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Ocimum Sanctum Linn. (Tulsi): An Ethnomedicinal Herb Used in the Prevention and Treatment of Cancer

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Abstract:
For thousands of years prior to the development of western medicine, people used traditional medicine to cure various ailments. With cancer being the most serious hazard to humanity, ethnomedicine can play an important role in cancer prevention and treatment. Among all therapeutic herbs, *Ocimum sanctum Linn* has chemo-preventive molecules and chemicals with anti-carcinogenic activity. In Ayurvedic medicine, its leaves, seeds, and roots are used. Numerous nutrients and bioactive substances may be found in Tulsi. The main chemical components of Tulsi include rosmalinic acid, oleanolic acid, caryophyllyne, and linalool. Some of its phytochemicals, such as eugenol, rosmarinic acid, apigenin, myretenal, luteolin, -sitosterol, and carnosic acid, have also been shown to prevent chemically induced skin, liver, oral, and lung cancers. These effects are mediated by increasing antioxidant activity, altering gene expression, inducing apoptosis, and inhibiting angiogenesis and metastasis. Studies on *Ocimum Sanctum's* possible effectiveness against conditions like breast, skin, and lung cancer have been conducted. All of these sorts of cancer diseases may be treated with this as an additional or complementary medication, and it can be included in many ways into a regular diet.
***Keywords**: Ocimum sanctum*, Ethanomedicine, Anti-carcinogen, DNA Damage, Anti-oxidant.

Introduction:

Medicinal plants are utilised as the sole accessible medications by 80% of the world's population, particularly in developing countries. The positive therapeutic effects of plant materials are generally caused by the interaction of secondary metabolites found in the plant (Mamun-Or-Rashid, et al 2013). Since the dawn of civilization, medicinal plants have been utilised to treat a variety of human maladies all throughout the world. The Indian traditional medical system comprises hundreds of medicinal plants with a variety of effects (Upadhyay,2017). Throughout the course of human history, ethno-medicines have been a crucial part of daily healthcare practises. Traditional medicine has been used by humans to cure various ailments for thousands of years prior to the development of western medicine. Since cancer is the biggest hazard to the human race, ethnomedicine can significantly contribute to the prevention and treatment of cancer. *Ocimum sanctum Linn*, a medicinal herb, possesses certain chemo-preventive molecules and chemicals that have anti-carcinogenic activities (HepzibahandRaj,2022).In India, Tulsi is revered as a sacred herb. In Ayuveda, Tulsi (*Ocimum sanctum*) is an aromatic herb. It belongs to the family Labiateae. It is grown in a number of tropical and subtropical nations (Kumar et al.,2022). *Ocimum sanctum* can be found in two varieties: black (Krishna Tulsi) and green (Rama Tulsi), both with similar chemical compositions (Mondal, 2009).This plant, also known as 'The Queen of Herbs,' has been valued in India for over 5000 years as a healing balm for body, mind, and soul (Kumar et al.,

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2011). Tulsi is regarded as an adaptogen, harmonising many systems in the body and aiding in stress adaptation. Marked by its strong aroma and astringent taste, it is regarded in Ayurveda as a kind of "elixir of life" and believed to promote longevity (Mandal et al., 2015).

Biological source*:* The Lamiaceae family includes Ocimum species including *Ocimum sanctum L.* and *Ocimum basilicum* (Kumar et al., 2011). To make Tulsi, you need to use both fresh and dried leaves from these plants.

GEOGRAPHICAL SOURCE:

It is a revered Hindu plant that is a herbaceous, multi-branched annual plant found throughout India. The plant is often grown in gardens as well as around temples. Seeds are used to propagate it. Tulsi is grown commercially nowadays for its volatile oil.

SCIENTIFIC CLASSIFICATION:

Table1: Scientific Classification of *Ocimum Sanctum* (Pattanayak et al., 2010).

Kingdom	Plantae
Subkingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliophyta
Class	Magnolipsida
Subclass	Asteridae
Order	Lamiales
Family	Lamiaceae
Genus	*Ocimum*
Species	*O.sanctum*

Morphology:

It is a 30-75 cm tall, upright, much-branched annual or biennial subshrub with hairy stems and simple, opposite, green leaves that are intensely fragrant (Fig. 1a and b).The leaves are up to 5 cm long, oval, oblong, obtuse, or acute, and frequently somewhat grooved (Fig. 1c). Flowers are tiny, purple, and arranged in elongate racemes in tight whorls (Fig. 1d). The fruits are tiny, with reddish-yellow seeds (Bhattacharyya and Bishayee, 2013). From the Himalayas (up to 1800 m above sea level) to the Andaman and Nicobar islands, the plant is cultivated across India.

