



A REVIEW OF ANTICANCER AND CYTOTOXIC PROPERTIES OF FICUS SPECIES LATEX IN INHIBITION OF BREAST CANCER

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Abstract: In recent times use of plant natural products has increased tremendously and there is a very high demand of herbal products for therapeutic, clinical, agricultural purposes. Plant latex is a rich source of pharmaceuticals, pesticides and immune allergins. Ficus (Fig fruit) latex exerts inhibitory effects on proliferation of various cancer lines, probably due to high amount of phytosterols and flavonoids, responsible for its free scavenging as well anticancer activity. The ayurvedic system of medicine also assures the effect of milky substance (latex) in lessening the inflammation in various cancer types. It is widely accepted that alterations of cyclooxygenase-2(COX-2) expression and the abundance of its enzymatic product prostaglandin E₂ (PGE₂) have a key role in influencing the development of breast cancer. The present review correlates antioxidant activity of ficus species with its pharmacological activities.

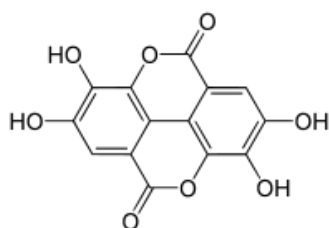
Key Words: Ficus, anticancer effects; cytotoxic effects; medicinal plant

INTRODUCTION

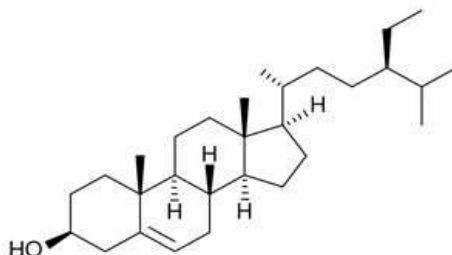
Plants have been the major source of drugs in Indian system of medicine and other ancient systems in the world. Earliest description of curative properties of medicinal plants is found in Rig-Veda. Information on medicinal plants in India has been systematically organized[1-4]. India has an ancient heritage of traditional medicine. Indian traditional medicines based on various systems including Ayurveda, Siddha, Unani and Homeopathy. Herbal medicine is based on the premise that plants contain natural substances that can promote health and alleviate illness Today, we are witnessing a great deal of public interest in the use of herbal remedies[5]. In Ayurveda, FICUS belongs to a class of drugs called rasayana. Rasayana are rejuvenators, antioxidants and relieve stress in the body[6, 7]. Apart from the usage in traditional medicine, scientific studies indicate FICUS to possess various biological effects such as hepatoprotective[8], chemopreventive[9], antidiabetic[10], anti-inflammatory[11], antipyretic[12], antitussive[13] and antidiuretic[14]. The bark has also been evaluated for cytotoxic effects using various cell lines and found to be safe and less toxic than aspirin, a commonly consumed anti-inflammatory drug[15].

PHYTOCHEMICAL COMPOSITION OF FICUS LATEX

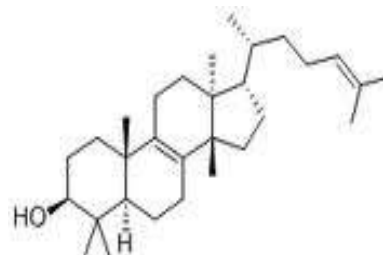
The crude latex of FICUS shows the presence of a serine protease, named religiosin. Religiosin is an acidic protein optimally acts at p^H 8.0 – 8.5 and temperature 50°C. The major phytochemical constituents of latex includes α-amyrin, β-sitosterol, cycloartenol, cycloeuphordenol, 4-deoxyphorbol and its esters, euphol, euphorbinol, isoeuphorbol, palmitic acid, taraxerol, tinyatoxin, tirucallol, ellagic acid.



Ellagic acid



β -sitosterol



Euphol

ETHNO-PHARMACOLOGY:

Traditional Uses

FICUS is a well known ethnomedicinal tree used in Ayurveda. Its use in the Indian traditional folk medicine also well documented. The use of different parts of *F. religiosa* in traditional system of medicine (Table 1). The bark of FICUS is an important ingredient in many Ayurvedic formulations, such as Nalpamaradi tailam, Chandanasavam, Nyagrodhadi churna and Saribadyasavam[21, 22]. In children, the latex is given along with sugar to combat diarrhea and dysentery. The latex mixed with sugar is benevolent in sexual debility in males. The juice of its fruit is a panacea for hiccup. According to Unani system of medicine, latex is applied externally on chronic infected wounds to alleviate edema, pain and to promote the healing.

