Review

Anticancer Effects of Sandalwood (*Santalum album*)

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Abstract. *Effective management of tumorigenesis requires development of better anticancer agents with greater efficacy and fewer side-effects. Natural products are important sources for the development of chemotherapeutic agents and almost 60% of anticancer drugs are of natural origin. α-Santlol, a sesquiterpene isolated from Sandalwood, is known for a variety of therapeutic properties including anti-inflammatory, anti-oxidant, anti-viral and anti-bacterial activities. Cell line and animal studies reported chemopreventive effects of sandalwood oil and α-santalol without causing toxic side-effects. Our laboratory identified its anticancer effects in chemically-induced skin carcinogenesis in CD-1 and SENCAR mice, ultraviolet-B-induced skin carcinogenesis in SKH-1 mice and in vitro models of melanoma, non-melanoma, breast and prostate cancer. Its ability to induce cell-cycle arrest and apoptosis in cancer cells is its most reported anticancer mechanism of action. The present review discusses studies that support the anticancer effect and the mode of action of sandalwood oil and α-santalol in carcinogenesis.*

Plants are important natural sources of anticancer compounds and many anticancer agents in current use have been isolated from various plant sources (1). A majority of chemotherapeutic agents, including those isolated from plants such as taxol and vincristine, induce cancer cell apoptosis. At the same time, they also severely damage normal cells of the host (2). The sandalwood tree and its products have been known for their medicinal properties since ancient times. A number of studies including those from our laboratory have shown anticancer effects of sandalwood oil and its major chemical constituent α-santalol, without causing any visible side-effects (3-14). It is non-mutagenic and has low acute oral and dermal toxicity in laboratory animals (15).

Sandalwood is a root hemiparasitic tree belonging to the family Santalaceae and depends on host trees to obtain nutrients for its growth. The wood is highly aromatic and is the second most expensive type of wood in the world, after African Blackwood, *Dalbergia melanoxylon* (16). Sandalwood grows in tropical Asia, Australia, Pacific islands and Hawaii. There are many species of sandalwood, one of which the Indian sandalwood (*Santalum album* Linn.) (Figure 1A), called the 'Royal Tree' in India (17), is a well-known and economically important species, having the most fragrant wood and highest oil content. It has been categorized as 'vulnerable' by the International Union for Conservation of Nature (IUCN) in 1997 (16). Historically, sandalwood is considered as one of the most sacred trees and an important part of devotional and spiritual rituals of certain religions. Statues of gods and parts of many ancient temples have been made of this wood. The Egyptians used it in embalming the dead and in ritual burning to venerate the god (16). The products of sandalwood have been widely used for incense, wood carving, funeral pyres; in the food industry as a flavor ingredient, and in insect repellents, perfumes, soaps, detergents and cosmetics to add fragrance.

The essential oil of sandalwood develops in the heartwood and root of the trees and this process requires about 15 to 20 years. Fully matured trees of 60-80 years develop the greatest oil content with high quality and a high level of fragrance. The average yield of the essential oil is 4.5-6.25% with *Santalum album,* the highest being in the roots (up to 10% in weight) (18). More than 230 constituents that belong to different chemical classes have been identified in the heartwood. These are mainly terpenoids (18). Phytochemical evaluation of sandalwood extracts revealed that the tree is rich in saponin, phenolics and tannins in addition to terpenoids (19).

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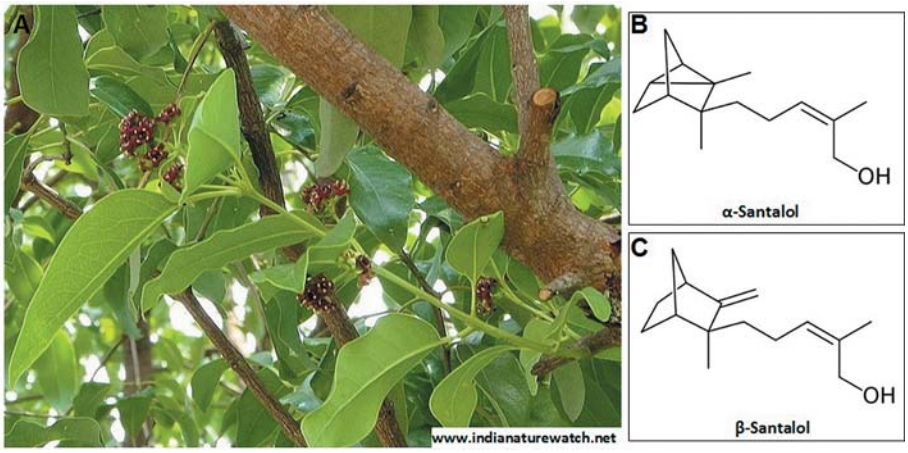