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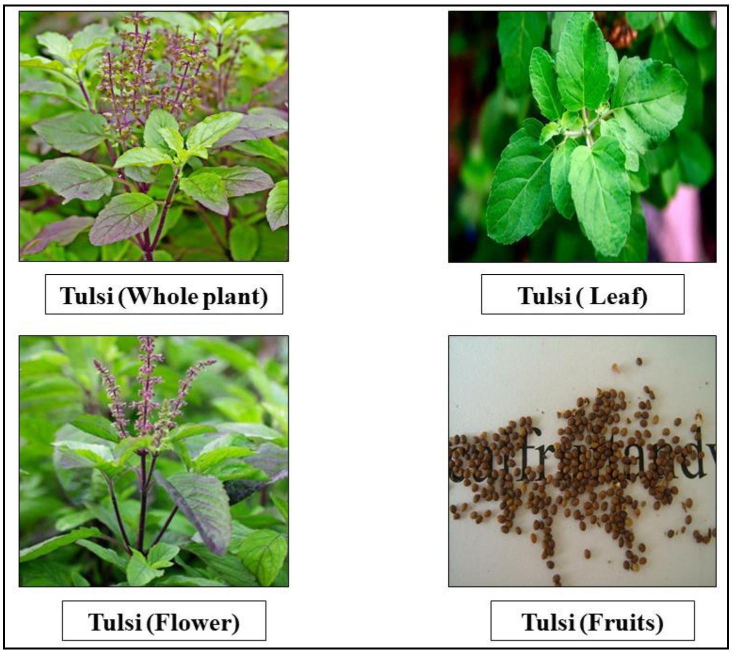

Fig 1: Various parts of Tulsi

Chemical Constituent*:* (Kumar et al., 2022, Shival et al., 2020, Bhattacharyya and Bishayee, 2013, Pattanayak et al., 2010)

The chemical composition of *O. sanctum* is highly complex, containing many nutrients and other biologically active compounds, the proportions of which may vary considerably between strains and even among plants within the same field. Because of differences in growing, harvesting, processing, and storage circumstances, the presence of phytochemicals in this plant may vary.

The volatile oil consists of about 70% eugenol (Fig. 2) . The other constituents of volatile oil include carvacrol, ursolic acid, linalool, limatrol, and caryophyllene. The volatile oil in seed contains sitosterol and fatty acid (Farombi,2014, Singh et al., 2007). Fresh leaves and stems include apigenin, rosmarinic acid, cirsilineol, cirsimaritin, isothymusin, and isothymonin, as well as significant levels of eugenol (Farombi,2014). Orientin and vicenin, as well as ursolic acid, luteolin, and molludistin, have been extracted from the leaf extract (Mondal et al., 2009, Sharifi-Rad et al., 2021). Tannins and a variety of sesquiterpenes and monoterpenes, including bornyl acetate, b-elemene, neral, a-pinene, b-pinene, camphene, campesterol, stigmasterol, and cholesterol, have also been identified in *O. sanctum* (Niture et al., 2006, Wihadmadyatami et al.,2019).

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Table 2: Chemical constituents present in Tulsi.

Sr No	Extract	Phytochemicals	Plant Part
1	**Fixed Oil**	Linoleic acid, Linolenic acid, Oleic acid, Palmitric acid, Stearic acid	Seeds
2	**Essential Oil**	6, 7, 27 Aromadendrene oxide, Benzaldehyde, Borneol, Bornyl acetate, Camphor, Caryophyllene oxide, cis-α-Terpineol, Cubenol, Cardinene, D-Limonene, Eicosane, Eucalyptol, Eugenol, Farnesene, Farnesol, Furaldehyde, Germacrene, Heptanol, Humulene, Limonene, n-butylbenzoate, Ocimene, Oleic acid, Sabinene, Selinene, Phytol, Veridifloro, α-Camphene, αMyrcene, α-Pinene, β-Pinene, α-Thujene, β-Guaiene, βGurjunene, methyl chavicol and linalool.	Leaves
3	**Mineral Content**	Vitamin C, Vitamin A, Calcium, Phosphours, Chromium, Copper, Zink, Iron.	Whole Plant
4	**Alcoholic Extract**	Aesculectin, Aesculin, Appgenin, Caffiec acid, Chlorgenic Acid, Circineol, Gallic Acid, Galuteolin, Isorientin, Isovitexin, Luteolin, Molludistin, Orientin, Procatechuic acid, Stigmsterol, Urosolic acid, Vallinin, Viceni, Vitexin, Vllinin acid	Leaves/areal parts

