Phytochemistry and Pharmacological Properties of *Santalum album* L.

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Abstract

Santalum album L. (Sandalwood) is one of the pharmacologically valued tree species. The essential oil derived from its heartwood has much more commercial importance, and is an active ingredient in various traditional medicine systems for the management and prevention of various illnesses all over the world. The versatile therapeutic and healthcare importance of Sandalwood is attributed to the rich source of phytochemicals, particularly sesquiterpenes. A variety of biological properties and impending health benefits of Sandalwood have been testified, including anti-microbial, anti-oxidant, anti-inflammatory, anti-cancer, anti-diabetic activities, and protecting properties on the gastric mucosa, liver and nervous system. No significant toxicity has been indicated by Sandalwood oil or its individual constituents. The present chapter discusses traditional uses, phytochemistry and pharmacological activities of Sandalwood. Also, it provides an

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understanding of Sandalwood oil extraction methods, chemistry of the compounds and their medicinal importance.

Keywords

Ethnomedicine · Heartwood · Aromatherapy · Ayurveda · Unani medicine · Sandalwood oil · Pharmacology · Phytochemistry · Biological activities

5.1 Introduction

The usage of plants as medication is older than documented history. Since from the past years, medicinal plants are being appreciated for their therapeutic properties, and utilized in different sectors, including the pharmaceuticals, perfumery, and cosmetic productions (Swamy and Sinniah 2015, 2016). Plants containing various bioactive chemicals create a central collection of industrial produces. Noteworthy to mention that several of the present days' drugs are obtained from herbs or they are the derivatives of phytocompounds. Despite a considerable advancement made in the synthetic medicine investigation, plant-based compounds are still recognized as the best resources for treatments, and have wide-ranging uses in the drug business (Swamy and Sinniah 2015; Swamy and Rudramurthy 2016; Mohanty et al. 2017; Lodh and Swamy 2019; Kirubakari et al. 2019; Karthikeyan et al. 2020). Several health issues are being treated based on the understandings from the traditional plant-based medications, especially the Ayurveda, Unani, Siddha, Tibetan, Chinese and other systems of health practices. The ethnic understanding of many plants has been acknowledged and accepted in the ancient Indian literature. The traditional information on medicine, ever since the period of great sage Charaka, the Indian father of medicine, has helped in discovering numerous indispensable drugs of contemporary age. The great Indian sages Charaka and Sushruta and other early intellectuals have documented various medicinal plant species, their description and therapeutic uses in their writings Charakasamhitha and Sushruta Samhita, respectively (Bhandary and Chandrashekar 2011). Thus, it can be said that the applications of herbs for human well-being are highly deep-rooted ever since from the existence of human life. Nevertheless, the latest vivid upsurge in sales of plant products in world marketplaces emphasizes the increasing acceptance of herbal treatments. India, China and several other South-East Asian countries use traditional systems of medications, involving different plant species for treating flue, stomach ulcers, malaria and many other health issues. In these regions, there is a continued public support for protecting and promoting the traditional and spiritual principles of folk medications. It has been estimated that herbal products worth in the world marketplace is around US$ 62 billion, and it may raise up to US$ 5 trillion by the end of 2050 (Kumara Swamy et al. 2011; Swamy et al. 2016, 2017; Arumugam et al. 2016; Swamy and Sinniah 2016; Ahmed et al. 2018; Swamy 2020a, b).

Santalum album L. (Sandalwood) (Family, Santalaceae) is one such treasurable tree species in the globe, possessed with multiple therapeutic properties. It is

commonly recognized as Srigandha in Sanskrit, Safed Chandan in Hindi, White sandalwood in English, and it is measured to be a well-regarded donation of the flora entangled into the Indian customs and heritage (Fox 2000; Kumar et al. 2015). Sandalwood producers are used throughout the world, and it is one amongst the costly woods in the globe. With more than 2000 years of antiquity, Sandalwood is much-admired for its perfumery ingredient. Along with the cultural significance, it is admired for fragrant and therapeutic qualities. Sandalwood tree grows under diverse edaphic conditions, eco-climatic environments; however, it is indigenous to South regions of India, particularly grows well in the Western Ghats, and foothills of Shevaroy and Kalrayan. The commercial significance of Sandalwood is for its fragrant heartwood and its essential oil, which is vastly utilized in the cosmetic and perfumery companies. The heartwood is ascetically hard, dense, and has high durability with an oily consistency, and hence is highly preferred as an attractive material for making wood crafts with intricate designs. The harvest and superiority of oil differ and depend on the locality, development phases of the trees and distillation methods (Kumar et al. 2015).

