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OCIMUM SANCTUM LINN. (HOLY BASIL): PHARMACOLOGY BEHIND ITS ANTI- CANCEROUS EFFECT

BABY JOSEPH [1] AND VRUNDHA M. NAIR [1, 2*]

[1]Interdisciplinary Research Centre, Department of Biotechnology, Malankara Catholic College, Mariagiri, Kaliakkavilai- 629 153, Kanyakumari District, Tamil Nadu, India.
[2]Department of Bioinformatics, Malankara Catholic College, Mariagiri, Kaliakkavilai- 629 153, Kanyakumari District, Tamil Nadu, India.

ABSTRACT

Presently, researchers have been given remarkable attention to complementary and alternative medicine to deal with cancer treatment from medicinal plants mainly due to its fewer side effects and ease availability. Several scientific studies deep- rooted the anti- cancerous property of *Ocimum sanctum* Linn., a traditional medicinal plant commonly known as Tulsi. The chemopreventive and radiopreventive property of *O. sanctum* along with its anti- oxidant, anti- inflammatory and anti- stress property reside as a backbone for it anti- cancerous effect. It is demonstrated that the cornerstone behind this effect is the various phytochemical constituents such as eugenol, orientin, vicenin- 2, linolenic acid and ursolic acid. The present review is an effort to amalgamate the various scientific studies underlying the anti-cancerous effect of *O. sanctum* under one roof. In this review, the anti-cancerous activity of *O. sanctum* in numerous cancers such as lung, skin, oral, cervical, gastric, breast and prostate were comprehensively represented.

KEYWORDS: Tulsi,essential oil,*Ocimum* genus,eugenol,gastriccancer,skincancer,lung cancer

VRUNDHA M. NAIR
Department of Bioinformatics, Malankara Catholic College, Mariagiri, Kaliakkavilai- 629 153, Kanyakumari District, Tamil Nadu, India.

INTRODUCTION

Cancer still remains as a leading cause of death in economically developed countries and ranks second in developing countries. Many herbs have been evaluated in clinical studies and are currently being investigated phytochemically to understand their tumoricidal actions against various cancers. The herbs mentioned in Ayurveda for cancer therapy results not only in total healing, but also reduce the side effects and cancer associated complications[1]. *Ocimum sanctum* Linn. commonly known as Tulsi (Holy Basil in English) is the sacred plant of India. Tulsi is a rich source of phytochemical compounds and hence the plant exhibits innumerable pharmacological effects including anti-cancerous activity. This review focuses on the anti- cancerous effects of *Ocimum sanctum* L. A brief description of the *Ocimum* genus with world- wide production[2] areas (Table- 1) and a glimpse in to *Ocimum* genus in India underlining the various species including *Ocimum basilicum* Linn., *Ocimum canum* Sims., *Ocimum gratissimum* Linn., *Ocimum kilimandscharicum* Guerke., *Ocimum sanctum* Linn. and *Ocimum viride* Willd were included. The review also highlights few phytochemicals in *O. sanctum* showing anti- cancerous properties, evidences showing the anti-cancerous property of Holy Basil predominantly its chemopreventive and radioprotective effect and articulate it with various carcinogenesis.

Table 1
World-wide Production Areas of Genus Ocimum

Climatic Condition	Country of Cultivation
Warm Climate	India, Pakistan, the Comores, Madagascar, Haiti, uatemala, Reunion, Thailand, Indonesia, Russia (Georgia,East-Caucasus) and South Africa
Mediterranean Climate	Egypt, Morocco, France, Israel, Bulgaria, USA (Arizona, California, New Mexico), Italy, Greece and Turkey
Temperate Climate	Hungary, Poland, Germany, Balkan countries, Slovakia

INSIGHT IN TO GENUS OCIMUM

Ocimum L., commonly named Basil is a member of the Lamiaceae family. *Ocimum* was first listed by Linnaeus[3] who listed five species. The genus *Ocimum* comprised of about 200 species of herbs and shrubs[4]. It is widespread over Asia, Africa, Central and Southern America. It is an important economic and medicinal herb. *Ocimum* requires warmth for growth and should be protected from frost. Square stem, opposite and decussate leaves with many gland dots are the typical characteristics of the family. The flowers are zygomorphic with two distinct lips.

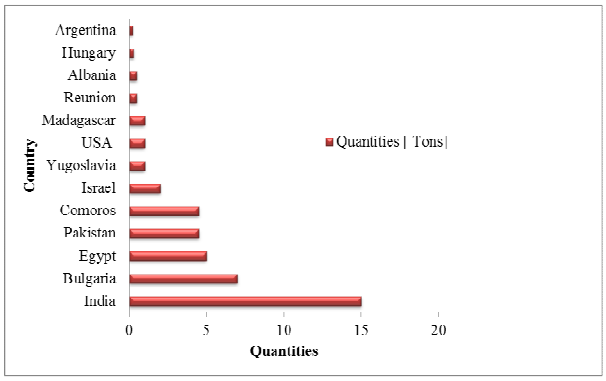
Taxonomy

Kingdom	:	Plantae
Subkingdom	:	Tracheobionta
Superdivision	:	Spermatophyta
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Subclass	:	Asteridae
Order	:	Lamiales
Family	:	Lamiaceae
Genus	:	*Ocimum* L.

