Review Article

Phytochemical evaluation and anticancer activity of *Ocimum sanctum* L. - A review

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ABSTRACT

Aim: The purpose of the paper is to review especially the phytochemical evaluation and anticancer activity of Tulsi. **Methods:** Several publications and books were electronically searched in Google using the keywords "Tulsi as a medicinal plant," "Tulsi and its anticancer activity," and "Anticancer activity of *Ocimum sanctum*. The search was restricted to books and articles related to anticancer activity of Tulsi from the year 1972 to 2017 by encountering the title and abstracts, and further short listing articles for full content. **Conclusion:** The present review revealed that *Ocimum sanctum* possesses an extensive anticancer efficacy still limited because of the lack of clinical trials on humans.

KEY WORDS: Anticancer activity, *Ocimum sanctum*, Tulsi

INTRODUCTION

Since 1000 years, human beings have been using medicinal plants for treating various diseases. Traditional medicines are, however, preferred by communities who cannot incur pharmaceutical products for their physical and psychological requirements. In several developing countries, especially in rural areas, people depend on traditional medicines for their primary health care. These are safer and cheaper than the synthetic medicines.[1] Medicinal plants have been playing an important role all through human history. Medicinal plants have phytoconstituents that possess biological activity. Over 12000, such compounds have been isolated from various medicinal plants so far.[2] More than 120 active compounds have been isolated from different medicinal plants, which are being used as herbal medicines. Nearly 80% of resemblance is shown between their modern therapeutic use and traditional. Traditional medicinal practices such as Siddha, Ayurveda, and Unani are studied for their chemical and pharmacological potential.[3]

Cancer is the second leading cause of human death. The American Cancer Society assessed that 1,665,540 new instances of tumor were required to be analyzed in 2014. However, extraordinary gatherings of medications work in various approaches to battle growth cells and psychologist tumors, these days, herbs are utilized for malignancy cure.[4,5] Chemotherapy may be used alone for certain types of cancer or in conjunction with other therapy such as radiation or surgery.[6] Recent researches concentrate in developing suitable chemotherapy consistent with their new exploration in cell biology for the treatment of cancer with less or no toxic effect.[7,8]

Ocimum sanctum L. (also known as Tulsi) has been used for several decades in Ayurveda for its assorted healing potential. Tulsi, the Queen of herbs, the unbelievable "Unique one" of India, is one of the holiest and most valued of the numerous mending and sound giving herbs of the orient. The hallowed basil, Tulsi, is prestigious[9] for its religious and profound sacredness and for its critical part in the customary Ayurvedic and Unani arrangement of all-encompassing well-being and natural prescription of the East. It is specified by Charaka in the Charaka Samhita, an Ayurvedic content. Tulsi is thought to be an adaptogen, adjusting diverse procedures in the body, and supportive for adjusting to pressure. Set apart by its solid smell and astringent taste, it is viewed in Ayurveda as a sort of "remedy of life" and accepted to increase lifespan. Tulsi extracts are utilized as a part of Ayurvedic solutions for normal colds, cerebral pains, stomach issue, aggravation, coronary illness, and intestinal sickness. In general, *O. sanctum* L. is taken in different forms, as natural

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tea, dried powder, or fresh leaf. For thousands of years, the dried leaves of Tulsi have been blended with stored grains to repel insects.[10]

Family Description

- Kingdom: Plantae
- (Unranked) Angiosperms
- (Unranked) Eudicots
- (Unranked) Asterids
- Order: Lamiales
- Family: Lamiaceae
- Genus: *Ocimum*
- Species: *O. tenuiflorum*
- Binomial name: *Ocimum tenuiflorum* or *O. sanctum* L.

O. sanctum L. (Tulsi) is an erect, much-branched subshrub 30–60 cm tall, with simple opposite green or purple leaves that are strongly scented and hairy stems. Leaves have petiole and are ovate, up to 5 cm long, usually somewhat toothed. Flowers are purplish in elongate racemes in close whorls. Tulsi is native throughout the world tropics and widespread as a cultivated plant and an escaped weed. It is mainly cultivated for religious and medicinal purposes and for its essential oil. Tulsi is an important symbol in many Hindu religious traditions, which link the plant with Goddess figure. The name Sanskrit meaning of "Tulsi" is "the incomparable one."