Medicinally, Sandalwood possesses tranquilising and recreation effects. It reduces depression, stress, anxiety, uneasiness and restlessness. It is useful in enhancing meditation, hence used in spiritual practices. Various traditional curative practices, such as Unani, Ayurveda and Siddha medicines employ Sandalwood for treating a wide range of health issues. Sandalwood products possess several pharmacological effects such as anti-microbial, anti-cancer, anti-oxidant, anti-inflammatory, hepatoprotective, anti-pyretic and palliative properties (Desai and Hiremath 1991; Biradar et al. 2009; Zhang and Dwivedi 2011; Bommareddy et al. 2007, 2019; Matsuo and Mimaki 2012; Misra and Dey 2013a; Rao et al. 2014; Khan et al. 2014; Kamalarajan et al. 2019). These biological activities are predicted for the occurrence of various chemical compounds, such as α- and β-santalol, (Z)-α-santalol, betulinic acid, vitexin, vicenin-2, isovitexin, isoorientin, orientin, chrysin-6-C-β-D-glucopyranoside, chrysin-8-C-β-D-glucopyranoside, etc. (Nikiforov et al. 1988; Zhu et al. 1993; Shukla et al. 1999; Chen and Lin 2001; Burdock 2002; Kim et al. 2005; Burdock and Carabin 2008; Kusuma and Mahfud 2018). So, in this chapter, a collation of works is prepared with the intention of producing an inclusive report linked to traditional uses, phytochemistry and pharmacological properties unveiled by Sandalwood crude extracts as well as its isolated pure phytocompounds.

5.2 Traditional Uses of Sandalwood

Since the early ages, plants have served for human adornment, and people have been using various kinds of herbs to maintain their beauty. Sandal, turmeric and other plants are used in the form of a paste to improve the complexion of a bride. The paste of Sandalwood and shikakai (*Acacia concinna*) is used for marking on the forehead. Brides use Sandalwood, rose (*Rosa damascena* Mill.) to perfume their body. Sandalwood is one of the few fragrances that are equally popular among men and women. The plant is known to pacify vitiated pitta, burning sensation, head ache,

hyper-perspiration, psychotic ailments, memory loss, cardio-myopathy, jaundice, ulcer, cough and inflammation. The wood is bitter with cooling and sedative effects. The essential oil extracted from its heartwood was popular in medicines up to 1930s.

