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REVIEW ARTICLE

Trends in Biotechnology and Plant Sciences

Therapeutic Potential of *Ficus Religiosa* Extract in Cancer Treatment

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Abstract

Cancer is one of the most dangerous diseases in the world and it needs to be cured through biological means. Medicinal plants and their derivatives are being increasingly recognized as useful complementary treatments for cancer. Many clinical research and studies have documented the valuable effects of plant-based medicines on the immune modulation, survival and quality of life of a diseased patient when these herbal medicines are used in combination with conventional therapeutics. Thus, the use of plants as medicine is therapeutic the disease of cancer is increasing with the demand of the environment – friendly sustainable curation. The use of it enhances the immunity and lessen the risk of cancer. From all the data presented we concluded that plant-based medicine in the treatment of most diseases especially cancer-related diseases is the need of the present time so that we can prevent from the intake of chemicals as well as from economics may be under consideration. This review should provide useful technological support for evidence-based application of herbal medicines in cancer therapy.

KEYWORDS
Cancer; Herbal; Medicine; *Ficus religiosa*.

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1 | INTRODUCTION

Background Cancer

Cancer has appeared as one of the most alarming diseases during the last few decades (Mathers et al. 2005). The cancerous cells in the human body constantly multiplying with an inability to stop, forming a tumor of malignant cells with the potential to be metastatic. A quick increase in the number of cancers may be due to the use of tobacco, alcohol, exposure to harmful radiations, chemicals, change in food habits, chronic infection, environmental pollution and change in lifestyle (Thun et al. 2009). Globally cancer has been a persistent conflict after a lot of investigation and preventative therapies. All over the world cancer remains one of the serious reasons for death on a large scale.

Common Types of Cancer and its Status in the World

According to World Health Organization (WHO), it was assessed that about 7.6 million people died in 2008 and 12.7 million people were diagnosed with Cancer. It was estimated that 9.6 million deaths occur in 2018 due to this disease. Globally, about 1 of 6 deaths is due to cancer. More than 13 million deaths and 21 million new cancer cases will be reached in 2030. While, approximately 13% of all deaths in the world are due to cancer and more than 30% of cancer deaths can be prevented by stopping or altering key risk factors (World Health Organization, 2008). All over the world liver, lung, stomach, colon, breast, etc. are most common (Luk et al. 2007). In women ovarian and breast cancer are the most common type of cancer. Universally colon cancer is also a common type of cancer (Al-Kuraya et al. 2006). Both the female and male are equally affected by this deadly disease. In the

United States during past years, about 140,000 people were diagnosed with colon cancer and the assessed survival was 50% or less (ACS, 2014). Hepatocellular carcinoma is the fifth most common cancer in the world (McGlynn et al. 2001).

Cancer Treatment Conventional Methods

Nevertheless, at initial stages, cancer can be cured. A large number of therapeutic drugs which are proved to be useful have been developed due to the development and discovery of systematic drugs from the past 5 decades. Some therapies which are commonly used in cancer treatments are: Hormonal therapy is used to treat cancer at very initial stage. This therapy uses in clinical exercise is based on a progesterone receptor (PGR) and a positive estrogen receptor (ER) of an easily accessible metastasis (Glass et al. 2003; Mueller and Gooren, 2008).