Figure 1. *A: Sandalwood tree (Santalum album). Structure of α-santalol (B) and β-santalol (C).*

Properties of Sandalwood Oil

The chipped heartwood is used for extraction of commercially valuable sandalwood oil by steam distillation. The oil is colorless to yellowish and viscous (5). In addition to the Indian sandalwood, the Australian sandalwood (*Santalum spicatum*) and Hawaiian Sandalwood (Santalum ellipticum) are two major species used for the production of sandalwood oil. The compositions of the oils are different and the quality of Indian sandalwood is considered superior. The major constituent of sandalwood oil is santalol, a mixture of two isomers, α-santalol and β-santalol ($C_{15}H_{24}O$) (Figure 1B and C). These are the two molecules mainly associated with sandalwood's fragrance (18, 20), while α-santalol is mainly reported for its anticancer properties (5-14). α-Santalol is a sesquiterpene with a molecular weight of 220.35 g mol^{-1}, boiling point of 166˚C and density of 0.9770 g/cm^3. Nikiforov *et al*. identified α-santalene, α-santalal, β-santalal, epi-β-santalal, α-santalol, β-santalol, (E)-β-santalol, α-bergamotol and spirosantalol as the odorant components in sandalwood oil (21). α-Santalol has a slightly woody fragrance, while β-santalol is responsible for the highly prized typical warm-woody, milky, musky, urinous, animal aspects of sandalwood (18).

Isolation of α-Santalol from Sandalwood Oil

Our laboratory isolated α-santalol from sandalwood oil by column chromatography with n-hexane:ethyl acetate (3:1) as a solvent system (13). Different fractions were analyzed by thin-layer chromatography and the purity was assessed by gas chromatography–mass spectrometry (22). Studies indicated that the major component of sandalwood oil is α-santalol, constituting 61%, followed by β-santalol at 28% (5). Other constituents include cisnuciferol, α-bisabalol, *cis*bergamatol, epi-β-santalol, γ-curcumen-12-ol, β-curcumen-12-ol, cis-lanceol and *trans*-farnesol (23).

Medicinal Properties

The products of *Santalum album* have been used for the treatment of various diseases since ancient times. It is non-toxic and exhibits a wide variety of medicinal properties including anti-microbial, anti-oxidant, anti-inflammatory, anti-spasmodic, diuretic, expectorant and antiseptic activities. In Chinese medicine, sandalwood products are used to treat dysentery, stomach ache, gonorrhea, skin diseases, and anxiety (24). Emulsion, paste and essential oil of sandalwood have been used for centuries in India for the treatment of inflammatory and eruptive skin diseases (25-27). It is used in the traditional Unani system of medicine to treat gastric ulcers and various cardiac, brain, liver, stomach and skin disorders (28, 29). Anti-ulcer potential of hydro-alcoholic extract of *Santalum album* stem at 500 mg/kg was reported in gastric ulceration models of albino Wistar rats (28).

Sandalwood oil is widely used in aromatherapy to relieve anxiety, stress, and depression (30). It has neuroleptic, relaxing, soothing, bronchial dilating and astringent effects. α-Santalol has been reported to have central nervous system depressant effects, such as sedation (31). It promotes restful sleep and helps to ease an anxious mind. In sleep-disturbed rats, inhalation of α-santalol affected the sleep-wake cycle, and caused a significant decrease in total waking time and an increase in total non-rapid eye movement sleep time. Results also suggest the action of α-santalol *via* the circulatory system by absorption into the blood through the respiratory mucosa rather than the olfactory system (31). The results of a pilot study in patients receiving palliative care to

evaluate the effectiveness of aromatherapy support the notion that sandalwood oil is effective in reducing anxiety (32).