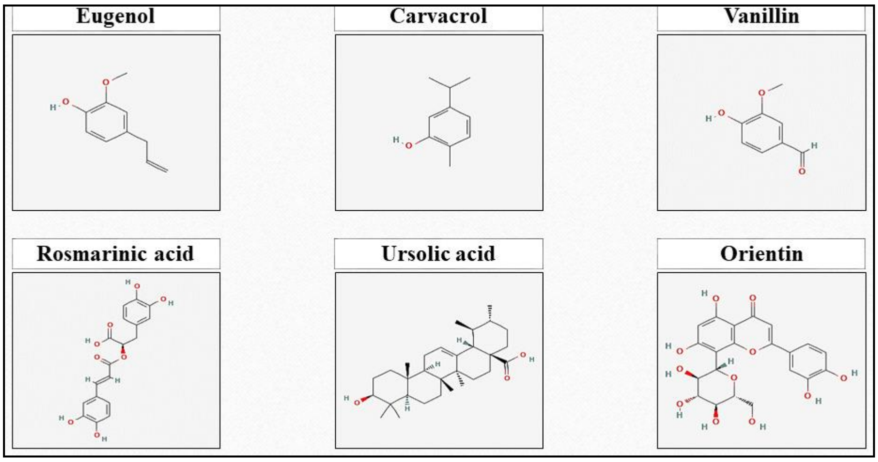

Fig 2: Chemical constituents present in Tulsi

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Pharmacological activity of *Ocimum sanctum*:

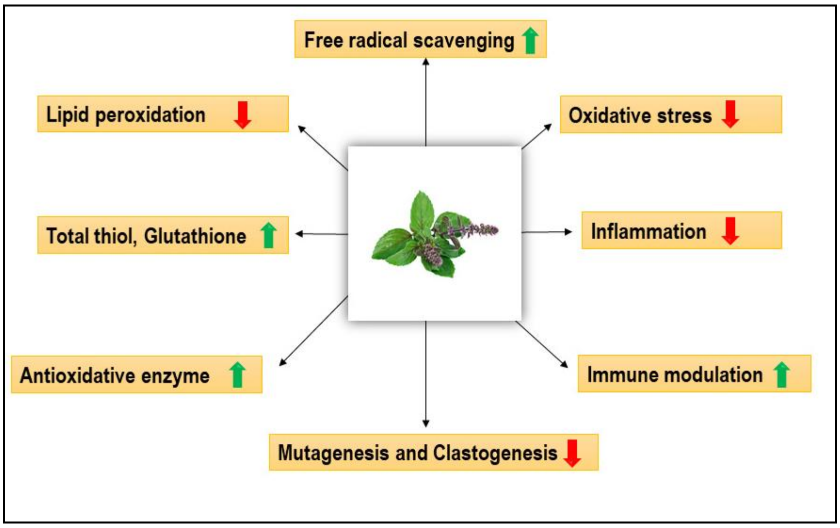

Fig 3: Pharmacological activity of *Ocimum sanctum*

Ocimum sanctum and Cancer:

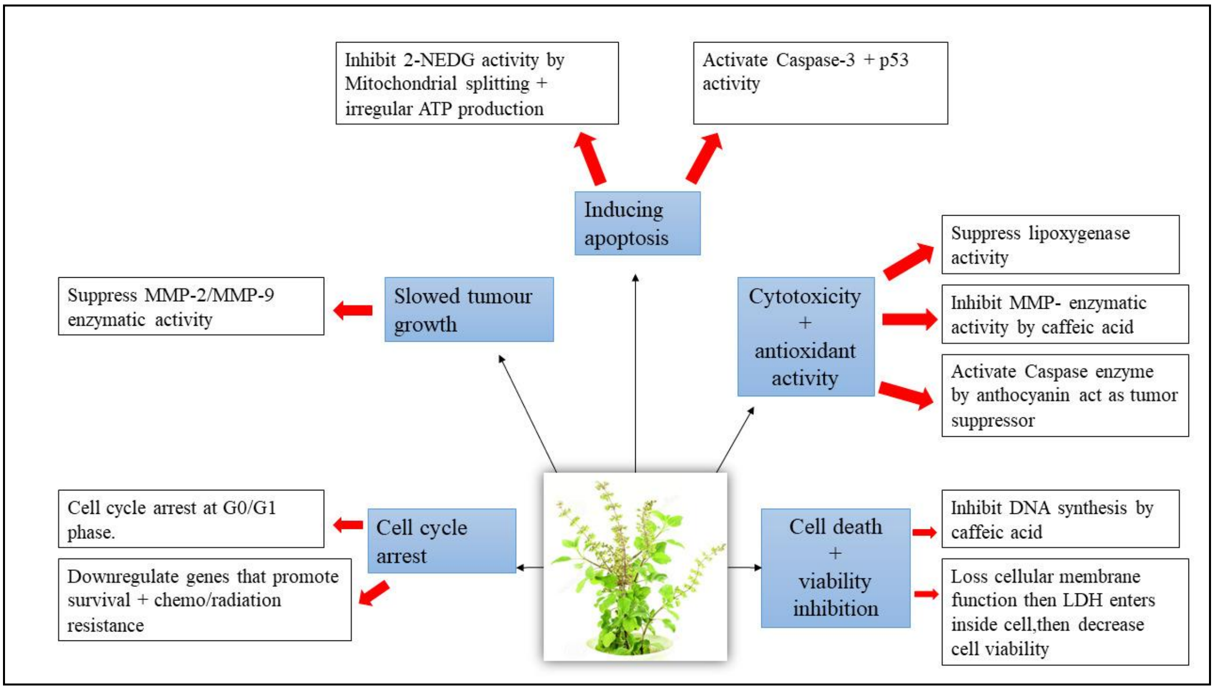

Fig 4: Anticancer activity of *Ocimum sanctum*.

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In-vitro studies:

When administered at concentrations of 50 g/ml and above, an ethanolic extract of *Ocimum sanctum* caused cytotoxicity. The cells' cytoplasm and nucleus were compressed morphologically. Biochemical analysis of the extract-treated HFS cells revealed decreased levels of intracellular glutathione and elevated concentrations of lipid peroxidation products (Sharifi-Rad et al., 2021). With a maximal 3-fold rise following a 72-hour treatment, holy basil (*Ocimum sanctum*) enhanced MGMT protein levels and its demethylation activity in a time-dependent way (Niture et al., 2006). Following the induction of apoptosis by EEOS treatment, the expression of caspase-3, reactive oxygen species (ROS), and the anti-apoptotic protein Bcl-2 were all upregulated. In addition to the GPx, this condition also inhibited SOD2 expression (Wihadmadyatami et al., 2019). EEOS was found to be cytotoxic to Lewis lung cancer (LLC) cells. In a concentration-dependent way, EEOS increased the activity of anti-oxidative enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) (Kim et al., 2010). 80% less MCF-7 cell growth at 1 mg/mL indicated that the extract has cytostatic effects. Additionally, AMPK was activated by the extract treatment. *Ocimum basilicum* stimulated mTOR signalling, another survival mechanism (Torres et al.,2018). In human cancer cells of HepG2, the chosen orientin analogue was non-cytotoxic/non-anti-carcinogenic up to 100 g/ml (202.389 M) concentrations for a prolonged exposure (Sharma et al.,2016). Oral squamous carcinoma cell line (Ca9-22) is sensitive to the cytotoxic compound O. sanctum. This plant has the capacity to combat oral cancer because it contains phytochemicals in its leaves (Luke et al.,2021). *O. sanctum* was evaluated in vitro using the MTT test and the Trypan blue exclusion assay. On the A549 malignant cell line, acetone and ethanol leaf extracts of *O. sanctum* demonstrated strong anticancer activity (Yadavalli,2019). M., S., and B. John studied the effect of ethanolic extract of *O. sanctum* on NCI-H460 cells and concluded that the extract (25-100g/ml) exhibited a substantial increase in ROS production in NCI-H460 cells. It significantly reduces NCI-H460 cell viability and colony formation capability, presumably due to increased oxidative stress. *Ocimum sanctum's* anticancer properties are further demonstrated by an increase in apoptotic cells. Apoptosis begins with the loss of mitochondrial membrane potential (Sridevi et al.,2016).

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Table 3: In-Vitro cell studies of Tulsi.