It is cultivated for their extraordinary essential oil which displays many therapeutic usages such as in medicinal application, culinary, herbs, perfume for herbal toiletries, aromatherapy treatment and as flavouring agents. Many of the *Ocimum* which belongs to

particularly to subfamily Nepetoideae are strongly aromatic due to essential oils[5]. Quality and quantity of essential oil afforded by aromatic plants rely on heterogenous factors such as seasonal variation, method of harvest, leaf development stages, climate and soil type[6,]. The herb including its leaves, seeds, flowers, stem, root and inflorescence are rich in secondary metabolites. The general composition of phytochemicals found in *Ocimum* are especially eugenol, (E)-β-caryophyllene, bicyclogermacrene, anethole, linalool, 1,8-cineole[8], linoleic acid, mucilage, camphor, ocimol, Vicenin- 2, Ocimarin, isorientin, aesculectin, orientin, chlorogenic acid, isovitexin, aesculin, gallic acid,[9, 10, 11, 12, 13, 14] a-truxillic acid dimethylester, glucose, galactose, arabinose, a-sitosterol, ocimic acid, xanthomicrol[15] , vitamins A, Vitamin C and rosmarinic acid. The chemical composition of basil oils are generally characterized by oxygenated monoterpenes and phenylpropane derivatives. Although basil products have wide popularity no up-to date figures can be found on the national and international trade statistics. Basil oil[16] (Figure- 1), dried basil herb and fresh basil were the basil products of huge market potential.

Figure 1
Countries Producing Basil oil



OCIMUM SPECIES IN INDIA

In India, Tulsi is considered as a sacred plant and its medicinal property are very well documented in Ayurveda. Two forms of Tulsi are more common in India: dark or Shyama (Krishna) Tulsi and light or Rama Tulsi. The former possesses greater medicinal value and is commonly used for worship. Commonly found species of tulsi in India include *Ocimum basilicum* Linn., *Ocimum canum* Sims., *Ocimum gratissimum* Linn., *Ocimum kilimandscharicum* Guerke., *Ocimum sanctum* Linn. and *Ocimum viride* Willd[17, 18, 19]. The epidemiology of these species is discussed in Table- 2.

Ocimum basilicum Linn.

Ocimum basilicum L., (Figure: 2) is used as a medicinal, culinary and an ornamental herb[20]. The plant is stomachic, alexipharmic, antipyretic, antihelminthic, diaphoretic, anti - emetic and anti diarrhoeaic[21]. The seeds of these plants have been ascribed to show diuretic, aphrodisiac and anti-dysenteric actions. The juice of the plant shows carminative, stimulant properties[22, 23] and essential oil possesses anti- bacterial, anti-fungal and insecticidal effects[24]. The flower shows properties such as diuretic, demulcent, stimulant, carminative, antispasmodic[22, 25]. The major constituents of essential oil from leaves are linalool (up to 55%), methyl ether (estragole) up to 70% and eugenol; caffeic acid derivatives, flavanoids. Thymol, xanthomicrol , Aesculetin, *p*- coumaric acid, eriodictyol, its 7- glucoside and vicenin-2[17].

Ocimum canum Sims.

Ocimum canum Sims (Figure: 3) shows a pungent, aromatic flavor and is commonly cultivated for culinary purposes. The plant is used in the treatment of various diseases such as cold, fever, parasitic infestations on the body and inflammation of joints and

headaches[26]. The plant acts as stimulant, carminative, and diaphoretic and leaves as bechic, febrifuge and are used in cold, bronchitis, externally in skin disease. The antifungal property is shown by the essential oil of *Ocimum canum* Sims. The seed is effective as a hypoglycaemic; also used in the treatment of leucorrhoea and other diseases of urinogenital system. The essential oil at the flowering stage contains citral as a major component along with methylheptenone, methylnonylketone and camphor. Leaves yield beta- sitosterol, betulinic acid and ursolic acid and flavanois, pectolinarigenin-7-methylether and nevadensin[17].

***Ocimum gratissimum* Linn.**

Ocimum gratissimum Linn. (Figure: 4) is also a major culinary herb with pungent sweet smell. The plant is shown to be effective in the treatment of upper respiratory tract infections, diarrhea, headache, fever, ophthalmic, skin disease and pneumonia[27]. The plant is also used in neurological and rheumatic affections, in seminal weakness and in aphthae of children. The seed of *O. gratissimum* is used in cephalagia and neuralgia and its essential oil as antibacterial and antifungal agents. A heterotic hybrid 'Clocimum' has been developed in India which yields 4.5- 5.7% essential oil having a eugenol content up to 95%. Direct production of methyl eugenol and eugenol acetate from 'Clocimum' oil is reported. Major constituents reported from 'Clocimum' oil are myrcene, eugenol, isoeugenol, methyl eugenol and other constituents are alpha- pinene, limonene, phellandrene, terpene 4- ol, alpha- terpineol, carveol, carvene, geranyl acetate, caryophyllone and caryophyllone oxide[17].

***Ocimum kilimandscharicum* Guerke.**

Ocimum kilimandscharicum Guerke (Figure: 5) known as Karpura tulasi in ayurveda is a perennial evergreen shrub[17]. Whole plant of *Ocimum kilimandscharicum* used as spasmolytic, antibacterial and the decamphorized oil obtained from leaves have been employed as insecticidal, mosquito repellent. *Ocimum kilimandscharicum* (Kapur tulsi) essential oil used in preparation of portable liquid disinfection. The essential oil contains camphor, pinene, limonene, terpinolene, myrcene, beta- phellandrene, linalool, camphene, p- cymene, borneol and alpha- selinene. The camphor content varies in different samples from 61- 80.5%.