In the Indian system of medicine usage of Sandalwood oil is an age-old practice. The major Indian traditional systems of medicine, like Ayurveda and Siddha largely employ Sandalwood oil as a demulcent, diuretic and mild stimulant. The daily recommended dosage of Sandalwood oil as per the German Commission E review is 1–1.5 g and advised for maximum 6 weeks. (Anonymous 1998). The oil is astringent, disinfectant and has a pronounced effect on the pulmonary (bronchial tracts) and genitourinary tracts. It is also a carminative, anti-septic, anti-spasmodic, diuretic, anti-phlogistic, emollient, stimulant, expectorant, sedative and tonic agent (Alagesaboopathi 2009; Bhowmik and Sampath Kumar 2011). The oil is useful for chronic chest problems, sore throat, bronchitis, asthma, cystitis and bladder infections, gonorrhoea infection, excessive sweating, cooling the body during fever, sun-stroke and heat-stroke, acute dermatitis, urethritis, vaginitis, eye diseases and sexual dysfunction. The oil gives relief to dehydrated skin (anti-ageing skin care). The oil, being astringent is useful on oily skin to prevent ugly scars and help in fighting dry eczema and scabies too. Because of its wonderful qualities, the oil is used for overcoming urinary tract and pulmonary infections. It helps in producing calming and harmonious influence on the mind, and to reduce stress and anxiety. It can be used against cough, bronchitis, asthma, irritability, insomnia, stress and for refreshment (Valnet 2015). The diluted oil can also be used in bathing as a blended massage oil as it amalgams well with lavender, black pepper, bergamot, geranium, rose, myrrh and vetiver oils) for relaxation. As a gargling agent, it may be useful in overcoming sore throat. It is also useful in the preparations of lotions and creams (Bhowmik and Sampath Kumar 2011; Pullaiah 2019). Sandalwood oil is a popular remedy for diseases like gonorrhoea, gleet, urethral haemorrhage, pyelitis and chronic cystitis. This oil, when given in a little carum seeds water or infusion of ginger is a valuable remedy for bronchial catarrh. The oil is an excellent application in scabies of every stages and forms if given externally. When mixed with a double quantity of mustard oil, Sandalwood oil is said to be a good application for pimples on the nose. It is also a digestive aid, especially when blended with ginger and pepper mint, it alleviates heartburn, nausea, diarrhoea and vomiting. Importantly, the oil should be administered in diluted form. However, pregnant women and breast-feeding women should avoid its uses in aromatherapy. The oil should be used externally, and is not meant for the internal use and cuts, open wounds and exposed skin. Every care should be taken to avoid contacts with eyes. The oil may cause dermatitis and photo-allergy, and hence individuals with a known allergy should avoid its use (Bakhru 1996; de Groot and Schmidt 2017; Pullaiah 2019). Sandalwood oil is used for inflammatory conditions of the efferent urinary tract. Sandalwood oil is a stimulant and disinfectant of the whole genitourinary tract. Sandalwood oil is also used in treatment of dysuria (to promote and facilitate urination), gonorrhoea and cough (Pullaiah 2019).

The Sandalwood paste is an admired household remedy for prickly heat. It prevents excessive sweating and heals inflamed skin. The wood is medicinally useful

in bilious fever. The dry Sandalwood powder can be mixed in rose water and applied as a paste over the body parts, where there is profuse sweating and inflammation. The powder is given internally as infusion or decoction as alterative, anti-septic, astringent, carminative, disinfectant, diuretic, expectorant, haemostatic, refrigerant, stimulant and a sedative. An emulsion or a paste of the heartwood is a cooling dressing in inflammatory and eruptive skin diseases, such as erysipelas and prurigo. In summer, regular application of Sandalwood paste on the body, especially for children has a refreshing effect, which heals any tiny infected spots. The Sandalwood paste applied on the forehead relieves headache and brings down the temperature in fevers. The powder of the wood is taken with coconut water in cases of morbid thirst. When the wood powder (20 g) is taken as a watery emulsion mixed with sugar, honey and rice water, it checks gastric irritability and dysentery, and also relieves thirst and body heat. The wood powder in the form of pills or added to cow's milk is administered for gonorrhoea, and if locally applied the powder allays prickly heat, and checks excessive perspiration (Alagesaboopathi 2009; Pullaiah 2019).

The Sandalwood paste and essential oil are utilized for curing skin diseases, burning sensation, cardiac debility jaundice, intermittent fever and gastric irritability. The heartwood paste is generally smeared on the forehead to get rid of headache. The stem bark ground into paste and taken orally for malarial fever. The oil obtained from the seeds is useful in curing skin diseases. The crude drug of the plant is the best medicine to control gallbladder and tuberculosis malfunctions. The Sandalwood is bitter in taste and used as a cooling agent, cardiac tonic and sedative. The wood paste when taken orally cures urinary problems, such as secretions, bleeding and promotes urination. It is also having soothing effect on the skin and mucous membranes (Pullaiah 2019).