Antimicrobial activity of leaf and stem aqueous extracts of *Santalum album* were observed against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas*, in which leaves extract showed significantly higher inhibition when compared to stem extract (33). In another study, the antibacterial activity of the aqueous extract was evaluated against two strains of *Escherichia coli*, one each of *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis* and Aeromonas species. It showed strongest inhibitory activity of 87% against *Staphylococcus aureus* whereas there was no inhibition of *Escherichia coli* and *Bacillus subtilis*. For the other strains, the inhibition was between 66% and 78% (34). Sandalwood oil had *in vitro* antiviral activity against *Herpes simplex virus* (HSV)-1 and HSV-2. It inhibits viral replication in a dose-dependent manner and is more effective against HSV-1 (35).

Anticancer Effects of Sandalwood Oil

Chemoprevention is a means of cancer control by the use of natural or synthetic agents allowing suppression, retardation or reversion of carcinogenesis (36). Chemopreventive agents can be broadly classified as blocking and suppressive agents. The blocking agents inhibit the initiation step by preventing carcinogenic agents from reaching or acting on critical target sites, whereas suppressive agents inhibit malignant cell proliferation during the promotion and progression steps of carcinogenesis (37). The available experimental evidence suggests that sandalwood oil could function as an inhibitor of tumor initiation and promotion stages of carcinogenesis. Studies in male Swiss albino mice indicate the anticarcinogenic potential of sandalwood oil *via* enhancing the excretion of carcinogens. In that study, oral gavage feeding of sandalwood oil induced a time- and dose-responsive increase in the activity of glutathione-S-transferase (GST) and acid soluble sulfhydryl levels in the liver (38). GSTs are a family of phase II detoxification enzymes that function to protect cellular macromolecules from attack by reactive electrophiles. They catalyze the conjugation of glutathione to a wide variety of endogenous and exogenous electrophilic compounds, leading to the elimination of toxic compounds (39). Enhancement of GST activity and acid-soluble sulfhydryl levels indicate a possible chemopreventive action of sandalwood oil on carcinogenesis through a blocking mechanism.

Studies from our laboratory have shown skin cancer chemopreventive effects of sandalwood oil in chemically induced skin carcinogenesis in CD-1 mice. Topical application of sandalwood oil (5% in acetone, w/v) prevented skin tumor development initiated by 7,12-dimethylbenz [a]anthracene (DMBA) and promoted by 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) and TPA-induced ornithine decarboxylase (ODC) activity in CD-1 mice. It significantly reduced papilloma incidence by 67%, multiplicity by 96%, and TPA-induced ODC activity by 70% (3). Sandalwood oil pre-treatment reduced papilloma incidence and multiplicity in a concentration- and time-dependent manner in CD-1 mice. Pre-treatment with 5% sandalwood oil 1 hour before DMBA and TPA treatments produced the most effective chemopreventive effects (4).

A recent study on HaCat keratinocytes reported the induction of autophagic cell death with Indian sandalwood oil treatment (40). A number of autophagy-modulating agents have been proposed as potential anticancer therapeutics when used as either single or combinatorial treatments (41). Autophagy is a self-degradative process which involves the engulfment and degradation of cytoplasmic components within lysosomes. It is designated as type II programmed cell death, while the process of apoptosis is referred to as programmed cell death type I (41). Treatment of HaCat cells with sandalwood oil up to a concentration of 0.0005% resulted in a concentration-dependent reduction of UV-induced activator protein-1 activity and inhibition of cellular proliferation. UV-induced activator protein-1 activity has been linked to cellular proliferation and survival and is a major causative factor in UV-induced skin cancer. Study showed an induction of microtubule-associated protein light chain 3-II (LC3-II) formation and poly (ADP-ribose) polymerase (PARP) cleavage by UV-irradiation. However, sandalwood oil treatment blocked PARP cleavage and UV-induced apoptosis but increased the level of LC3-II formation, which is marker of active autophagosome formation (40).