Modern Uses

In warm, humid climates, figs are generally eaten fresh and raw without peeling, and they are often served with cream and sugar. Peeled or unpeeled, the fruits may be cooked in various ways, as in pies, puddings, cakes, bread or other bakery products, or added to ice cream mix. Home owners preserve the whole fruits in sugar syrup or prepare them as jam, marmalade, or paste. Fig paste (with added wheat and corn flour, whey, syrup, oils and other ingredients) forms the filling for the bakery product. Other modern uses are as poultice, eating, ointment, drink, gargle, simultaneously eating pickled figs, fumigation, rubbed externally, liniment, on sponge, enema, skin application, and ophthalmic etc[23].

Table 1. Ethnomedicinal uses of different parts of *FICUS*

Plant Parts	Traditional Uses (as/in)
Bark	Astringent, cooling, aphrodisiac, antibacterial against <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> , gonorrhoea, diarrhoea, dysentery, haemorrhoids and gastrohelcosis, anti-inflammatory, burns [17].
Leaves and tender shoots	Purgative, wounds, skin diseases [17].
Leaf juice	Asthma, cough, sexual disorders, diarrhea, haematuria, toothache, migraine, eye troubles, gastric problems, scabies [17-19].
Dried fruit and Fruit	Tuberculosis, fever, paralysis, hemorrhoids [20], Asthma, laxative, digestive [17].
Seeds	Refrigerant, laxative [17].
Latex	Neuralgia, inflammations, haemorrhages [17].
Leaf decoction	Analgesic for toothache [19].

**ACTION OF PHYTOCHEMICAL**

Alkaloids: In nature, the alkaloids exist in large proportions in the seeds and roots of plants and often in combination with vegetable acids. Alkaloids have pharmacological application as anesthetics and CNS stimulants.

Glycosides: This group of drugs are usually administered in order to promote appetite and aid digestion[24, 25]. The extracts of the plants that contain cyanogenic glycosides are used as flavoring agents in many pharmaceutical preparations. Amygdalin has been used in the treatment of cancer and also as a cough suppressant in various preparations.

Flavonoids: They are important group of polyphenols widely distributed among the plant flora. Numerous reports support their use as antioxidants or free radical scavengers.[26]

Phenolics: They play an important role in plant defense against pathogens and herbivore predators, and thus Phenolics essentially represent a host of natural antioxidants, used as nutraceuticals, and found in apples, green-tea and red-wine for their enormous ability to combat cancer and as anti-inflammatory agents.

Saponins: Saponins are also important therapeutically as they are shown to have hypolipidemic and anticancer activity. They are also necessary for activity of cardiac glycosides.

Tannins: They are used as antiseptic and this activity is due to presence of the phenolic group. Tannin-rich medicinal plants are used as healing agents in a number of diseases. In ayurvedic formulations based on tannin-rich plants have been used for the treatment of diseases like leucorrhoea, rhinorrhoea and diarrhoea.

Terpenes: Diterpenes are classically considered to be resins and taxol, the anticancer agent, is the common example. Triterpenes include steroids, sterols and cardiac glycosides with anti-inflammatory, sedative, insecticidal or cytotoxic activity.

Steroids: Steroids have been observed to promote nitrogen retention in osteoporosis and in animals with wasting illness. Caution should be taken when using steroidal glycosides as small amounts would exhibit the much needed stimulation on a diseased heart, whereas excessive dose may even cause death.

PHARMACOLOGICAL ACTIVITIES**Free Radical Scavenging Activity**

The ultrasonic-assisted extraction of total flavonoids of Ficus and their scavenging activities against hydroxyl and superoxide anion free radicals[27] are studied. The total flavonoids extract from Ficus had marked scavenging effects on both hydroxyl and superoxide anion free radicals in a concentration-dependent fashion.