The decoction of bark is used as good diuretic and sedative (Alagesaboopathi 2009). The extract of Sandalwood leaves mixed with cow milk when taken orally can control gonorrhoea. Stems and roots of Sandalwood are used as anti-pyretic, aphrodisiac, antibilious agents and also for treating asthma (Ravikumar and Theerthavathy 2012). One teaspoon of Sandalwood powder and turmeric powder is mixed with milk to make the paste, and is applied on the face to control pimples (Jamal et al. 2005; Bhowmik and Sampath Kumar 2011).

The powder from the heartwood mixed with gum arabic and saltpetre and often with other aromatic materials is employed for making incense sticks. Also, it is burnt as an incense in homes and holy places. The pieces of heartwood is kept in sachets and placed in linen cupboards for scenting clothes and repel insects. Finely ground Sandalwood paste is applied on the body for cooling effect (http://tropical.theferns.info/viewtropical.php?id=Santalum+album). It can be used externally and internally or in aromatherapy. It has a sedative effect on the mental and emotional levels, and can be used to reduce stress, depression and anxiety (Valnet 2015). Sandalwood paste is taken orally for several ailments such as abdominal pain, headache, abnormal thirst and vomiting. It also stimulates digestive enzymes, respiratory system and excretory system.

Several researchers documented the usage of Sandalwood for curing skin diseases and skin care. One teaspoon of Sandalwood powder and a pinch of powdered

camphor is prepared into a paste by adding small quantity of water, and smeared on the affected areas of rashes and allergies, psoriasis, eczema and burns. After 1 h wash with cold water. Sandalwood powder and turmeric powder are mixed and prepared into a paste with lime juice, and smeared on the affected areas to get relief from itching. Sandalwood paste is applied on the skin to heal rashes. Powders of Sandalwood bark, wood and turmeric powder are mixed and prepared into a paste, and smeared on the area of snake bite (Pooja and Vidyasagar 2015). Bark and leaf paste is applied once in day for 4–6 days to cure skin allergy (Shivakumar Singh and Vidyasagar 2013). The stem bark of Sandalwood is pulverized into a paste and applied externally to cure herpes (Bhandary and Chandrasekhar 2011). Sandalwood paste is smeared superficially to cure herpes and skin eruptions (Rajagopal Reddy et al. 2015).

5.2.1 Ayurvedic Perspective

In Ayurveda, Sandalwood has the highest priority for medicinal uses. The aroma of wood and essential oils brings pleasantness and holistic environment. Interestingly, Ayurveda believes that there is a central node of nerves on the forehead (Sthapani marma) between the eyebrows. The application of Sandalwood paste in between the eyebrows (Sthapani marma) stimulates the nervous system, and serves to tranquilize the individual. According to Ayurveda, the Sandalwood is claimed to be medhavardhaka, smrutivardhaka, buddhivardhaka, surabhi, santapasantipradam, saumanasyajanana, hrudya, ahladakaraka, pittashamaka, trsnahar, pipasahara, dahasamaka, etc. It relieves sunmada, angamarda, arochak, shira-shoola, shwas, shirovibhram and pittaja shirahshoola. The Kalpa (formulations) containing Sandalwood are claimed to improve brain functions and intelligence (medhya, medhavardhaka, smrutivardhaka, buddhivardhaka), and useful in different psychiatric disorders (manasroga, mastishkaroga, siroroga).

The Bhavprakash nighantu, i.e., the classical texts of Ayurveda states that Sandalwood is known with the names of Srikhanda, Chandan, Madhrashri, Tilaparnaka, Gandhasara, Malayaja and Chandradyuti. It is white in colour, bitter in taste, and after being rubbed gives yellow colour. If it is broken in pieces, it gives red colour, and appears white from the outside. It is considered as the best if it is rough in texture. This has properties like cold potency, pacifies pitta in the body, it manages fatigue, weakness, thirst, heat and blood impurities (Pandey 1998).