The genus *Ocimum* is highly variable and possesses wide genetic diversity at intra- and inter-species levels. Nine species of *Ocimum,* namely *Ocimum tenuiflorum* L., *Ocimum basilicum* L., *Ocimum gratissimum* L., *Ocimum kilimandscharicum*, *Ocimum micranthum* L., *Ocimum campechianum* L., *Ocimum americanum* L., *Ocimum minimum* L., and *Ocimum citriodorum* L., are found in India, three of which (*O. americanum* L., *O. minimum* L., and *O. citriodorum* L.) are exotic.[11] It is difficult to distinguish all these species on the basis of leaf morphology alone.

Phytochemical Constituents

Tulsi contains many nutrients and other biologically active compounds. The proportions of the phytoconstituents may vary significantly among strains and even among plants within the same field. The nutritional and pharmacological properties of Tulsi may due to the synergistic interactions of many different active phytochemicals. Consequently, the overall effects of Tulsi cannot be completely duplicated with extracts and isolated compounds. This may be due to the inherent botanical and biochemical complexity of Tulsi; institutionalization has, up until this point, evaded the present day science.

The volatile oil[12] obtained from the leaves of *O. sanctum* L. contains the phytochemicals shown in Table 1.

Seed oil[12] has some fatty acids and sitosterols. Green leaves contain eugenol and methyl eugenol,[16,17] anthocyanins, and certain levels of sugars, which are composed of xylose and polysaccharides present in seed mucilage. The leaves and stem contain various bioactive compounds such as flavonoids, saponins, tannins, and triterpenoids.[14] The essential oil from leaves contains α-thujene, benzene, (Z)-3-hexanol, octane, nonane, ethyl 2-methyl butyrate, toluene, α-pinene, β-pinene, citronellal, sabinene, camphene, myrcene, dimethylbenzene, ethylbenzene, 1,8-cineole, limonene, p-cymene, Cis-β-ocimene, trans-β-ocimene, terpinolene, butyl-benzene, allo-ocimene, trans-linalool oxide, α-cubebene, geraniol, γ-terpene, α-copaene, β-cubebene, eugenol, linalool, α-guaiene, α-amorphene, β-bourbonene, β-caryophyllene, methyl eugenol, β-elemene, β-farnesene, (E)-cinnamyl acetate, isocaryophyllene, γ-humulene, 4, 11-selinadiene, borneol, iso-eugenol, myrtenylformat, α-humulene, α-terpineol, α-salilene, α-muurolene, β-salilene, δ-cadinene, calamenene, isoborneol, germacrene-D, iedol, humulene oxide, caryophyllene oxide, cuparene, geraneol, α-guaiol, τ-cadinol, nerolidol, α-bisabolol, cis-sesquisabinene hydrate, elemol, (EZ)-farnesol, tetradecanal, and 14-hydroxy-α-humulene selin-11-en-4-α-ol.[18-25]

The alcoholic extract of the aerial parts of *O. sanctum* L. contains ursolic acid, rosmarinic acid, luteolin, apigenin, luteolin-7- O-glucuronide, isorientin, molludistin, apignin-7-O-glucuronide, stigmasterol, gallic acid, gallic acid methyl ester, β-stigmasterol triacontanol ferulate, orientin, vicenin-2, isovitexin, aesculectin, vitexin, aesculin, galuteolin, gallic acid ethyl ester, circineol, vanillin, chlorogenic acid, protocatechuic acid, vllinin acid, 4-hydroxybenzoic acid, caffeic acid, phenylpropane glucosides-1, and phenylpropane glucosides-2.[26-32]