Materials tested	Cell lines	Mechanisms	References
Ethanolic extract of leaves	HFS-1080 human fibrosarcoma	Increase Lipid peroxides; decrease GSH Showed cytotoxicity.	(Sharifi-Rad et al., 2021)
Aqueous and ethanolic extracts of leaves	HT29 human colon cancer	Increase MGMT; Increase GSTP1 proteins and mRNAs Attenuated alkylation-induced carcinogenesis	(Niture et al., 2006)
Ethanolic extract of leaves	A549 human non-small-cell lung carcinoma	Increase Sub-G1; Increase apoptosis; Increase PARP; Increase cyt. c; Increase caspase-9, Increase caspase-3; Increase Bax; decrease Bcl-2; decrease pAKT; decrease pERK Showed cytotoxicity	(Wihadmadyatami et al., 2019)
Ethanolic extract of leaves	Mouse Lewis lung carcinoma	decrease MMP-9 Exerted a decrease in cell viability and inhibition of cell adhesion and invasion	(Kim et al., 2010)
Aqueous extract of leaves	MCF7 Human Breast Cancer cell line	Activation of mTOR signaling Showed cytotoxicity	(Torres *et al.*,2018)
Ethanolic extract of leaves	Human Lung Adenocarcinoma Cells (A549)	Decreased the levels of integrin v3, integrin 51, and VEGF.	(Kustiati et al.,2022)
Ethanolic extract of leaves	LNCaP prostate cancer cells	Elevated the activities of caspase-9 and caspase-3	(Dhandayuthapani et al.,2015)
Ethanolic extract of leaves	MCF-7,MDA-MB-231 and MDA-MB-453	TNF-α, GST and SOD gene were significantly reduce	(*Gupta et al., 2021)*

In-vivo studies:

As recognised cancer therapies, surgery, radiation, and chemotherapy are expensive, mutilating, and have significant side effects, as well as frequent relapses. Ayurvedic botanicals contain anticancer and antitumor effects. D gajula investigated the chemopreventive impact of three varieties of o.tenuiflorum at 1 to 2% AOM generated abreent crypt foci (ACF) in fisher 344 male rats and concluded that holy basil leaves decreased the AOM induced ACF in male fisher rats and had potential chemopreventive effect (Shackelford et al.,2009). O. sanctum showed chemopreventive activity against subcutaneously injected 20 methylcholanthrene induced fibrosarcoma tumors in Swiss albino mice In Swiss albino mice, O. sanctum exhibited chemopreventive effect against subcutaneously injected 20 methylcholanthrene-induced fibrosarcoma tumours. It was found that the survival rate of mice was enhanced and tumor spread rate delayed in seed oil supplemented mice which showed

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its chemopreventive property (Upadhyay,2017). ManjuVaiyapuri reported that Orientine, a flavonoid found in Tulsi, reduces the development of abnormal crypt foci and restores DMH-induced cell proliferation, as seen by AgNORs staining of experimental rats' colonic tissues. As a result, orientin may help to prevent DMH-induced precancerous lesions and has been shown to be a powerful antioxidant and antiproliferative agent (Thangaraj et al.,2018). This anti-tumorigenic ability of Tulsi has been proven experimentally using tumor-bearing nude mice and breast cancer generated by dosing Sprague-Dawley rats with dimethylbenz[a]anthracene (DMBA) and medroxyprogesterone acetate (MPA). MPA enhances VEGF and decreases VEGF receptor-2 (VEGFR-2) in hyperplastic areas, according to the study findings (Kaushal et al.,2018). additionally presence of flavonoids in Tulsi is been able to protect normal tissue cells from harmful effects of radiation including anticancer properties (Singh et al.,2012). The administration of a 50% alcoholic aqueous extract of several Ocimum species orally (200 mg/kg, p.o.) resulted in a considerable reduction in tumour volume, an increase in average body weight, and an increase in mouse survival rate (Monga et al.,2011).

Tulsi and anti-oxidant property:

Oxidative stress, ageing difficulties, and chronic illnesses are inevitable phenomena that cause numerous biochemical and functional changes in an organism's body (Moreira et al.,2014). Excess ROS generation in living beings causes neurodegenerative diseases and DNA damage. Antioxidants can assist to prevent life-threatening illnesses by slowing the destructive effects of ROS and protecting the DNA during free radical production. Plants are the richest source of phytochemicals with therapeutic potential.