5.2.2 Unani Perspective

According to Unani physicians, there are three varieties of Sandal, viz., yellow, red (Sandal Surkh) and whitish yellow (Sandal Safed). The last variety is more fragrant than the other two varieties. In view of Galen and Ibne Maswaih Sandal Surkh is more potent, but according to some other physicians, the Sandal Safed is relatively stronger (Ibne Sina and Al-Qanoon 2007). In Unani classical texts, Sandal

Safed (*S. album*) and Sandal Surkh (*Pterocarpus santalinus*) have been mentioned along with their medicinal properties and therapeutic uses. It is used both internally and externally, since antiquity. Therapeutically, this drug is widely used in many cardiac, brain, liver, stomach and intestinal ailments as well as in various skin disorders for its Mufarrreh wa Muqawwie qalb (exhilarant and cardio tonic), Muqawwie dimag (brain tonic), Muqawwie hararategareezi, Qabiz (astringent), Muhallile warm (anti-inflammatory), Musaffie dam (blood purifier) and Mujaffif (desiccant) properties (Ibne Sina and Al-Qanoon 2007).

There are claims in Unani medicine that the Sandalwood is musakkin (soothing, sedating), mubarrid (cooling), mufarreh (exhilarant, pleasure promoting, mood uplifting); useful in the du'fidimagh (weak function of the brain) and relieves du'fiquwwatihafizah (amnesia); useful in sivdaV-har (hot-type headache) or suc/a'sa/iraiv/(bilious headache) and khafqan-i-har (palpitation due to heat); is muqawwiqalb (cardiotonic) and relieves du'fiqalb (heart's weakness). Sandalwood plays a potential role of Unani medicinal plant in management of Kalaf (chloasma), and can be used as a mufrad (single) or with other compounds (Ahmad 2006). It has been found that α–santalol present in Sandalwood inhibits tyrosinase, an essential enzyme for the synthesis of pigment melanin. This property helps in limiting the abnormal pigmentation associated with ageing and exposure. It contains raade-mawaad (divergent) and blood purifier activities (Kauser et al. 2014). The raade-mawaad (divergent) property of Sandalwood helps in diverting the fasidmawaad of chloasma from the site of lesion and hence helps in reducing the condition. In Unani system of medicine, UBTAN is a semisolid preparation of powdered drugs in the form of lubdi (mass) used to remove the dead cells from the skin enhancing lecture of the body. For that Basen (Bengal Gram, *Cicer aietinum*), Haldi Sandal Safed (*Santalum album*), Khas (*Vetiveria zizanioides*) 5 g each and Roghan Chameli oil (*Jasminum officinale*) are prepared into a paste. The whole paste is smeared on the body regularly get charismatic look. In West and South Asia, a popular drink, Sherbat is made from fruits and flower petals of Sandalwood. The common Ashriba is made by using one or more of Sandalwood powder, bael (an Ayurvedic ingredient), rose water, gurhal, mango, pineapple, lemon, orange and falsa. It is utilized in the Unani system of medication for the treatment of gastric ulcers and various cardiac, brain, liver, stomach and skin disorders. There is a good medicine for excessive pigmentation in Unani system of medicine. The application of Sandalwood paste or Sandalwood oil reduces the excessive pigmentation (Ahmad et al. 2013; Kausar et al. 2014).

5.3 Phytochemistry

The impending benefits of Sandalwood and its products have been well discovered in current times by several researchers. Different investigations on its phytochemistry and therapeutic properties are well defined, and many present studies have focused to isolate pure bioactive compounds and their mechanisms of action. The

title tree species constitute several phytoconstituents, including many oxygenated terpenes, sesquiterpene hydrocarbons, sesquiterpenic alcohols, organic acids, lignans, glycosides and aldehydes.