The uses of radiation to destroy cancer cells are Radiotherapy. In radiation therapy, to halt cancer cells from replication high-intensity x-rays are used. This treatment also depresses the immune system, kills the healthy cells, very disagreeable side effects, and greatly raises the risk of developing leukemia later (Larsen, 1996). Now, after the removal of the primary tumor, radiation therapy has major roles in protection management (Parker, 2001). The status of the patients' immune system is the key to the physiological factor affecting the consequence of cancer immunotherapy. Immune cells play a vital role in mediating the effects of immunotherapy, and precise nutritional complements that improve immune cell function can be effective in preparing patients for vaccination or immunotherapy (Wurzenberger, 2009; Kantoff et al. 2010). Chemotherapy is one of the slightest valued and most hazardous of all conventional treatment methods. To kill the cancer cells, a diversity of highly toxic drugs is used in this therapy. Possibly the extreme problem with chemotherapy is that it extremely weakens the immune system (Larsen, 1996). Chemotherapeutic treatments are responsible for toxicities because they have intrinsic problems of their own. Several types of toxicities occur due to chemotherapeutic treatments. If cancer cells become unable to perform many regulatory functions that are present in normal cells and they start gradually to multiply when usual cells do not. The cancerous cells become receptive to chemotherapeutic drugs due to these features.

A Need to Develop Safe ands1111111 Chemo-preventive Anticancer Drugs

During the last decades, the new synthetic chemotherapeutic agents recently used in clinics have not attained attention, due to the significant cost of their success. Moreover, there is a continuous demand to develop new and inexpensive anticancer drugs (Coseri, 2009). Botanical-based medicines are reported in ancient developing nations, like China and Egypt. Over the years these essential pharmaceutical agents from medicinal plants have been given for many disorders. In the developed nations people are interested in alternative or natural therapies to avoid the burden impacts and high expenses of chemotherapy. So, they turned back to nature for a wide alimental and safe therapies (Abd-Rabou, 2017; Gupta et al. 2021). Many studies have examined that some naturally occurring phytochemical agents, such as phenolic compounds (e.g. alkaloids and flavonoids), trigger cancer-cell death and can be used as chemopreventive candidates against certain cancerous cell types (Abd-Rabou, 2017; Ahmed et al. 2015; Gao et al. 2002; Goodman, 2000).

Plants-based Anticancer Drugs

The plant kingdom has been the most important source of drugs, about 60% of medicines recently used in cancer therapy have been separated from natural by-products (Gordaliza, 2007). From the National cancer institute (NCI) about 35,000 plant species have been recognized for potential anticancer activity. Between them, about 3,000 plant species have expressed reproducible anticancer activity. The phytochemicals in the plants have different bioactivities, including anti-inflammatory, antioxidant and anticancer functions. Some research has described that natural extracts, for example, medicinal herbs, vegetables, and fruits have more positive effects against cancer than chemotherapy or recent hormonal therapies (Wu et al. 2002, Utami et al. 2021). These days various anticancer agents have been separated and recognized from plants and their components are recently used in clinical trials. The plant-derived anticancer drugs are as given in Table 1.

Table 1: Different drugs obtained from plant sources

Drug class	Examples	Source plant
Vinca Alkaloid	Vinblastine	*Catharanthus roseus*
Taxanes	Paclitaxel, Docetaxel	Taxus species
Lignans	Etoposide, Teniposide	Podophyllu species
Cephalot axenes	Homohamngtonine	Cephalotaxus
Camptot becins	Topotecan Innotecan HCl	*Camptotheca acuminate*
Flavones	Flavopiridol	*Dysoxylum binectanierum*

Herbal Extracts and Phytochemicals

In mammalian cells, the biological targets of phytochemicals were involved in oncogenic transformation and inflammatory processes, like angiogenesis, metastases, apoptosis evasion, and alteration of cell cycle control (Surh and Nat, 2003; Yueniwati et al. 2021). Furthermore, proposed by epidemiological studies the consumption of phytochemicals on the daily basis can minimize the occurrence or risk of different types of cancer. Consequently, to reduce the risk of cancer growth dietary phytochemicals act as chemo preventive and immerges as one of the most auspicious approaches. Additionally, specific phytochemicals also permit the usage of minor concentrations of drugs in cancer therapy with increased efficacy. In other words, to control cancer cell drug resistance phytochemicals act in interaction with chemotherapeutic drugs. According to WHO, about 80% of the world's populations depend on traditional plant-derived medicine for their prime health care (Farnsworth et al. 1985). With anticancer potential, the phytoconstituents antioxidants are carotenoids, vitamins (e.g.,A, C, E, and K), terpenoids, polyphenols (e.g.,gallic ellagic acid, and tannins), enzymes (e.g., superoxide dismutase, catalase, and glutathione peroxidase), flavonoids (e.g. quercetin, flavanones, anthocyanins, isoflavones, catechins, flavones, and isocatechins), minerals (e.g., copper, zinc, iodine, manganese, chromium, and selenium), polysaccharides saponins, alkaloids, lignins, xanthones and certain pigments (Madhuri and Pandey, 2009; Sultana et al. 2024).