***Ocimum sanctum* Linn.**

Ocimum sanctum L. (Figure: 6) has been used for thousands of years in Ayurveda for its diverse healing properties. The chemical composition of *O. Sanctum* is highly complex containing many nutrients and other biologically active compounds (For detailed review; see Joseph and Nair, 2013[28]). Moreover, the quantity of many of these constituents is significantly affected by differing growing, harvesting, processing and storage conditions that are not yet well understood. *O. Sanctum* has a rich source of phytochemical compounds such as oleic acid, rosmarinic acid, eugenol, linoleic acid, Vicenin- 2, Ocimarin, isorientin, aesculectin, orientin, chlorogenic acid, isovitexin, aesculin, gallic acid, Citronellal, galuteolin, circineol, Dimethyl benzene, Camphene, Myrecene, Ethyl benzene, Limocene, Sabinene, Vitamin C, Calcium, Phosphorous and various other micronutrients[9, 10, 11, 12, 13, 14]. The plant exhibits innumerable pharmacological effects and a few includes Anti- coagulant, Immunomodulatory effect, Analgesic, Anti-fertility, Anti- oxidant, Neuroprotective, Anti-microbial, Anti- diabetic, Anti- inflammatory, Radiopreotective, Hepatoprotective, cardioprotective, and Anti- cancerous[29, 30, 31, 32, 33, 34].

***Ocimum viride* Willd.**

Ocimum viride Willd (Figure: 7) is known as 'fever plant' in Sierra Leone since its decoction is prescribed as a remedy for fever. The leaves are febrifungal and are used as a remedy for coughs and fevers. The oil of *O. Viride* acts as antiseptic[17]. The chemical constituents eugenol and thymol are thought to be responsible for its antiseptic action. Maximum oil yield (0.4%) at full bloom stage and highest percentage of thymol (55.12%), which can be used as a substitute for thyme-ajowan oil.

Table 2
Epidemiology of *Ocimum* Species in India.

Ocimum sp.	Characteristics
***O. basilicum* Linn**	Synonym : *O. caryophyllatum* Roxb., *O. minimum* Linn., *O. pilosum* Willd. Habitat : Lower hills of Punjab; cultivated throughout India English : Sweet Basil, Basil Herb
O. canum Sims.	Synonym : *O. americanum* Linn Habitat : Plain and lower hills of India English : Hoary Basil
O. gratissimum Linn.	Habitat : Throughout India English : Shrubby Basil

Figure 2
***Ocimum basilicum* Linn.**

Figure 3
***Ocimum canum* Sims**

Figure 4
***Ocimum gratissimum* Linn.**

O. kilimandscharicum Guerke. Synonym: *O. camphora* Guerke
Habitat : Cultivated on a small scale in West Bengal, Assam, Tamil Nadu, Karnataka,Kerala and Dehra Dun
English : Camphor Basil

Figure 5
***Ocimum kilimandscharicum* Guerke**.

O. sanctum Linn Synonym : O. tenuiflorum Linn.
Habitat : Throughout India; grown in houses, gardens and temples
English : Holy basil, Sacred basil

Figure 6
Ocimum sanctum Linn.

O. viride Willd Habitat : Native to Africa; introduced to India: Jammu- Tawi
English : Fever plant of Sierra Leone

Figure 7
***Ocimum viride* Willd.**

FEW PHYTOCHEMICAL CONSTITUENTS IN O SANCTUM WITH ANTI- CANCEROUS ACTIVITY

The flavonoid, Orientin (Figure: 8) isolated from the leaf extract of *O. sanctum* was shown to provide protection against radiation. It shows significantly greater free radical-inhibiting activity in vitro than DMSO. Orientin inhibited free radical formation in the absence of EDTA. Free radical scavenging appears to be a likely mechanism of radiation protection by this flavonoid[35]. A study on prostate cancer shows Vicenin- 2 (Figure: 9) effectively induced anti-proliferative, anti-angiogenic and pro-apoptotic effect in Prostate cancer cells irrespective of their androgen responsiveness or p53 status. Vicenin- 2 inhibited EGFR/Akt/mTOR/p70S6K pathway along with decreasing c-Myc, cyclin D1, cyclin B1, CDK4, PCNA and hTERT *in vitro*[36].Vicenin- 2 has been investigated for radioprotection and anti-inflammatory properties. Vicenin- 2 also shown to protect mice against radiation by inhibiting free radical formation. Eugenol (Figure: 10) is a member of the allyl-benzene class of chemical compounds. The molecular mechanism of eugenol- induced apoptosis in melanoma, skin tumors, osteosarcoma, leukemia, gastric and mast cells have been studied[37]. In a study[38], eugenol was evaluated for its chemopreventive effects on N-methyl-N(')-nitro-N-nitrosoguanidine (MNNG)-induced gastric carcinogenesis in Wistar rats by analyzing markers of apoptosis, invasion and angiogenesis. Administration of eugenol induced apoptosis via the mitochondrial pathway by modulating the Bcl-2 family proteins, Apaf-1, cytochrome C, and caspases and inhibiting invasion, and angiogenesis as evidenced by changes in the activities of MMPs and the expression of MMP-2 and -9, VEGF, VEGFR1, TIMP-2 and RECK confirming eugenol as an attractive candidates for preventing tumour progression. Linolenic acid (Figure: 11), an omega – 3- fatty acid, contained in the oil contained in the oil should act as a reducing agent or antioxidant, and thereby could be responsible for the biological activities of the cell. *O. sanctum* fixed oil containing Linolenic acid is mainly responsible for the production of DHA and EPA. DHA has been reported to inactivate Bcl-2 (an anti-apoptotic gene) and increases apoptosis[39] hence acts as a chemopreventive agent. Ursolic acid [3-hydroxy-urs-12-en-28-oic acid] (Figure: 12) is a pentacyclic triterpenoid and a member of the cyclosqualenoid family derived from diverse plant species including *Ocimum sanctum*. This phytochemical of significant biological potential could be isolated from berries, fruits, leaves and flowers of medicinal plants. Ursolic acid has been shown to inhibit tumorigenesis, tumor promotion, and suppress angiogenesis[40]. They are found relatively non-

toxic to normal cells[41]. Using high performance thin layer chromatography[42] it was found that the Green variety of Ocimum sanctum was found to contain higher amounts of ursolic acid than the black variety.