Anticancer activity

A mixture of 6-O-acyl- β -D-glucosyl- β -sitosterols (where acyl moiety being primarily palmitoyl and linoleyl with minor amount of stearyl and oleyl) found in Ficus latex are potent cytotoxic agents[28]. Both the natural and the synthetic compounds showed in vitro inhibitory effects on proliferation of various cancer cell lines. Polyphenols particularly are among the diverse phytochemicals that have the potential in the inhibition of carcinogenesis. Phenolics acids usually significantly minimize the formation of the specific cancer-promoting nitrosamines from the dietary nitrites and nitrates. Human Papilloma Virus (HPV) that may cause uterine cancer was specifically inhibited by Indole-3-carbinol mostly found in broccoli. It also blocks the estrogen receptors specifically present in the breast cancer cells as well as down regulates CDK6 and up regulates p21 and p27 in prostate cancer cells. Phytosterols block the development of tumors (neoplasm) in colon, breast and prostate glands. The exact mechanism underlying the blockade is not clearly known yet [24]

Antioxidants

Antioxidants protect cells against the damaging effects of reactive oxygen species otherwise called, free radicals such as singlet oxygen, super oxide, peroxy radicals, hydroxyl radicals and peroxynite which results in oxidative stress leading to cellular damage. These free radicals are involved in a number of diseases including: tumor inflammation, atherosclerosis, diabetes, asthma, rheumatoid arthritis etc. Free radicals generated during oxidative stress damage the insulin receptors and thereby decrease the number of sites available for insulin function. Literature suggests that Ficus, a rasayana group of plant drug have antidiabetic along with antioxidant potential which was beneficial in treatment of type 2 diabetes.[24, 29]

**Immunomodulatory effect**

The immunomodulatory effect of ethanolic extract of the leaves of *Ficus* (Moraceae) was investigated in mice^[30]. The study was carried out by various hematological and serological tests. Administration of extract remarkably ameliorated both cellular and humoral antibody response.

Anti-inflammatory activity

The probable anti-inflammatory effect of petroleum ether, chloroform and ethanol extracts obtained from *Ficus*^[31]. Anti-inflammatory activity was studied by carrageenan-induced rat paw edema and cotton pellet granuloma methods. The petroleum ether, chloroform and ethanol extract significantly reduced carrageenan-induced paw edema and cotton pellet granuloma in rats. These extracts showed a greater anti-inflammatory effect comparative to standard drug Indomethacin.

COX-2 INHIBITOR AS ANTICANCER AGENT

The pathophysiological role that COX-2 plays in inflammation, recent evidence implies that this isoform may also be involved in multiple biologic events throughout the tumorigenic process. Many epidemiological studies demonstrate that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the risk of a wide range of tumors. Further, COX-2 is chronically overexpressed in many premalignant, malignant, and metastatic human cancers, and levels of overexpression have been shown to significantly correlate to invasiveness, prognosis, and survival in some cancers. Pharmacological studies consistently demonstrate that COX-2 inhibitors dose-dependently inhibit tumor growth and metastasis in various relevant animal models of cancer. Importantly, several investigators have also shown COX-2 inhibitors may act additively or synergistically with currently used cytotoxics and molecularly targeted agents. In a broad overview, it is evident that COX-2 plays a pivotal role throughout oncogenesis and future work has to explore the use of COX-2 inhibitors for the prevention and/or treatment of cancer as a single agent or in combination with current anticancer modalities.

CONCLUSIONS

Presently there is an increasing interest worldwide in herbal medicines accompanied by increased laboratory investigation into the pharmacological properties of the bioactive ingredients and their ability to treat various diseases. Numerous drugs have entered the international through exploration of ethno pharmacology and traditional medicine. Although scientific studies have been carried out on a large number of Indian botanicals, a considerably smaller number of marketable drugs or phytochemical entities have entered the evidence-based Therapeutics^[32]. In summary, COX-2 is over expressed in both early and late stages of carcinogenesis and has been shown to be efficacious as monotherapy and in combination with conventional chemotherapeutics in relevant animal models. Taken together, the epidemiological data and preclinical studies in animal models have generated compelling interest in the potential use of COX-2 inhibitors in chemoprevention and chemotherapy of human tumors. Clinical trials will be necessary to determine whether COX-2 inhibitors will provide clinical benefit, as well as to define the intervention points during tumor progression that will allow for optimal efficacy. Recent research has clearly established that specific COX-2 inhibitors are associated with less toxicity than the conventional mixed COX inhibitors.^[33]

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