Ficus religiosa

Ficus religiosa Linn. (*Moraceae*), regularly familiar as peepal. The genus *Ficus* (*Moraceae*) founds one of the main genera of angiosperms with more than 800 species of trees, shrubs and epiphytes in the subtropical and tropical areas all over the world. One of the most diverse plant genera is *Ficus religiosa* (Table 2) with respect to its development with evergreen free-standing trees, and deciduous trees, stranglers, creepers, climbers, small shrubs, rheophytes and lithophyte (Ronsted et al. 2008). Ficus spp. usually known as fig, is moderately a small size deciduous tree native to Asia, Persia, Minor, Iraq Syria, and Mediterranean region and extensively originate in subtropical and tropical regions of India (Al-Yousuf, 2012).

Table 2: Taxonomy of *Ficus religiosa* (Sirisha et al. 2010)

Domain	*Eukaryota*
Kingdom	*Plantae*
Sub Kingdom	*Viridaeplantae*
Phylum	*Tracheophyta*
Subphylum	*Euphyllophytina*
Class	*Magnoliopsida*
Subclass	*Dilleniidae*
Order	*Urticales*
Family	*Moraceae*
Genus	*Ficus*
Species	*Religiosa*

Botanical Description

Ficus religiosa is a huge deciduous tree epiphytic when it young, and crown wide when it matures. Hight of this plant is up to 35m (Fig. 1. A). Its plummeting branches bear coriaceous, dark color stipulate leaves (Fig. 1. B). Base approximately cuneate to cordate, margin whole or undulate; on respectively the midvein secondary veins seven to five, with finely reticulate venation lateral veins eight in pair, (Fig. 1. C); petioles 7.5-10cm in length, slender; stipules tiny ovate, severe (Fig. 1. D) paired or solitary, red on maturity axillary on leafy branchlets (Fig. 1. E), (Zhekun and Gilbert, 2003; Warrier et al. 1995; Kirtikar and Basu, 1993). With thin or membranous flakes, the bark is frequently enclosed with crustose lichen coverings (Fig. 1. F) is flat or slightly curved. Exfoliated with uneven curved flakes of 2-2.5cm thickness and the outer bark is ash or grayish colored. The central segments of the bark seem light reddish-brown or brownish in color. The innermost part comprises of the sheets of orange-brown or light yellowish colored granular tissue. The taste of bark is as stringent, and it is odorless. Few adventitious roots are present on the plant (Fig. 1. G) (Koilpillai et al. 2010; Warrier et al. 1995).

Ethnomedicinal Potential

Ficus religiose has been demonstrating dominant various therapeutic effects, and sell for ayurvedic activity (Patil et al. 2011) antitumor activities (Gulecha and Sivakuma*,* 2011). Conventionally, leaf juice was used in the

treatment of cough, asthma, sexual disorders, earache, gastric problems, diarrhea, haematuria, migraine, toothache, eye troubles, and scabies. The fruits of *ficus religiosa* plant were used in the treatment of scabies and other respiratory disorders and asthma. Stem bark was used in the treatment of paralysis, diabetes, gonorrhea, diarrhea, bleeding, bone fracture, as antiseptic, astringent and antidote (Fig. 2).