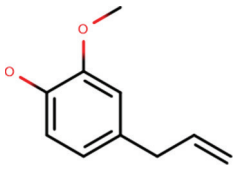
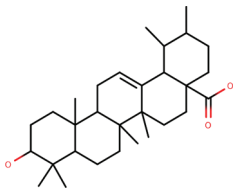
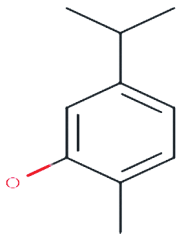
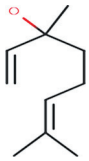
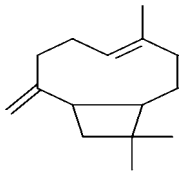
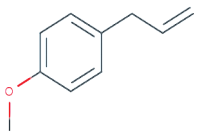
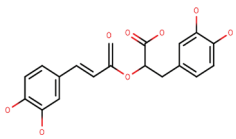
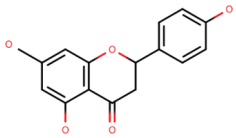
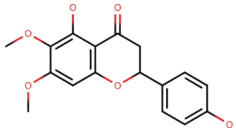
The leaves contain carotene and ascorbic acid. The oil extracted from the seed of *O. sanctum* L. is called fixed oil which contains the following fatty acids stearic acid, palmitic acid, linoleic acid, oleic acid, sitosterol, linolenic acid hexourenicacid, linolenodilinolin, and dilinolenolinolins.[33,34] The mineral content per 100 g of the whole plant contains carotene (2.5 mg), Vitamin C (83 mg), calcium - 3.15%, chromium - 2.9 µg, phosphorous - 0.34%, zinc - 0.15 µg, vanadium - 0.54 µg, iron - 2.32 µg, nickel - 0.73 µg, copper - 0.4 µg, and insoluble oxalate.[35]

GC–MS evaluation of methanolic extract of leaves showed the presence of eugenol, methyl isoeugenol, and caryophyllene.[36] Devendran *et al*. have identified the presence of 10 bioactive compounds in the hydroalcoholic extract of *O. sanctum* L. leaves by GC–MS analysis[37] is shown in Table 2.

Anticancer Activity of *O. sanctum* L.

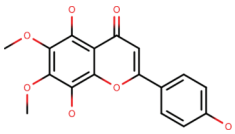
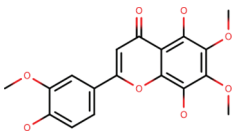
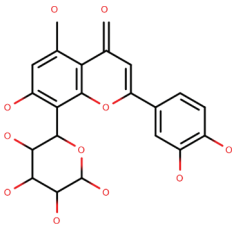
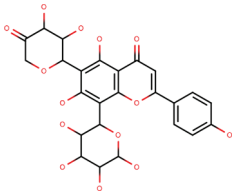
O. sanctum Linn. is a rich source of phytoconstituents and possesses an outstanding role in medicine. These phytochemicals are not essential for its survival but are of substantial importance to human community to carry out various protective functions in human body.

Table 1: Phytoconstituents isolated from various parts of *Ocimum sanctum* L

Name of the compound	IUPAC naming	Structure
Eugenol[12]	1-hydroxy-2-methoxy-4-allylbenzene	
Ursolic acid[13]	2,3,4,5,6,6a, 7,8,8a, 10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid	
Carvacrol[13]	5-isopropyl-2-methylphenol	
Linalool[13]	3,7-dimethylocta-1,6-dien-3-ol	
Caryophyllene[13]	4,11,11-trimethyl-8-methylene-bicyclo[7.2.0]undec-4-ene	
Methyl chavicol[13] also called estragole	1-allyl-4-methoxybenzene	
Rosmarinic acid[14]	s(2*R*)-2-[[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]] oxy]-3-(3,4-dihydroxyphenyl) propanoic acid	
Apigenin[14]	5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	
Cirsimaritin[14]	5,4'-dihydroxy-6,7-dimethoxyflavone	

(Contd...)