Figure 8
Orientin

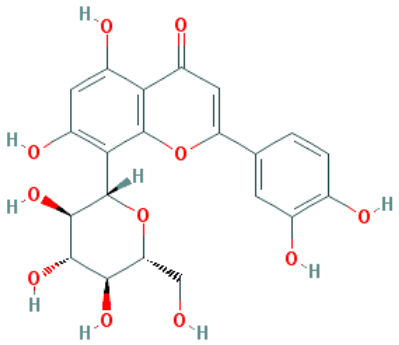


Figure 9
Vicenin- 2

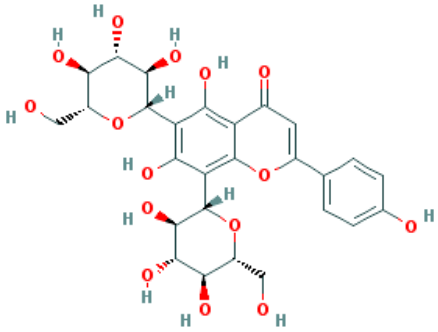


Figure 10
Eugenol

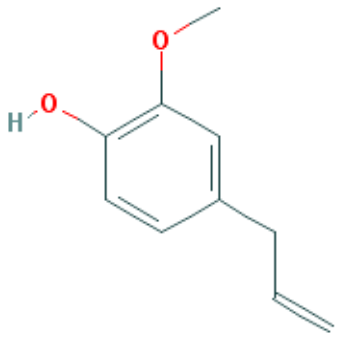


Figure 11
Linolenic Acid

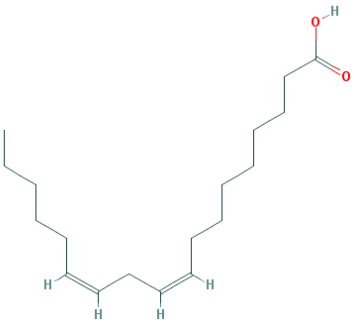
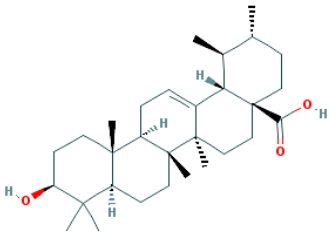


Figure 12
Ursolic Acid



ANTI- CANCEROUS ACTIVITY OF O SANCTUM

Herbal anti-cancer compounds are unique in their feature of having anti-oxidant and immunostimulant activity preventing cancer growth indirectly along with a direct cytotoxic effect towards malignant and/or other apoptotic cells. *Ocimum sanctum* is beneficial against the stress and depression during tumor[43]. Human fibrosarcoma cells in culture treated with an ethanolic extract of *O. sanctum* induced cytotoxicity at 50 µg/ml and above. Morphologically the cells showed shrunken cytoplasm and condensed nuclei. The cells also showed depleted intracellular glutathione and increased levels of lipid peroxidation products. Administration of aqueous and ethanolic extracts of *O. sanctum* to mice bearing Sarcoma-180 solid tumors mediated a significant reduction in tumor volume and an increase in lifespan. These observations clearly indicate *O. sanctum* extracts possess anticancer activity[44]. Anti-inflammatory and anti- oxidant activities are also important in preventing proliferation of certain cancer cell lines. Curcumin and Ursolic acid in *O. sanctum* are known to have anti-inflammatory, cyclo-oxygenase inhibitory and antioxidant activities. A study reported[45] that administration of *O. sanctum* to mice significantly elevated glutathione and more than 78% glutathione-S-transferase activity. These effects could enhance survival though may not affect the tumor directly[44]. The anti-tumor activity and chemopreventive potential of *O. sanctum* L., were evaluated using Dalton Lymphoma ascites tumor model in Swiss Albino mice. Oral administration of crude herb increased the survival time and decreased the peritoneal ascitic fluid content significantly[46]. DMBA (7,12-dimethylbenz[a]anthracene) induced rat hepatocytes pretreated with *O. sanctum* extract showed significant reduction in the levels of DMBA-DNA adducts. The results suggest that *O. sanctum* leaf extract blocks or suppresses the events associated with chemical carcinogenesis by inhibiting metabolic activation of the carcinogen [47]. The

seed oil of *O sanctum* was evaluated for chemopreventive activity against subcutaneously injected 20-methylcholanthrene induced-fibrosarcoma tumors in the thigh region of Swiss albino mice[48]. The enhanced survival rate and delay in tumor incidence was observed in seed oil supplemented mice. Liver enzymatic and lipid peroxidation end product, malondialdehyde levels were significantly modulated with oil treatment as compared to untreated 20-methylcholanthrene injected mice. The results of this study suggest that the potential chemopreventive activity of the oil is partly attributable to its antioxidant properties and it significantly reduced tumor size and volume. The radioprotective effect of *O sanctum* on the salivary gland of rats administered radioiodine ((131)I) and compared its efficacy with a known radioprotectant, amifostine. *O. sanctum* and amifostine pre-supplemented and subsequently exposed to (131)I rats at 3 and 6 months duration exhibited comparable histopathology with controls indicating the possible radioprotective effect against high-doses of (131)I exposure[49]. Table-3 shows other *Ocimum* species with anti- cancerous effects.

Table 3
Other Ocimum species with Anti- cancerous effects.