Chemo-preventive Phyto-chemicals in *Ficus religiosa* Plant

Ficus religiosa contains various active phytoconstituents, which was confirmed by preliminary phytochemical screening as given in Table 3. The special investigation was performed by using TLC and HPTLC procedures (HimaBindu et al. 2013).

Due to the presence of certain phytochemicals, the medicinal plant Ficus religiosa has anticancer potential. Some phytochemicals which are present in Ficus religiosa plant has strong anticancer potential. The specific portions of *Ficus religiosa* used in traditional medicinal manufacture a synergistic effect and reduce the side effect of chemotherapeutical drugs inconclusive samples (Chandrasekar et al. 2010). Different parts of *Ficus* species have shown apoptotic effects, and have anti-proliferative potential in cancer cell lines, thereby assuming a preparatory pharmacological help as anticancer drug (Gulecha and Sivakumar, 2011; Murugesu et al. 2021).

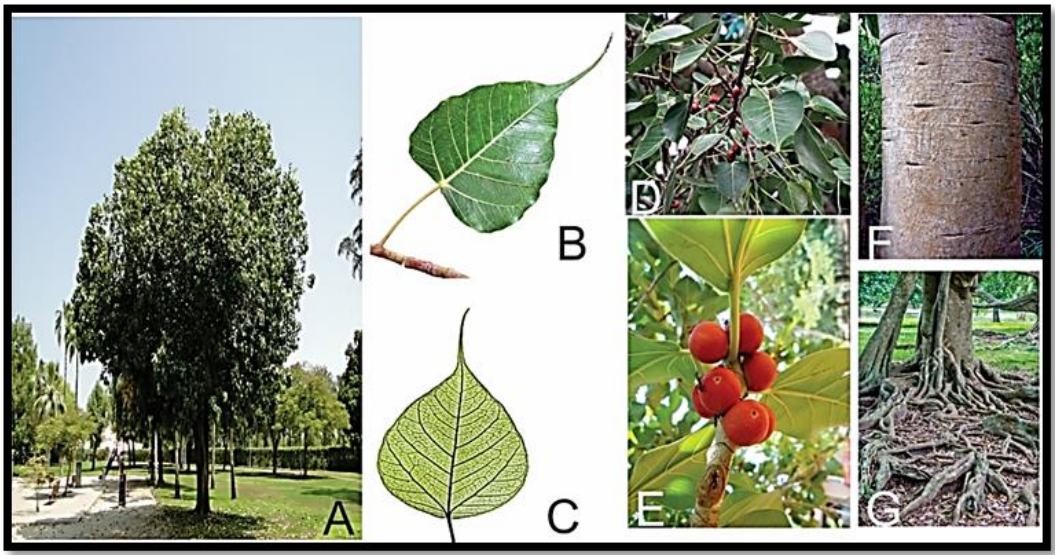

Fig. 1: Botanical features of *Ficus religiosa*. A: Mature tree; B: Mature Leaf; C: Reticulate venation in mature leaves; D: slender, tiny stipules E: fruits in paired or solitary formation on leafy branchlets; F: the bark showing crustose lichen coverings; G: adventitious roots of *Ficus rel`igiosa*.

