared to controls, indicating AGG efficacy in inhibiting human Head and Neck Squamous-Cell Carcinoma (HNSCC) tumour growth with no effect on normal cells **(Sinha *et al.*, 2017)**. AGG also reported as an efficient inhibitor of the growth of MDA-MB-231 tumour xenografts in athymic nude mice by inhibiting both proliferation and angiogenesis **(Sujit K. Bhutia *et al.*, 2016)**. In the mice models of Ehrlich's ascites cancer (EAC) and B16 melanoma (B16M), bioanalysis of 10kDAGP predicts the existence of anionic anticancer peptides, which have shown 82% and 58.8% decreases in tumour volume, respectively **(Behera *et al.*, 2014)**. Furthermore, utilising a hollow fibre model, it was able to suppress cervical cancer cells in an *in-vivo* system **(Behera *et al.*, 2014)**. In the splenocytes of mice treated with abrin, upregulation of Fas R, Fas L, FADD, caspase-8, caspase-3, and their substrates activated the Fas pathway **(Saxena *et al.*, 2013)**. **Sofi *et al.* (2018)** demonstrated the treatment with the combination of stigmasterol and β-monolinolein in DMBA-induced female Sprague Dawley (SD) rats resulted in the recovery of body weight, decreased tumour weight and volume without any severe side effects. Immuno-histochemical analysis including H and E staining, TUNEL assay, and Ki-67 index data demonstrated the minimal proliferation and a significant cell death in the treated tumour tissues compared to the control animal group **(Sofi *et al.*, 2018)**.

In conclusion, the findings suggest that *Abrus*-derived bioactive chemicals may have a chemopreventive effect on cancer cells. However, additional research and studies are needed to further justify the findings.

CONCLUSION AND FUTURE PERSPECTIVE

Medicinal plants continue to remain a crucial point of origin in developing new pharmacological leads. *A. precatorius* has been recognized as a well-known plant in traditional medicine for the treatment of a plethora of ailments. During the previous few decades, its bioactive compounds have been thoroughly investigated for their potential to suppress and cure cancer, demonstrating its significance as a chemo-prophylactic and chemotherapeutic drug. However, the promising activity of *A. precatorius* in chemoprevention and chemotherapy, along with its molecular pathways in cancer, are unknown. This article reviewed preclinical *in-vitro* and *in-vivo* investigations and provided a complete evaluation of known findings on the anticancer effects of *Abrus*-derived components, with a focus on their plethora of molecular targets.

Both primary and secondary metabolites of *A. precatorius* have been reported to have cytotoxic and antiproliferative effects on a variety of cancer cells. Furthermore, *Abrus*-based herbal compounds inhibited the growth and development of xenografted and/or chemically-induced tumours in mice. The antitumor activities of *Abrus*-derived lectins; abrin and *A. agglutinin* could be mediated by anti-proliferative, cytotoxic, anti-inflammatory, antioxidant, immune-modulatory, apoptosis, autophagy, protein synthesis inhibition and antiangiogenic effects as well as regulation of various tumor-inducing and tumor-suppressive signalling cascades. According to the findings, a variety of *Abrus* bioactive metabolites have the potential to inhibit tumour cell proliferation and/or limit tumour development and growth. Bioactive phytochemicals of *Abrus* have been reported to exhibit anticancer and cancer preventive effects by targeting distinct signalling pathways. Hence, it suggested that metabolites of *A. precatorius* may impart the perceived chemoprotective and anticancer effects via promoting multifactorial effects through synergism. However, there are some limitations which need to be addressed. Firstly, the molecular crosstalk between the bioactive compounds and various signalling molecules is elusive and requires further investigation. Secondly, to fully understand the effect of *A. precatorius* on cancer inhibition and prevention, interaction of bioactive compounds in different signalling cascades can be investigated through *in-silico* strategies such as molecular docking, which can further be validated using different *in-vitro* and *in-vivo* strategies. Additionally, further in-depth experimental studies need to be undertaken that could prove and interpret the correlation of the identified bioactive compounds from *A. precatorius* with their pharmacological effects.

Furthermore, *Abrus*-derived lectins have proven to be promising chemo-preventive agents in multiple murine models of human cancers. However, further investigations are required in the following aspects: 1) improving the bioavailability, aqueous solubility, and pharmacologic properties, and 2) more clear understanding of the underlying mechanisms of action to predict its efficacy. *Abrus*-derived lectins and other bioactive compounds have yet to be tested in cancer clinical trials. As far as the clinical trials are concerned, the clinical trials database mentions a few completed trials-based investigations on ricin against infections including cancer, however, to the best of our knowledge, no such data is available on abrin related clinical trials. Based on the constraints discovered, we encourage future research to evaluate the anticancer effects of *A. precatorius* metabolites in synergy as the majority of studies investigated the activities of compounds individually. Additional to assess the anticancer effect against different cancers, there is a need to identify different molecular targets that should be investigated to further explain the anticancer properties of *Abrus*. The findings that have been conducted *in-vivo* and *in-vitro* should be confirmed by clinical trials with larger sample sizes, to analyse the endpoints and biomarkers of cancers. Newly formulated and improved drug delivery methods, such as nanoparticles, nano-emulsions, micelles and liposomes should be used to improve the bioavailability of its phytochemicals. Furthermore, the efficacy of *Abrus* metabolites in combination with conventional chemotherapy needs to be investigated. Based on the extensive evidence gathered and analysed in this review, metabolites of *A. precatorius* appear to be remarkably propitious as both chemopreventive and chemotherapeutic agents. This emphasizes the significance of upcoming research building on earlier studies to fully understand the role of this plant in combating a lethal disease like cancer, as well as its therapeutic properties.

LIST OF ABBREVIATIONS

AKT: Protein kinase; **ALA**: Alanine; **AMPK:** AMP-activated protein kinase; **ARE**: anti-oxidant response element; **ASN**: Asparagine; **ATM**: ataxia telangiectasia mutated serine-protein kinase; **BAT3**: HLA-B associated transcript 3; **BAX**: Bcl2 associated X protein; **CYS**: Cysteine; **EAE-AP**: *A. precatorius* ethyl acetate leaf extract**; EF-2**: Elongation Factor-2; **ER**: endoplasmic reticulum; **FFAs**: Free fatty acids**; GLY**: Glycine; **HeLa:** Henrietta Lacks; **ILE**: Isoleucine; **JNK**: Jun amino-terminal kinases; **kDa:** Kilo Dalton; **LEU**: Leucine; **MAPK**: Mitogen Activation Protein Kinase; **MCF-7**: Michigan Cancer Foundation-7; **NRF2**: nuclear erythroid 2-related factor 2; B; **PUMA**: p53 upregulated modulator of apoptosis; **RIP**: ribosome-inactivating protein**; ROS**: reactive oxygen species; **SAPK**: Stress-activated protein kinases; **TGN**: trans-Golgi network; **TNF-*α*:** Tumour Necrosis Factor-alpha; **VAL**: Valine; **WHO**: World Health Organization

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