***Ocimum* sp.**	**Extract**	**Type of cancer**
Ocimum gratissimum	Caffeic acid	Cervical cancer[50]
	Organic solvent extract	Prostate cancer[51]
	Aqueous leaf extracts	Breast cancer[52]
	Aqueous extract	Lung adenocarcinoma[53]
Ocimum canum	Essential Oil	Breast cancer[54]
Ocimum basilicum	Leaf powder	Colon tumors [55]
	Organic extract	Breast cancer [56]
	Essential oil	Cervical cancer [57]
Ocimum tenuiflorum	Leaf powder	Colon tumors[55]

OCIMUM SANCTUM LINN *RELATED CARCINOGENESIS*

Lung Carcinogenesis

Lung cancer has been the most common cancer in the world for several decades and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths. The majority of the cases now occur in the developing countries. Lung cancer is still the most common cancer in men, with high rates in Central-eastern and Southern Europe, Northern America and Eastern Asia. In females, incidence rates are generally lower, but, worldwide, lung cancer is now the fourth most frequent cancer of women and the second most common cause of death from cancer. The highest incidence rate is observed in Northern America and the lowest in Middle Africa[58]. Apparently it is found that *O sanctum* is used to control cough and shortness of breath especially for lung cancer patients. Approximately 40% of lung cancers are adenocarcinomas, the most common subtype of non-small cell lung cancer, is responsible for more than 500,000 deaths per year worldwide[59]. There is accumulating evidence that the overall dietary intake of phytochemicals reduces the risk of cancer. It is also noted that the chemopreventive agents such as retinol, beta- carotene, synthetic retinoids and alpha- tocopherol are known to have antitumor potential against lung cancer.In a study[60], apoptotic mechanism of ethanol extracts of *Ocimum sanctum* was investigated in A549 cells *in vitro* and in the LLC (Lewis lung carcinoma) tumor model *in vivo*. The ethanolic extract exerted cytotoxicity against A549 cells, increased the sub-G1 population and exhibited apoptotic bodies in A549 cells. Furthermore, the extract cleaved poly (ADP-ribose) polymerase (PARP), released cytochrome C into cytosol and simultaneously activated caspase-9 and -3 proteins. Also, ethanolic extract from *O*

sanctum increased the ratio of proapoptotic protein Bax/antiapoptotic protein Bcl-2 and inhibited the phosphorylation of Akt and extracellular signal regulated kinase (ERK) in A549 cancer cells. In addition, it was found that the extract can suppress the growth of LLC inoculated onto C57BL/6 mice in a dose-dependent manner. The study concluded that the ethanol extracts of *Ocimum sanctum* could induces apoptosis in A549 cells via a mitochondria caspase dependent pathway and inhibits the *in vivo* growth of LLC, suggesting that the ethanolic extracts of *Ocimum sanctum* can be applied to lung carcinoma as a chemopreventive candidate. In another study, the anti-metastatic activity of ethanol extracts of *O. sanctum* through activation of anti-oxidative enzymes was confirmed[61]. Ethanolic extract exerted cytotoxicity against Lewis lung carcinoma (LLC) cells. The extract also significantly inhibited cell adhesion and invasion as well as activities of matrix metalloproteinase-9 (MMP-9), but not MMP-2. This indicates the important role of MMP-9 in anti-metastatic regulation through ethanol extracts of *O. sanctum*. In addition, the extract significantly reduced the tumor nodule formation and lung weight in LLC-injected mice. Inhibitory effect of ethanol extract on metastasis was further confirmed by using hematoxylin and eosin staining. Notably, we also found that *Ocimum* extract enhanced activities of anti-oxidative enzymes such as superoxide dismutase, catalase and glutathione peroxidase in a concentration-dependent manner. Apparently, this study supports that ethanol extracts of *O. sanctum* can be a potent anti-metastatic candidate through inactivation of MMP-9 and enhancement of anti-oxidant enzymes.

Skin Carcinogenesis

Skin cancers are those cancers that form in the tissues of the skin and are named after the type of skin cell from which they arise. There are several types of skin cancer such as melanoma, Basal cell carcinoma and squamous cell carcinoma. Skin cancer that forms in melanocytes *i.e.,* skin cells that make pigment is called melanoma. Skin cancer that forms in the lower part of the epidermis (the outer layer of the skin) is called basal cell carcinoma. Skin cancer that forms in squamous cells (flat cells that form the surface of the skin) is called squamous cell carcinoma. Most skin cancers form in older people on parts of the body exposed to the sun or in people who have weakened immune systems[62]. In United States about 44, 250 males and 32, 000 females were the new cases estimated with melanoma of the skin[63]. Excessive exposure of the skin to solar ultraviolet radiation is one of the major factors for the development of skin cancers, including non-melanoma. For the last several centuries the consumption of dietary phytochemicals has been linked to numerous health benefits including the photo- protection of the skin. A study confirmed [64] the chemopreventive potential of quercetin isolated from *O sanctum* in DMBA (7, 12- dimethyl benz(a) anthracene) and croton oil induced skin carcinogenesis in mice model system. The researchers of this study suggest that chemopreventive effect of quercetin would be due to its antioxidant potential. Methanolic extract of *Ocimum* leaves subjected to fractionation by column chromatography and subsequently a yellow powder was yielded from this methanolic extract. Spectroscopic analysis of this compound revealed the presence of high content of the flavonoid quercetin. To access the chemopreventive potential of quercetin, it was orally administered at a concentration of 200 mg/kg and 400 mg/ kg body weight daily up to 16th week. The development of skin carcinogenesis was then assessed by histopathological analysis. Reductions in tumor size and cumulative number of papillomas were seen due to quercetin treatment. Average latent period was significantly increased as compared to carcinogen treated control. Quercetin produced significant decrease in the activity of serum enzyme; serum glutamate oxalate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase and bilirubin when compared with control. Also it increased the levels of enzyme involved in oxidative stress glutathione, superoxide dismutase and catalase. Thus the study concluded the quercetin isolated from *Ocimum sanctum* could play a significant role in detoxification pathway as well as a