Studies on J82 human bladder cancer cells showed that sandalwood oil induced cell death *via* DNA damage and cell-cycle arrest (42). In this study, sandalwood oil was shown to up-regulate growth arrest genes [(Growth arrest and DNA-damage-inducible protein 45 alpha (GADD45A), *GADD45B*, and protein phosphatase 1 regulatory subunit 15A (PPP1R15A)] and proapoptotic genes [(Caspase 9 and Inhibitor of growth protein 5 (ING5]. Sandalwood oil treatment led to negative regulation of protein kinase activity and activation of G-protein-coupled receptors. In addition, the expression of transcription factors, such as Activating transcription factor 3 (ATF3), DNA damage-inducible transcript 3 (DDIT3), Early growth response protein 1 (EGR1), FOSB, JUN, JUNB, MYC, and several inhibitors of DNA binding (ID1, ID2, and ID3), along with members of the zinc finger family were also modulated by sandalwood oil.

In another study, five lignans isolated from sandalwood heartwood were evaluated for their cytotoxic activities against HL-60 human promyelocytic leukemia cells and A549 human lung adenocarcinoma cells (43). Two of these

compounds exhibited cytotoxicity against HL-60 cells with IC_{50} values of 1.5 and 4.3 μM, and against A549 cells with IC_{50} values of 13.6 and 19.9 μM, respectively. These tumor cell deaths were shown to be mediated through induction of apoptosis. The aldehyde group was identifided as a structural requirement for the appearance of cytotoxicity in this type of lignans.

Anticancer Effects of α-Santalol

The efficacy of α-santalol as chemopreventive agent appears to be very promising in skin cancer control. Studies from our laboratory indicated the chemopreventive potential of α-santalol similar to that of sandalwood oil in DMBA-initiated and TPA-promoted skin tumors in CD-1 and SENCAR mice (5). Chemopreventive effects were determined during the initiation and promotion phases; α-santalol treatment did not show any significant effects during initiation phase. However, it significantly prevented papilloma development during the promotion phase of the DMBA and TPA carcinogenesis protocol in both CD-1 and SENCAR mice. The treatment resulted in a significant inhibition of TPA-induced ODC activity and incorporation of ^{3}H-thymidine in DNA in the epidermis of both strains of mice. Since DMBA-induced initiation was not affected by treatment, the anticancer effects of α-santalol on TPA-induced promotion is unlikely to be due to the blocking of TPA absorption.

In chemically-induced skin carcinogenesis, α-santalol reduced tumor incidence and multiplicity in a time- and concentration-dependent manner in a dose–response study. Maximum effect was shown by 5% of α-santalol compared to 1.25% and 2.5% and it significantly reduced skin tumor incidence and multiplicity, and inhibitied TPA-induced ODC activity and DNA synthesis (6). In animal models, topical application of α-santalol used at concentrations of 2.5 and 5% (w/v in acetone) did not result in any visible side-effects. Gas chromatography–mass spectrometry studies detected α-santalol in the serum, skin, and liver of animals which received topical application of α-santalol and suggested systematic absorption of α-santalol in its chemopreventive action (44).

In addition to chemically-induced skin carcinogenesis, α-santalol had a strong chemopreventive potential in UVB-induced skin tumorigenesis of SKH-1 hairless mice under three different protocols (DMBA-initiated and UVB-promoted; UVB-initiated and TPA-promoted and UVB-initiated and UVB promoted) (8). The treatment was most effective, with 72% reduction in tumor multiplicity on UVB-induced complete tumorigenesis. In another study on UVB-induced skin tumor development, α-santalol was shown to inhibit *in vitro* lipid peroxidation in skin and liver microsomes and prevent tumor development possibly by acting as an anti-peroxidant (9). In dose-response study, 5% α-santalol led to optimal chemoprevention as compared to 1.5% and 2.5%, and the minimum possible concentration of α-santalol potentially able to reduce UVB-induced skin tumor development was identified as 2.5% (9). A study which used a physiologically relevant dose of UVB (30 mJ cm^2) to induce photocarcinogenesis in SKH-1 mice showed that α-santalol pretreatment has potential to target various pathways involved in photocarcinogenesis. This dose of UVB is in the range of human exposure to sunlight that can cause skin cancer (14). α-Santalol has been shown to suppress proliferation of non-melanoma and melanoma skin cancer cells in culture (7, 11).