Table 1: (*Continued*)

Name of the compound	IUPAC naming	Structure
Isothymusin[14]	6,7-dimethoxy-5,8,4'-trihydroxyflavone	
Isothymonin[14]	5,8,4'-Trihydroxy-6,7,3'-trimethoxyflavone	
Orientin[15]	8-C-beta-glucopyranosyl-3',4',5,7-tetrahydroxyflav-2-en-3-one	
Vicenin[sss]	6-C-beta-D-xylopyranosyl-8-C-beta-D-glucopyranosyl apigenin	

O. sanctum has been shown to possess anti-fatigue activity,[38] adaptogenic property,[39] antimicrobial activity,[40-44] anticonvulsant activity,[45,46] antifertility activity,[47] antidiabetic activity,[48] radioprotective activity,[49,50] anti-inflammatory activity,[51-54] cardioprotective activity,[55,56] immunomodulatory activity,[57] hepatoprotective activity,[59,60] anticarcinogenic activity,[61,62] mosquito repellent activity,[63] and analgesic activity.[64]

O. sanctum has been shown to possess an excellent anticancer activity.[65] Detoxification of mutagens and cancer-causing agents which is accomplished by enzymes such as cytochrome P450, glutathione-S-transferase, and cytochrome b5 and aryl hydrocarbon hydroxylase is regulated by the alcoholic leaf extract of *O. sanctum*. The anticancer efficacy of Tulsi against human fibrosarcoma cells culture has been reported; the results revealed that the alcoholic leaf extract induced cytotoxicity at the concentration of 50 mg/mL and above. The microscopical examination has shown the cells with contracted cytoplasm and shrunken nuclei. Agarose gel electrophoresis study has shown the DNA fragmentation.[66] Various types of mutagen have been attempted for evaluating the anticarcinogenic ability in the experimental animals induced by *O. sanctum* leaves when fed to experimental rats for 10 weeks with 600 mg/g diet, promisingly reduced the 3,4-benzo (a) pyrene [B (a) P] and 3'-methyl-4-dimethylaminoazobenzene (3'MeDAB)-induced squamous cell carcinoma and hematoma incidences.[67]

Prashar et al. in their study suggested that Tulsi leaf extract obstructs or overcomes biochemical issues accompany with chemical carcinogenesis by hampering metabolic stimulation of the procarcinogen to carcinogen. Primary cultures of rat hepatocytes were treated with 0–500 µg of O. sanctum L. extract for 24 h and then with 7,12-dimethaylbenz[a] anthracene (DMBA, 10 or 50 µg) for 18 h. Cells were then harvested and their DNA was isolated and analyzed by 32 p postlabeling. A significant reduction in the levels of DMBA/DNA adducts was observed in all cultures pretreated with O. sanctum L. extract. Hepatocytes that were treated with the highest dose of extract (500 µg) showed a maximum reduction of 93% in the mean values of DMBA/DNA adducts. This suggests the inhibition of metabolic activation of carcinogen.[68] Papilloma genesis induced by DMBA (7,12-dimethylbenz[a]anthracene) in mice has shown promising reduction in tumor size on topical application of Tulsi leaf extract. Banerjee *et al*. in their study reported that the application of *O. sanctum* leaf extracts in the form of paste has shown significant prevention of DMBA-induced buccal pouch carcinogens.[69]

O. sanctum ethanol leaf extract (70%) significantly reduces the incidence of cancer induced by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG), a nitroso compound extensively used as an experimental gastric mutagen. MNNG is an efficient carcinogen and induces destruction of gastric mucosa which initiates stomach carcinogenesis. Intragastric administration