chemopreventive agent. Both histology and enzyme activities suggest that environmental effects that lead to skin carcinogenesis can be inhibited by oral combination of quercetin in the daily diet to achieve some protection against skin cancer. Prashar and colleagues[65] reported the chemopreventive property of an ethanolic extract of the leaves of *Ocimum sanctum* (a traditional medicinal plant) on 7,12-dimethylbenz[a]anthracene induced skin papillomagenesis in male Swiss albino mice. A significant reduction in the values of tumor incidence, average number of tumors per tumor bearing mice and the cumulative number of papillomas was observed in mice treated topically with the leaf extract of *O. sanctum* at either the peri-initiational, post-initiational stages or continuously at peri- and post-initiational stages of papillomagenesis as compared to the corresponding control group. Topical application of *Ocimum* leaf extract for 15 days resulted in significant 2-fold elevation of reduced glutathione content in the skin of mice ($p < 0.05$). Similarly, glutathione S-transferase activity was also observed to be significantly elevated by 25% compared with the control group ($p < 0.05$) following *Ocimum* extract treatment. This study thus suggests the chemopreventive potential of *Ocimum sanctum* in skin papillomagenesis. The protective effect of alcoholic extract of the leaves of *Ocimum sanctum* on 3-methylcholanthrene (MCA), 7,12-dimethylbenzanthracene (DMBA) and aflatoxin B1 (AFB1) induced skin tumorigenesis in a mouse model has been investigated by Rastogi and his co- workers[66]. The study involved pre-treatment of mice with the leaf extract prior to either MCA application or tetradecanoyl phorbol acetate (TPA) treatment in a two-stage tumor protocol viz, DMBA/TPA and AFB1/TPA. The results of the present study indicate that the pre-treatment with alcoholic extract of the leaves of *O. sanctum* decreased the number of tumors in MCA, DMBA/TPA and AFB1/TPA treated mice. The skin tumor induced animals pre-treated with alcoholic extract led to a decrease in the expression of cutaneous gamma-glutamyl transpeptidase and glutathione-S-transferase-P protein. The histopathological examination of skin tumors treated with leaf extract showed increased infiltration of polymorphonuclear, mononuclear and lymphocytic cells, decreased ornithine decarboxylase activity with concomitant enhancement of interleukin-1beta and tumor necrosis factor-alpha in the serum, implying the in vivo anti- proliferative and immunomodulatory activity of leaf extract. The decrease in cutaneous phase I enzymes and elevation of phase II enzymes in response to topical application of leaf extract prior to MCA, AFB1, DMBA/TPA and AFB1/TPA treatment indicate the possibility of impairment in reactive metabolite(s) formation and thereby reducing skin carcinogenicity. Furthermore, pre-treatment of leaf extract in the carcinogen induced animals resulted in elevation of glutathione levels and decrease in lipid peroxidation along with heat shock protein expression, indicating a scavenging or antioxidant potential of the extract during chemical carcinogenesis. Thus they concluded that the leaf extract of *O. sanctum* provides protection against chemical carcinogenesis in one or more of the following mechanisms: (i) by acting as an antioxidant; (ii) by modulating phase I and II enzymes; (iii) by exhibiting anti- proliferative activity.

Cervical Carcinogenesis

Cervical cancer is the third most common cancer in women, and the seventh overall, with an estimated 529,000 new cases in 2008. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers. It is responsible for 275,000 deaths in 2008, about 88% of which occur in developing countries: 53,000 in Africa, 31,400 in Latin America and the Caribbean, and 159,800 in Asia[58]. Carvacrol is one among the major phytochemical component of *Ocimum* [67]. However, there are no studies indicating the role of carvacol isolated from *Ocimum sanctum* against cancer studies. Carvacrol is a component of numerous aromatic plants which has been evaluated for substantial pharmacological properties. In a study the carvacrol induced cytotoxicity against human cervical cancer, HeLa and SiHa cells were attempted[68]. Cytotoxicity induced by carvacrol was determined by different assays like MTT assay

and LDH assay. Apoptosis was measured by DNA fragmentation assay. The study clearly showed the dose dependent cytotoxic effect of carvacrol in HeLa and SiHa cells at an IC 50 of 50 mg L by both the cytotoxic assays respectively. The dying cells showed characteristics of apoptosis such as, DNA fragmentation. The data in the present study clearly demonstrated cytotoxic effects of carvacrol on human cervical cancer cells. Carvacrol could have a potential therapeutic significance in treating cancer. Human epidemiological data indicates that regular use of certain medicinal plants suppress carcinogenesis in various organs[69]. The role of *Ocimum* extracted carvacol in cervical carcinogenesis is yet to be studied. Consequently a study was conducted by Jha and co- workers[70] in squamous cervical cancer cell line, SiHa to identify the apoptosis effect of phytochemicals from medicinal plants. It was observed that the treatment of SiHa cell line with the ethanolic extracts of leaves of *Ocimum sanctum* and *Azadirachta indica*; and roots of *Withania somnifera* at IC50 values for 48 h resulted in formation of internucleosomal fragments of DNA. The study of morphological changes also showed the formation of apoptotic bodies after treatment with these plant extracts. The study indicates that these plant extracts, which have previously been shown to have anticarcinogenic activity, can induce apoptosis in SiHa, a cervical cancer cell line. These plant extracts contain natural compounds which do not have any cytotoxic effects on normal cells.