Recent studies demonstrated the anticancer effects of α-santalol in non-skin cancer models including breast and prostate cancer. Studies on PC-3 and LNCaP human prostate cancer cell lines, as well as in PC-3 tumor xenograft models, demonstrated the efficacy of α-santalol against androgen-dependent and -independent prostate cancer (12, 45). In both studies, α-santalol produced less toxic effects on normal cells. In PC-3 tumor xenograft models, α-santalol had a chemopreventive effect at the level of tumor promotion by inhibiting angiogenesis and growth of prostate tumor. We reported the anti-neoplastic effects of α-santalol on estrogen receptor-positive and -negative breast cancer cells (13). A strong time and concentration-dependent reduction in cell viability and proliferation was observed in MCF-7 and MDA-MB-231 cells treated with 10-100 μM concentrations of α-santalol. At the same time, normal breast epithelial cell line, MCF-10A was more resistant to α-santalol treatment. Our laboratory is investigating the transdermal and transmammary application of α-santalol for the prevention and treatment of breast cancer in animal models. Tumor-selective cytotoxicity of santalol derivatives were shown in a study on HL-60 human promyelocytic leukemia cells (46).

Mechanisms of Action of α-Santalol Against Cancer

Induction of cell-cycle arrest. Various *in vitro* and *in vivo* studies have shown strong anticancer activities of α-santalol mediated by different modes of action. The most published anticancer mechanism of action of α-santalol is its ability to induce cell-cycle arrest and apoptosis in cancer cells. Cellular growth and proliferation is a highly regulated event, in which complex series of signaling pathways control the growth and division of DNA. Disorders in the regulation of the cell cycle can lead to uncontrolled proliferation and contribute to a malignant phenotype. The cell cycle consists of G_1, S, G_2 and M phases in which G_1 and G_2 are gap phases between the processes of DNA synthesis (S phase) and mitosis (M phase), respectively (47). Progression of the cell cycle through each phase is regulated by specific cyclin and cyclin-dependent kinase (CDK) complexes. Bindings of

CDK inhibitory proteins such as p21 and p27 negatively regulate the cell cycle (48, 49).

Previous studies from our laboratory on non-melanoma and melanoma skin cancer cells indicated G_2/M phase cell-cycle arrest upon α-santalol treatment in *p53*-mutated A431 human epidermoid carcinoma cells and *p53* wild-type UACC-62 human melanoma cells (11). α-Santalol up-regulated the expression of wild-type p53 in UACC-62 cells and suppressed the expressions of mutated *p53*, along with up-regulation level of CDK-inhibitor p21 in A431 cells. Further studies indicated a p53- and p21-independent G_2/M phase arrest in these cells. Knockdown of *p21* in A431 cells or knockdown of both *p21* and *p53* in UACC-62 cells did not change G_2/M phase arrest caused by α-santalol treatment. Furthermore, in UACC-62 cells, α-santalol treatment caused microtubule depolymerization similar to the positive control vinblastine used in the study.

Consistent with the studies on skin cancer cells, our studies on MCF-7 (*p53* wild-type) and MDA-MB-231 (*p53*-mutated) breast cancer cells also showed α-santalol induced G_2/M phase cell-cycle arrest regardless of their estrogen receptor or *p53* status (13). Up-regulation of p21 along with suppressed expression of mutated *p53* was observed in MDA-MB-231 cells. On the contrary, α-santalol did not increase the expression of wild-type *p53* and *p21* in MCF-7 cells. α-Santalol-induced cell-cycle arrest was associated with a decrease in the protein levels of G_2/M regulatory cyclins (cyclins A and B), CDKs (CDK2 and CDC2), CDC25B and CDC25C accompanied by strong increase of phospho-CDC25C (Ser216) in both cell lines (13). Cyclin A is able to bind CDK2 and CDC2 and promote the cell-cycle progression through S and G2 phases. Entry into mitosis is regulated by the activation of cyclin B–CDC2 complex (47). Down-regulation of CDK activity involves phosphorylation at Thr 14 and Tyr 15; dephosphorylation of these residues and activation of CDKs for cell-cycle progression is controlled by members of the CDC25 phosphatase family (50, 51). CDC25B and CDC25C play an important role in G_2/M transition. CDC25B dephosphorylates and activates CDK2–cyclin A and CDC2–cyclin B, whereas CDC25C dephosphorylates and activates CDC2–cyclin B mitotic kinase complex and thereby permits cell entry into mitosis. Phosphorylation of CDC25C at Ser-216 block the cells from mitotic entry (52).