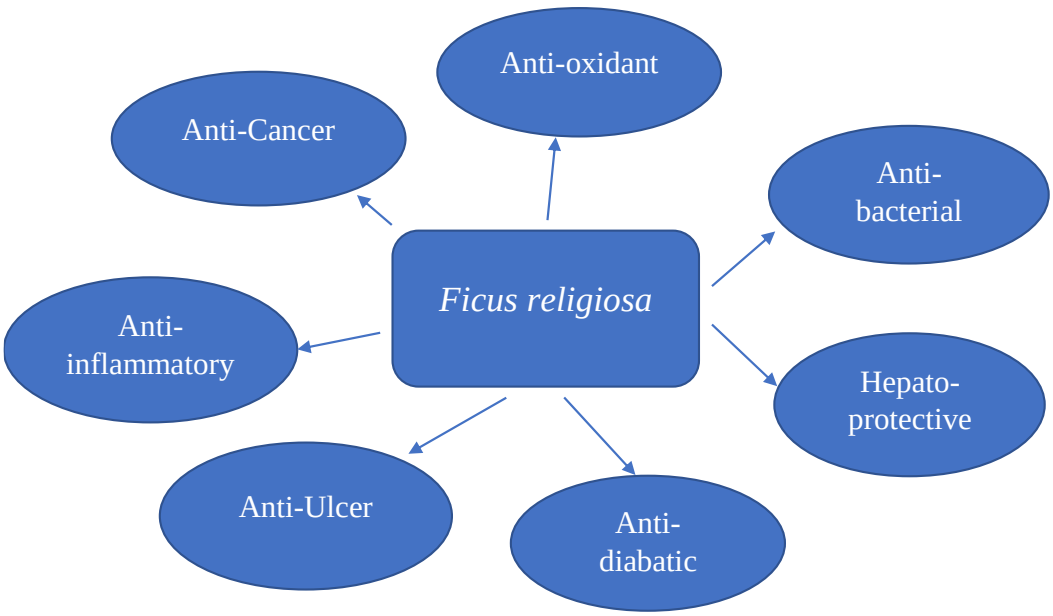

Fig. 2: Therapeutical potential of *Ficus religiosa* as evident from ethnobotanical survey (personal communication).

Table 3: Preliminary phytochemicals analysis of *Ficus religiosa* LINN (Aqueous extract)

S.No.	Phytochemicals	Plant Samples			
		Leaves	Stem	Bark	Fruits
1.	Sterol	-	-	-	-
2.	Reducing sugar	-	-	-	-
3.	Sugar	-	+	+	-
4.	Alkaloids	-	-	+	-
5.	Phenols	-	-	+	+
6.	Flavonoids	-	+	-	+
7.	Tannins	+	+	+	-
8.	Saponins	-	-	-	-
9.	Amino acids	-	-	-	-
10.	Glycosides	+	+	+	+
11.	Terpenoids	+	+	+	+

+: present, **-**: absent

Flavonoids

To estimate the protective effect of flavonoids against cancer, a huge number of epidemiological studies had been conducted. It has a great impact on the immune activities related to the development of cancer cells. Research relating to animal models revealed the positive and strong protective effect of flavonoids against the cancer cells (Batra et al. 2013; Ghadigaonkar et al. 2021).

Alkaloids

They have many such compounds that possess the anti-cancer effects. Many in-vitro and in-vivo studies revealed that they exhibit anti-proliferation and anti-metastasis effects on different types of cancer cells. they have many compounds possess the anti-cancerous activities (Lu et al. 2012). Primitive anticancer drug was found from the plant *Vinca rosea* i.e. Vinca alkaloids. Few more alkaloids such as berberine, colchicine and morphine, etc. were found effective against the cancer cells.

Phenolics

Their derivatives induced the anti-proliferative effects on cancer cells, for example, as in terms of topoisomerase or phosphatidylinositol-3-kinase inhibition, or even cell cycle arrest. It is usually considered that the toxicity related to the phenolic derivatives are mediated via their oxidative activity, oxidative damage can increase in vitro conditions, either protein or DNA and carbohydrates compounds. Some studies revealed that the mechanism of phenol cytotoxicity is related to their pro-oxidant properties (Gomes et al. 2003; Ghadigaonkar et al.2021; Shahid 2021).

Glycosides

In the 1960s inhibition of cancerous cells of cardiac glycosides was observed in an in vitro study. After that, many such anti-malignant effects of these compounds have been reported yet. Breast cancer treatment via cardiac glycosides was reported in 1979 (Winnicka et al. 2006).

Saponins

New research experiments found that saponins have an anti-cancer effect in many tumor cells. Their derivatives inhibit cancer cell proliferation via apoptosis and cell cycle arrest with IC50 values up to 0.2 mM.