Oral Carcinogenesis

Oral cancers are part of a group of cancers commonly referred to as head and neck cancers, and of all head and neck cancers they comprise about 85% of that category. Often oral cancer is only discovered when the cancer has metastasized to another location, most likely the lymph nodes of the neck. According to American Cancer Society about 35,000 people will get oral cavity or oropharyngeal cancer with an estimated 6,800 people will die of these cancers[71]. In a study[44], *Ocimum sanctum* L., a plant having multi-medicinal properties, has been investigated for its chemopreventive activity against 7,12-dimethylbenz (a) anthracene (DMBA)- induced hamster buccal pouch carcinogenesis. *O. sanctum*, in the form of fresh leaf paste, aqueous extract and ethanolic extract were topically applied and the extracts were orally administered to buccal pouch mucosa of animals exposed to 0.5% of DMBA. Incidence of papillomas and squamous cell carcinomas were significantly reduced, and increased the survival rate in the topically applied leaf paste and orally administered extracts to animals. Among them, the orally administered aqueous extract showed profound effect than the other two forms. Histopathological observations made on the mucosa confirmed these findings. Further fluorescent spectral studies at 405 nm excitation on the mucosa of control, DMBA and extracts orally administered experimental animals showed a prominent maxima at 430 nm for control, 628 nm for DMBA induced carcinomas while aqueous and ethanolic extracts administered animals showed at 486 nm and 488 nm, respectively. The fluorescent intensity at 630 nm (FI630 nm) was significantly reduced and the ratio of fluorescent intensities at 520 nm and 630 nm (FI520 nm/630 nm) were significantly increased in orally administered extracts compared to DMBA treated animals. These observations suggest that the orally administered extract of *O. sanctum* may have the ability to prevent the early events of carcinogenesis.

Prostate Carcinogenesis

Prostate cancer is the second most frequently diagnosed cancer of men (914,000 new cases, 13.8% of the total) and the fifth most common cancer overall. Nearly three-quarters of the registered cases occur in developed countries (659,000 cases). With an estimated 258,000 deaths in 2008, prostate cancer is the sixth leading cause of death from cancer in men (6.1% of the total). Because prostate specific antigen testing has a much greater effect on incidence than on mortality, there is less variation in mortality rates worldwide than is observed for incidence and the number of deaths from prostate cancer is almost the same in developed and developing regions[58]. A study[72] was conducted to determine the

efficacy of novel flavonoid vicenin-2, an active constituent of the medicinal herb *Ocimum Sanctum* Linn or Tulsi, as a single agent and in combination with docetaxel in carcinoma of prostate. Vicenin-2 effectively induced anti-proliferative, anti-angiogenic and pro-apoptotic effect in prostate carcinoma cells (PC-3, DU-145 and LNCaP) irrespective of their androgen responsiveness or p53 status. Vicenin-2 inhibited EGFR/Akt/mTOR/ p70S6K pathway along with decreasing c-Myc, cyclin D1, cyclin B1, CDK4, PCNA and hTERT in vitro. Vicenin-2 reached a level of 2.6 + 0.3 µM in serum after oral administration in mice which reflected that vicenin-2 is orally absorbed. The intra venous administration of docetaxel, current drug of choice in androgen-independent prostate carcinoma, is associated with dose-limiting toxicities like febrile neutropenia which has led to characterization of alternate routes of administration and potential combinatorial regimens. In this regard, vicenin-2 in combination with docetaxel synergistically inhibited the growth of prostate tumors in vivo with a greater decrease in the levels of AR, pIGF1R, pAkt, PCNA, cyclin D1, Ki67, CD31, and increase in E-cadherin. Vicenin-2 has been investigated for radio-protection and anti-inflammatory properties. This is the first study on the anti-cancer effects of vicenin-2. In conclusion, our investigations collectively provide strong evidence that vicenin-2 is effective against prostate carcinoma progression along with indicating that vicenin-2 and docetaxel co-administration is more effective than either of the single agents in androgen-independent prostate cancer.

Breast Carcinogenesis

Breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall. It is now the most common cancer both in developed and developing regions with 690,000 new cases estimated in each region. The range of mortality rates is much less because of the more favourable survival of breast cancer in developed regions. As a result, breast cancer ranks as the fifth cause of death from cancer overall, but it is still the most frequent cause of cancer death in women in both developing and developed regions[58]. A study[73] on mice found an extract of the herb *O sanctum* inhibited the progression of breast cancer. The study was conducted in two human breast cancer cell lines for tumorigenic studies; namely MDA-MB-435 and MCF10A DCIS.com (DCIS.com) cells. MDA-MB-435 cells form undifferentiated adenocarcinomas in nude mice. Injection of DCIS.com cells into nude mice results in lesions that are predominantly DCIS subtype. In 3 weeks, the lesions show a DCIS like pathology consisting of ducts surrounded by complete basement membrane and extensive angiogenesis in the stroma. The ducts develop into a complete comedo phenotype by 6 weeks. When *Ocimum sanctum* Linn extracts were fed to nude mice injected with MDA-MB-435 or DCIS.com cells, there was a significant reduction in the rate of tumor growth in the treated mice. The tumors in *Ocimum* fed mice grew at similar rates as the water fed controls initially, though their overall size was smaller than the controls. After reaching a tumor volume of approximately 150 mm^3 in DCIS.com or 200 mm^3 in MDA-MB-435 the growth rate started to slow down. The inhibition in tumor growth was due to reduced cell proliferation and angiogenesis as indicated by immunohistochemical analysis utilizing anti CD34 and anti- proliferating cell nuclear antigen antibodies. Furthermore, there was also a reduced expression of COX-2, MMP-9 and redistribution of VEGF from stromal epithelial compartments to epithelial compartment in the *Ocimum* treated xenografts. A comparative analysis of the temporal development between normal and *Ocimum* treated DCIS.com xenograft indicates a delay towards progression to DCIS-like phenotype by oral administration of *Ocimum* extracts. The data clearly indicates that *Ocimum* extract inhibit tumor growth and progression by affecting cell proliferation and angiogenesis and it could be developed into a breast cancer preventive and therapeutic agent.