In the UVB-induced skin carcinogenesis of SKH1 hairless mouse, inhibition of cyclins and CDKs of different cell-cycle phases were observed in a group pretreated with α-santalol (14). UVB exposure interrupts the cell-cycle checkpoint controls of epidermal cells and hence the resulting tumors are associated with an increase in cell-cycle-regulatory cyclins and CDKs, or decreased expression of CDK inhibitors. Significant decrease in the expression of cyclins A, B1, D1 and D2 and CDKs [Cdk1 (CDC2), CDK2, CDK4 and CDK6] and up-regulation of p21 were found in α-santalol-pretreated group. α-Santalol treament before UVB radiation strongly inhibited UVB-induced epidermal hyperplasia and the thickness of the epidermis and significantly reduced the expression of proliferation markers, proliferating cell nuclear antigen and Ki-67 (14).

Induction of apoptosis by α-santalol. Most anticancer drugs in current use primarily act by inducing apoptosis in target cells. Studies from our laboratory demonstrated the induction of apoptosis by α-santalol in various cancer cell lines and *in vivo* cancer models (7, 10, 12-14). Apoptosis is programmed cell death characterized by the activation of a group of intracellular cysteine proteases called caspases. In apoptotic pathways, caspase-3 functions as an executioner caspase and its activation leads to cleavage of various substrates, including PARP (53). In UVB-induced skin carcinogenesis, topical application of α-santalol before each UVB exposure resulted in the activation of caspase-3 and cleavage of PARP in skin of SKH-1 hairless mice, indicating its photoprotective effect through induction of apoptosis (14). In another study, α-santalol prevented skin cancer development in UVB-irradiated mouse skin by inducing pro-apoptotic proteins *via* an extrinsic pathway (10). *In vitro* studies using A431 skin cancer cells indicated the involvement of both caspase-dependent and -independent pathways of apoptosis in response to α-santalol treatment (7). In this study, apoptosis was found to be primarily through the intrinsic pathway with loss of mitochondrial membrane potential, release of cytochrome c, and subsequent activation of caspase-9 and caspase-3 in response to α-santalol treatment.

α-Santalol induced apoptotic cell death through extrinsic and intrinsic pathways in MCF-7 and MDA-MB 231 human breast cancer cell lines (13). Treatment with α-santalol induced activation of both caspase-8 and caspase-9. The executioner caspases involved in α-santalol-mediated apoptosis in MDA-MB-231 cells are caspase-3 and caspase-6, and in MCF-7 cells, α-santalol led to the activation of caspase-6 and caspase-7, along with strong cleavage of PARP in both cell lines.

α-Santalol effectively suppressed the growth of androgen-dependent LNCaP and androgen-independent PC3 human prostate cancer cells by causing caspase-3 activation, and inducing apoptosis (12). The LNCaP cell line, which expresses wild-type p53, was relatively more sensitive to apoptosis induction by α-santalol compared to p53-deficient PC-3 cells. The α-santalol-induced apoptotic cell death and activation of caspase-3 was significantly attenuated in the presence of pharmacological inhibitors of caspase-8 and caspase-9. In another study, seven α-santalol derivatives from the heartwood of *Santalum album* were evaluated for cytotoxicity against HL-60 human promyelocytic leukemia cells and TIG-3 normal human diploid fibroblasts. One of the