Tulsi is used to inhibit the oxidation of lipids, carbohydrates, proteins, and DNA, which can result in the production of aldehydes, ketones, esters, and other chemicals that are toxic to biological systems. (Gupta et al., 2021). Phenolic acids, hydroxycinnamates, and flavonoids are perhaps the major antioxidants (Girija,2008). Acyclic unsaturated oxygenated monoterpenes (e.g., linalool), aromatic oxygenated monoterpenes (e.g., eugenol), methylchavicol (estragole), sesquiterpene hydrocarbons (e.g., -bergamotene, germacrene D, -cadinene, -selinene, sesquiterpenes oxygenated (e.g. (Filip et al.,2016)

Pinderpal Kaur reported that the seeds of O. tenuiflorum have a high concentration of bioactive chemicals with antioxidant properties. Methanolic extract exhibited a higher DPPH value (Kaur et al.,2018). *O. basilicum extract had a greater phenol content and maximum levels of DNA protection and free radical scavenging against cadmium chloride toxicity (Thirugnanasampandan and Jayakumar, 2011).* The ursolic acid in Tulsi mitigated CP-induced oxidative stress and markedly raised GSH, SOD, and CAT levels while lowering MDA concentrations (Tripathi and Alshahrani, 2021).

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Tulsi and DNA Damage:

Deoxyribonucleic acid (DNA), a complex macromolecule, regulates vital genetic traits in all living things (Singh and Sharma, 2018). The vast majority of genetic data, flaws, and illnesses depend on various DNA types, their structures, and the activities they carry out within the human body. Endogenous and exogenous stimuli both have the potential to damage DNA and its crucial sections, posing a hazard to cells (Lu et al.,2015). Numerous genetic abnormalities that might be passed down from generation to generation could occur from the continuous exposure of live creatures' DNA and genome to harmful stimuli (Han et al.,2017). Antiproliferative, antibacterial, antioxidant, hypoglycemic, and DNA damage protective properties are all present in bioactive components (Salar and Purewal,2017).

Sallam, F. reported that TiO2-NP of holy basil essential oil raised serum biochemical indices, oxidative stress indicators, serum cytokines, DNA fragmentation, and DNA breakages; lowered antioxidant enzymes; and produced histological changes in the liver in Male Sprague-Dawley rats (Sallam et al.,2022). The presence of organophosphates in Tulsi leaf extract (Ocimum sanctum) was examined using the Comet test and by analysing zebrafish histological alterations. We have established that Tulsi extract not only offers protection but also has the power to repair DNA damage (Girinaath and Mahadevan,2019). Jebur, Ali B conclude that in β-Cyf effect on liver in male wister rat. Rats given basil essential oil extract then intoxicated with β-Cyf showed substantial changes in the majority of the parameters tested. Finally, basil essential oil extract was shown to have high antioxidant efficacy in combating β-Cyf toxicity because of its high phenolic content (Jebur et al.,2022). In a research by Manikandan, P, the chemopreventive effects of ethanolic Ocimum sanctum (OS) were assessed during gastric carcinogenesis caused by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Their results show that administering ethanolic OS leaf extract decreased the frequency of gastric carcinomas caused by MNNG. This was accompanied by increased levels of Bax, cytochrome C, and caspase 3 and reduced levels of PCNA, GST-pi, Bcl-2, CK, and VEGF (Manikandan et al.,2007).

Clinical study:

The antioxidant state of erythrocytes was studied in patients with squamous cell carcinoma of the mouth who were treated with radiation and an aqueous extract of O. sanctum flavonoids (1.32 mg/kg). The findings indicate that erythrocytes from cancer patients responded to oxidative stress by increasing GSH levels, whereas a drop in this endogenous antioxidant seen in extract-treated patients might be due to the free radical-scavenging impact of Ocimum flavonoids (Reshma et al.,2005).

Conclusion:

The ethnomedicinal herb O. sanctum has huge potential not just for cancer prevention but also for cancer therapy across a wide range of human malignancies. The antioxidant, anti-inflammatory, immunomodulatory,

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antiproliferative, proapoptotic, anti-invasive, antiangiogenic, and antimetastatic properties of O. sanctum fractions and pure compounds, as well as their ability to modulate a diverse array of enzymatic activities and signal transduction pathways, could explain the observed chemopreventive and antitumor therapeutic efficacy.

A thorough assessment of the in-vitro and in-vivo research reported here demonstrates that O. sanctum-derived compounds are beneficial in preventing or treating malignancies of many organs, including the oral cavity, stomach, colon, liver, skin, lung, and prostate. Nonetheless, phytoconstituents from O. sanctum may be effective in other cancer types, such as breast, esophageal, intestine, pancreas, and central nervous system cancer. Future study should concentrate on these unknown areas of cancer research.The probable negative impact of O. sanctum should be studied critically and clinically.if it is intended for long-term usage in concentrated form.This ethnobotanical 'wonder' plant has enormous potential for the prevention and treatment of human cancers.

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