Steroids

They have the potential to kill the cancer cells of ovary, lungs, stomach, and estrogen-dependent human breast cancer. It has been also observed that their derivative compounds prevent the initiation of tumor growth, invasion and metastasis, also enhance the apoptosis of cancer cells (Woyengo et al. 2009).

Terpenoids

It is considered as the largest class of the natural compounds and a reservoir of natural drug discovery. Recent research reports in the development of anti-tumor drugs obtained from the natural products leading to the

identification of many terpenoids compounds that prevent the growth of tumor cells via various biological mechanisms (Huang et al. 2012).

Anticancer Potential of *Ficus religiosa* Plant and their Future Direction

i. Leukemia Cancer

Sacred fig (*Ficus religiosa*) disclosed an extensive range of pharmacological behaviors like antibacterial, anthelmintic, antioxidant, antiulcer, anticonvulsant, antiamnesic, anti-asthmatic, antianxiety and anti-inflammatory (Utami et al. 2020 (Wu et al. 2002, Shahid et al. 2021). Khulood et al. (2014) observed the active List of Antiproliferative activity of *Ficus religiosa* compounds of *Ficus religiosa* leaves extract against K562 (leukemia) cell lines. The cytotoxic effects of the extract were estimated on human leukemic cancer cell lines. Sulforhodamine B assay (SRB) was used to check the anticancer potential. Tannic acid and Serotonin acid or their isomers showed cytotoxicity on cancer cells and were revealed as active compounds in chloroform extract of *F. religiosa* plant.

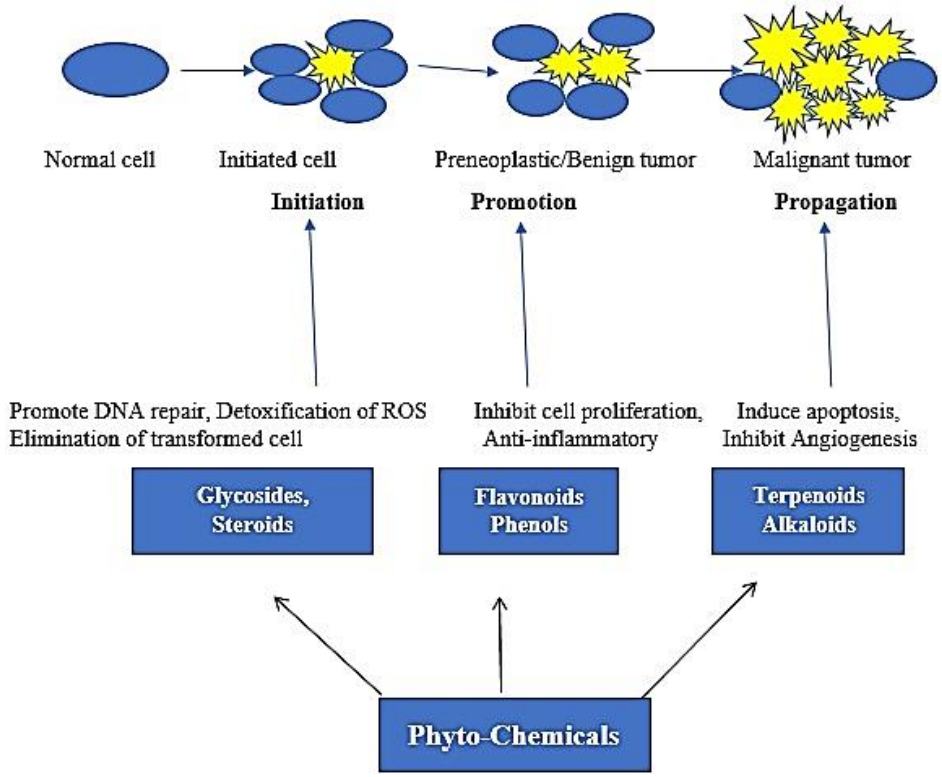

Fig 3: Carcinogenesis is a multistep process in which normal cells convert into cancerous cells. *Ficus religiosa* phytochemicals exert chemo-preventive effect by blocking tumor initiation and promotion. These phytochemicals induce apoptosis and inhibit angiogenesis in malignant cells