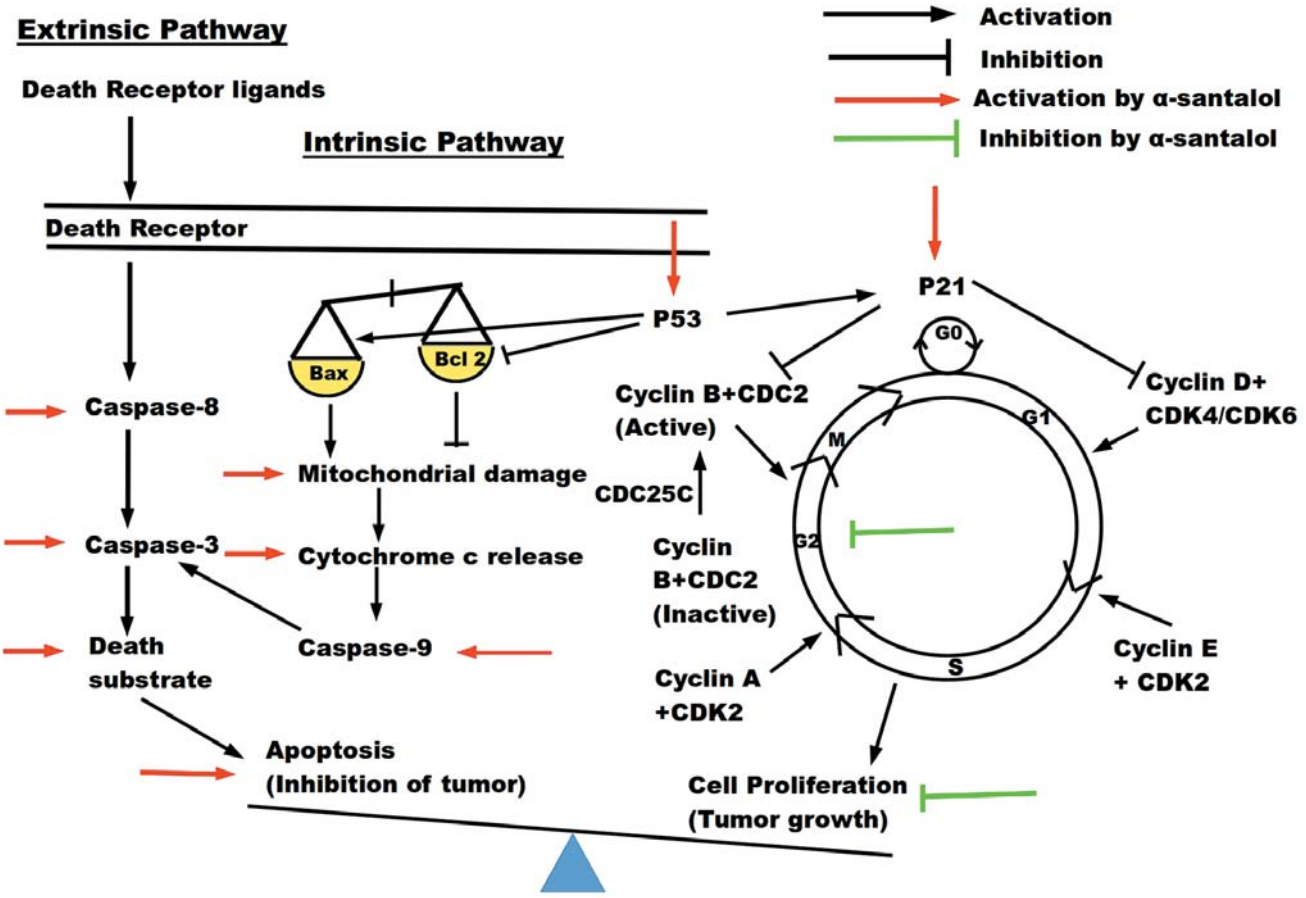

Figure 2. *Molecular targets for the anticancer effects of α-santalol in skin cancer chemoprevention (44, Reproduced by permission).*

derivatives exhibited tumor-selective cytotoxicity through induction of caspase-dependent apoptosis of HL-60 cells (46).