Table 2: GC-MS identified compounds from various extracts of *Ocimum sanctum*. L

Name of the identified compound	Molecular formula
Eugenol	$C_{10}H_{12}O_2$
Caryophyllene	$C_{15}H_{24}$
Cyclohexane, 1,2,4-triethenyl-	$C_{12}H_{18}$
Pentanedinitrile, 2-methyl-	$C_6H_8N_2$
10-Heptadecen-8-ynoic acid, methyl ester, (E)-	$C_{18}H_{30}O_2$
Benzene methanamine, N, N-a, 4-tetramethyl-	$C_{11}H_{17}N$
Cyclopentane, cyclopropylidene-	C_8H_{12}
Z, Z-4,16-Octadecadien-1-ol acetate	$C_{20}H_{36}O_2$
3',8,8'-trimethoxy-3-piperidyl-2,2'-binaphthalene1,1',4,4'-tetrone	$C_{28}H_{25}NO_7$
Octadecane, 1,1-dimethoxy-	$C_{20}H_{42}O_2$

of MNNG causes increased cell proliferation and angiogenesis with evasion of programmed cell death and leading to well-differentiated squamous cell carcinomas. Oral intake of *O. sanctum* has been shown to reduce these activities where Tulsi extract controls the critical molecules engage in invasion apoptosis, angiogenesis, and cell proliferation. A considerable decrease in the levels of cytokeratin, vascular endothelial growth factor (angiogenesis), antiapoptotic protein Bcl-2 glutathione-S-transferase pi (key proteins involved in proliferation), CK (infiltration), proliferating cell nuclear antigen with contemporary increase in cytochrome *c*, proapoptotic proteins Bax, and caspase 3 was disclosed.[70]

Tulsi curtails the expression of γ-glutamyl transpeptidase, a marker of tumor sequence, and glutathione-*S*-transferase-P, which is increased in chemically induced hepatic tumors. The heat shock protein, which is distorted at the time of carcinogenesis, has also shown a decrease in its concentration.[71] Tulsi extract reduced the efficacy of ornithine decarboxylase, an enzyme entangled in the regulation of cell proliferation and augmentation of cancer. There was also a contemporary reduction in the Phase I enzymes and lipid peroxidation implying that *O. sanctum* hinders the activity of carcinogen caused cytochrome P-450 - reliant enzymes and that this causes a decrease in the evolution of ultimate carcinogenic moiety.[72] The anticancer efficacy[73] of seed oil of Tulsi was examined against subsequently injected 20-methylcholanthrene-induced fibrosarcoma tumors in the thigh region of Swiss albino mice. Augmentation of 100 µL/kg body weight (maximum tolerated dose) of the oil significantly reduced 20-methaylcholathrene-induced tumor prevalence and tumor volume. The improved survival rate and delayed tumor occurrence were noted in seed oil supplemented mice.

CONCLUSION

Cancer keeps on being an overall killer in spite of great advances made in current system of medication amid the past decades. As indicated by late measurable information, malignancy is the second most basic reason for death after coronary illness.[74] Cancer is a hyperproliferative ailment which causes invasion, proliferation, angiogenesis, dysregulation of apoptosis, and metastasis.[75] Oncologists have noticed that advanced stage of cancers is impossible to treat. The reason behind the initiation, development, and evolution of cancer is not clearly known. Some oncologists believe that cancer is not a disease, anaerobic cell growth that ingests the carcinogens which kills patients. Oncologist Professor, Dr. Jones, declares "My studies have proven conclusively that cancer patient who refuses chemotherapy and radiation actually live up to 4 times longer than treated cases including untreated breast cancer cases."[76] There is a great scope and potential for the plant-derived compounds in the fight to control or delay the evolution of the carcinogenic process without any side effects.

Tulsi, a traditional medicinal herb**,** considered as sacred plant, grown all over India, has been used as adaptogen helping the body and mind to adopt and cope with a wide range of emotional, physical, and stress. *O. sanctum* Linn. is a rich source of secondary metabolites which has a significant physiological effects in humans and is used as medicine. From the results of various studies, and the isolated and identified secondary metabolites evident that the whole plant remarkably controls and reduces many diseases. Anticancer property of Tulsi may be due to the synergistic effect of various phytoconstituents present in it. Daily usage of Tulsi leaves helps in controlling various diseases and disease-associated pathogens. By this review, it is clear that so many studies have been accomplished in the field of medicine with animal models to prove its efficacy in the treatment of cancer. Further, clinical trials need to be carried out on humans to ascertain the real effects of this "holy basil."

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