Gastric Carcinogenesis

One of the major causative agents of gastric cancer, *Helicobacter pylori* infection is also

strongly associated with gastric and duodenal ulcer disease. The discovery of these relations has brought the long-controversial connection between peptic ulcers and gastric cancer into focus[74]. Asian Americans and Pacific Islanders have the highest incidence rates for liver and stomach cancers of all racial and ethnic groups in both men and women, and among the highest death rates for these cancer sites[71]. The Optimal effective dose (100 mg/kg) of methanolic extract of leaves of *O. sanctum* showed significant ulcer protection against ethanol and pyloric ligation-induced gastric ulcers[75]. Moreover, the extract significantly inhibited the offensive acid-pepsin secretion and lipid peroxidation and increased the gastric defensive factors like mucin secretion, cellular mucus, and life span of mucosal cells and had antioxidant effect, but did not induce mucosal cell proliferation. The study concluded that the ulcer protective and healing effects of *O. sanctum* leaf extract may be due to its effects both on offensive and defensive mucosal factors. Pre-clinical studies have shown that oral administration of Tulsi was effective in preventing N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and benzo(a) pyrene induced gastric carcinogenesis in rats and mice respectively [45, 76]. Studies [45] have shown that feeding Tulsi leaves in diet (200 mg/ g diet) two weeks prior to and during the period of benzo(a) pyrene administration for 8 weeks reduced the incidence of benzo(a) pyrene induced forestomach carcinogenesis in mice. When compared to the benzo(a) pyrene alone cohorts, were the tumor incidence was 77%, the animals administrated with Tulsi had only an incidence of 29% clearly indicating its chemopreventive effects. The chemopreventive effects of ethanolic *Ocimum sanctum* leaf extract on cell proliferation, apoptosis and angiogenesis during MNNG induced gastric carcinogenesis was studied. In their study Manikandan and co- workers[76] used rat as a model system. The rats were divided into four groups of ten each. Rats in group one were given MNNG (150 mg/kg body weight) by intragastric intubation three times, with a two-week interval between treatments. Rats in group two were administered MNNG as in group one, and in addition, they received intragastric intubation of ethanolic extract (300 mg/kg body weight) three times per week, starting on the day following the first exposure to MNNG. The intubation of ethanolic extract continued until the end of the experimental period. Rats in group three were given ethanolic leaf extract only. Group four served as controls. All the rats were killed after an experimental period of 26 weeks. Intragastric administration of MNNG-induced well-differentiated squamous cell carcinomas that showed increased cell proliferation, and angiogenesis with evasion of apoptosis, as revealed by the upregulation of proliferating cell nuclear antigen (PCNA), glutathione S-transferase-pi (GST-pi), Bcl-2, cytokeratin (CK) and vascular endothelial growth factor (VEGF) and with downregulation of Bax, cytochrome C and caspase 3 protein expression. Administration of ethanolic *Ocimum* leaf extract reduced the incidence of MNNG-induced gastric carcinomas. This was accompanied by decreased expression of PCNA, GST-pi, Bcl-2, CK and VEGF, and overexpression of Bax, cytochrome C, and caspase 3. The study thus provides evidence that, in MNNG-induced gastric carcinogenesis, the key proteins involved in the proliferation, invasion, angiogenesis and apoptosis, are viable molecular targets for chemoprevention using ethanolic *Ocimum sanctum* leaf extract. In another study[77] combination of two plant species; *Azadirachta indica* and *Ocimum sanctum* against MNNG-induced gastric carcinogenesis in rat model were investigated for its chemopreventive efficacy. Rats administered MNNG developed forestomach carcinomas that displayed low lipid and protein oxidation coupled to enhanced antioxidant activities, and overexpression of proliferating cell nuclear antigen, glutathione S-transferase-Pi, cytokeratin, vascular endothelial growth factor and Bcl-2 with downregulation of Bax, cytochrome C and caspase-3. Co- administration of *Azadirachta indica* and *Ocimum sanctum* extract suppressed MNNG-induced gastric carcinomas accompanied by modulation of the oxidant-antioxidant status, inhibition of cell proliferation and angiogenesis, and induction of apoptosis suggesting their chemopreventive effect.

CONCLUSION

The increasing life span and longevity pave the way for ascending trend of multifarious diseases and most vital among them identified or recognized is cancer. The eminent scientists with innovative foresight are looking forward to have an alternative or complementary and pristine natural medicine devoid of alarming deleterious side-effects caused to the cancer patients. *Ocimum sanctum* Linn, known as the "elixir of life" had proved its efficiency in treating a variety of diseases. Scientific studies proved that *O. sanctum* could be effective in treating cancer such as skin, lung, breast, prostate, cervical, oral and gastric carcinoma. "Tulsi", the anti-cancer agent, needs the promotion of advanced studies. Identification of the exact phytochemical compounds as well as developing its synthetic analogues would be the desired future directions in this regard. The significant literature survey and scope of the study would trigger obviously the effect or impact of anti- cancerous *O. sanctum*.

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