Anti-inflammatory effects of α-santalol. Many scientific studies have supported the anti-inflammatory activities of sandalwood oil and α-santalol. Potential anti-inflammatory action of sandalwood oil was shown in a clinical trial of sandalwood oil-containing treatment regimen for eight weeks in 50 patients with mild to moderate facial acne (54). Treatment was well tolerated by nearly all patients and 89% of patients showed improvement in their disease, with notable reductions in lesion counts in patients with more severe or inflamed lesions. In another study, topical application of sandalwood oil and turmeric-based cream effectively prevented radiation-induced dermatitis in patients with head and neck cancer who were undergoing radiotherapy (55). In male Sprague–Dawley rats, inclusion of sandalwood seed oil in their diet affected the levels of several inflammatory factors. Sandalwood seed oil inhibited the generation of pro-inflammatory factors such as prostaglandin F2α , prostaglandin E_2, thromboxane B_2, leukotriene B4, tumor necrosis factor-α and interleukin-1β (IL1β) in both liver and plasma of rats (56). Sharma *et al*. reported the anti-inflammatory effect of sandalwood oil, purified α-santalol and β-santalol in lipopolysaccharide (LPS)-stimulated human epidermal keratinocyte/dermal fibroblast models through the suppression of LPS-induced secretion of proinflammatory cytokines and chemokines, including IL6, IL8, Monocyte Chemoattractant Protein-1, C-X-C motif chemokine 5 and Granulocyte-macrophage colony-stimulating factor (57). Purified α-santalol and β-santalol also suppressed LPS-induced production of the arachidonic acid metabolites, prostaglandin E2 and thromboxane B2 by skin cell co-cultures. In this study, β-santalol was found to be as effective as α-santalol in suppressing LPS-induced proinflammatory events. In UVB-induced photocarcinogenesis, pretreatment with α-santalol resulted in a marked inhibition of UVB-induced

Table I. *Summary of anticancer effects of α-santalol at different sites and the mechanisms of action*

Sites	References
Skin	3-11, 14, 40
Prostate	12, 45
Breast	13
Liver	61
Other	42, 43, 46
Mechanism of action	
Cell cycle	11, 13, 14, 42
Apoptosis	7, 10, 12-14, 46
Angiogenesis	45, 61
Autophagy	40
Anti-oxidant	34, 59, 60
Anti-microbial	33-35
Anti-inflammatory 54-58	
CNS effects	30-32

cyclooxygenase-2 expression in mice (14). Baylac and Racine reported the anti-inflammatory activities of sandalwood oil by inhibiting 5-lipoxygenase activity which is a key marker of inflammation (58).

Anti-oxidant activity. *Santalum album* extract exhibited 1,1-diphenyl-2-picrylhydrazyl radical-scavenging activity in a concentration-dependent manner, with maximum scavenging of 64% in presence of 500 μl of aqueous extract (34). Antioxidant activity of *Santalum album* along with other six medicinal plants used in traditional Ayurvedic herbal preparations was explained by Scartezzini and Speroni (59). *In vivo* antihyperglycemic and antioxidant potential of sandalwood oil (1 g/kg) and α-santalol (100 mg/kg) has been reported in male Swiss albino mouse models of alloxan-induced diabetes and D-galactose-mediated oxidative stress, respectively (60).

Anti-angiogenic effect. Antiangiogenic effect of α-santalol was reported in PC-3 xenograft tumor model in nude mice *in vivo* and in human umbilical vein endothelial cells (HUVECs) *in vitro* (45). In this study, HUVECs were found to be more sensitive to α-santalol than PC-3 and LNCap prostatic cancer cells and α-santalol significantly inhibited endothelial cell proliferation with an IC_{50} value of 17.8 μM. α-Santalol inhibited migration of endothelial cells in a dose-dependent manner, and inhibited the invasion of HUVECs and capillary tube formation. It inhibited angiogenesis and growth of human prostate tumor growth by targeting vascular endothelial growth factor receptor 2-mediated AKT/mTOR/P70S6K signaling pathway. The antitumor and antiantiangiogenic activities of α-santalol were identified in human hepatocellular carcinoma cell lines and hepatocellular carcinoma induced by diethylnitrosamine in mice (61).

Conclusion and Future directions

Studies suggest that α-santalol is a safe and promising cancer chemopreventive/therapeutic agent with potential to target various pathways involved in carcinogenesis (Figure 2). Based on available data from cell line and animal studies, the mechanisms of action through which α-santalol functions as an anti-carcinogenic agent include proapoptotic, antiproliferative, antiangiogenic, antioxidant and anti-inflammatory activities (Table I). α-Santalol is relatively non-toxic to normal tissues, which minimizes undesirable systemic side-effects and improves patient compliance. It also has a pleasant fragrance thus facilitating compliance. However, further experimental and clinical studies are required to better understand the role of α-santalol in chemoprevention and treatment of various types of cancer.

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