Cancer model	Dose Conc.	Cell lines	Molecular Targets	References
Breast cancer	100µg/ml	MCF7	Cell cycle arrest inhibited cell proliferation, Induced cell death via ROS generation	Gulecha and Sivakuma, 2011
Prostate cancer	IC50 = 0.3 ± 0.02 mg/ml	PC3	Inhibition of growth of cell line via downregulation of ID signaling pathway	Niran *et al*., 2013
Cervical cancer	0-80µg/ml	SiHa and HeLa	Induces cell cycle arrest, exerts apoptosis, reduce invasion and migration	Choudhari *et al.,* 2011

ii. Breast Cancer

The anticancer potential of different extract of *Ficus religiose* (Moraceae) and *Tephrosia purpurea* (Fabaceae) was studied by (Gulecha and Sivakuma, 2011). The extracts of both the plants were prepared and human MCF7 cell lines were used. Trypan blue exclusion method was used to check the invitro-anticancer activity of different plants extract. The extract of FRI, FRIII, TPI, and TPIII showed maximum anticancer activity as compared to other extracts. The estimated IC50 value for FRI (160.3µM), FRIII (222.7µM), TPI (152.4µM) and TPIII (158.71µM). According to this study the FP and TP plants extract have anticancer potential against MCF7 cell lines (Fig. 3).

iii. Cervical Cancer

Ficus religiosa L. (Moraceae) familiar to have many therapeutics potentials in natural drugs. Choudhari *et al.* (2011) examined the cytotoxicity and antioxidant potential of *Ficus religiosa*. The ethanolic extract of bark of this plant was prepared. Cervical cell lines SiHa and HeLa were used to check the anticancer activity of the extract. The ethanolic and aqueous bark extract had dominant cytotoxicity and antioxidant potential as estimated by the Oxygen Radical Absorbance Capacity technique. In cervical cell lines, HeLa (HPV18 positive) and SiHa (HPV16 positive) of the ethanolic and aqueous extracts of *Ficus religiosa* showed maximum anticancer and cytotoxic activity. However, the ethanolic extract shows maximum cytotoxicity contrast to aqueous extract at much lower doses. This study revealed that with the special reference to cervical cancer cell lines *Ficus religiosa* would be explored more for its anticancer activity.

iv. Prostate Cancer

Active compounds of *Ficus religiosa* leaves chloroform extract against human prostate cancer (PC3) cell lines were determined by (Niran et al. 2013). Prostate cancer cell lines were docetaxel (PC3 TxR) resistant. Sulforhodamine B assay (SRB) was used to check the anticancer potential. The results showed that Ficus religiosa leaves extract Inhibit the growth of the PC3-TxR cell line via downregulation of ID signaling pathway.

Conclusion

The wide literature review has discovered *F. religiosa* as a significant medicinal plant used for the treatment of different diseases. Medicinal plants show a significant role in the lives of poor people, with few medical facilities. Phytochemical research was done in *F. religiosa* that led to the discovery and isolation of plant metabolites. This review exposes that *F. religiosa* has various phytochemicals like flavonoids, phenols, terpenoids, saponins, alkaloids, and glycosides. Various pharmacological activities like anti-cancer, anti-oxidant etc. have been studied in F. religiosa. Different parts of *Ficus* species had shown apoptotic effects, and have anti-proliferative potential in different cancer such as Breast cancer (MCF7), Prostate cancer (PC3) and Cervical cancer (HeLa and SeLa). Further research in vitro and in vivo, and human clinical trials are required to elucidate their mechanisms of action and their whole therapeutic potential against different cancer.

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