Sandalwood oil, one amongst the oldest perfume materials has been mentioned in Sanskrit manuscripts, and its uses are described by the people, ever since the early eighteenth century (Arctander 1960). The volatile oil is attained by steam distillation approach using the dehydrated Sandalwood tree trunk and roots. The Sandalwood oil appears to be pale-yellow liquid, having the distinctive woody odour, and a faintly bitter flavour (Burdock 2002; FCC 2003). The main constituents of the oil (>90%) are alcohols, namely α-santalol and β-santalol, giving specific odour and aroma (Burdock and Carabin 2008). The oil also constitutes supplementary constituents, mainly sesquiterpene hydrocarbons (6%), such as epi-β-santalene, α- and β-santalenes, in addition to trace amounts of santene, tricycloekasantalal, dendrolasin and β-farnesene, dihydro-b-agarofuran, borneol, teresantalic acid, teresantol, santanol and santalone (Taufel et al. 1996; Burdock 2002; Burdock and Carabin 2008). Kim et al. (2005) identified a new aromatic ester and three novel neolignans from the heartwood, in addition to other recognized 14 volatiles. Burdock (2002) identified stearolic acid and santalbic acid from the seed oil. Generally, the amount of α-santalol was found to be higher (46%), when compared to β-santalol with only 20% (Bauer and Garbe 1985; Taufel et al. 1996; Anonis 1998). Majorly, α- and β-santalol are credited for the pleasurable smell of Sandalwood, though 2-furfuryl pyrrole may possibly also contribute. Trace amounts of phenols, lactones and terpenes are also being reported. Nearly 2–4% of santalol occurs as ester, and in one of the Sandalwood oil sample, hentriacontan-16-one compound has been reported (Anonymous 1999).

The oil yield of the heartwood fluctuates conferring to the tree age, geographical distribution, and location of the tree (Lawrence 1991; Nautiyal 2019). Between 85 and 240 kg of heartwood can be obtained from trees having a girth size of 100 cm. Chemical constituents and oil yield fluctuates from one tree to another, and is greater in the older or matured tree. The roots have the highest oil content of almost 10%, while lowermost is observed in wood chips (1.5–2%). Also, it has been stated that about 3–6% oil yield is possible from the sap wood, while about 2.5% oil is obtainable from heart wood (Burdock 2002). It has been revealed that girth size of different trees can influence on the oil yield and chemical constituents (Bisht et al. 2019). Chemical profiling of the oil samples was carried out by gas chromatography-mass spectrometry (GC-MS-QP-2010 Ultra Auto Sampler). A chemically diversified alkanes, sesquiterpenoids, sesquiterpene, fatty acids and alcohols were detected. The major constituents were α-santalol (41.7–53.67%), β-santalol (18.2–27.9%), epi-β-santalol (2.7–7.18%), β-santalene (1.39–5.30%), α-santalene (0.4–4.87%) and α-bergamotol (3.1–9.3%). In this study, it was concluded that the oil yield and its composition vary among the trees with different girth. But no particular trends were observed between the girth size and oil yield.

Sandalwood heartwood and the root samples were pulverized and separated through 60μm sieves to obtain uniformity in the powder. Later, the oil was extracted from this powder using any one of the 8 approaches, i.e., solvent extraction

(benzene, toluene, ethyl alcohol and diethyl ether), subcritical carbon dioxide ($SC\text{-}CO_2$) extraction, steam distillation and hydrodistillation. Steam distillation for 10 h in a pilot plant yielded the highest level of α-santalol (54.7%) and β-santalol (29.2%), followed by $SC\text{-}CO_2$ extraction for 4 h, yielding 54.5% of α-santalol and 28% β-santalol (Nautiyal 2019). The heartwood and roots coarse powder affect the process of distillation. The tree parts, such as sapwood, heartwood and bark, the age of the tree, and agronomic and climatic conditions of cultivation can influence on the yield of oil. Up to 10.3% oil can be obtained from roots, while heartwood can yield up to 4%. For completing the oil extraction, it requires 48–72 h of distillation process (Zhang et al. 2012).

In Kupang (Indonesia), refiners are using the steam distillation to extract sandalwood oil, since from a long period (Ferhat et al. 2006). In general, steam distillation is run for about 40–70 h. High pressure can be applied to obtain higher yield of oil in a shorter time during the distillation. However, increasing the temperature could decompose the essential oil constituents and make it less odoriferous. A new technique, involving less energy and solvents was developed by Kusuma and Mehfud (2018) to extract oil by employing microwaves. Microwave hydrodistillation technique comprised of three apparatuses, a compressor, microwave and condenser. Compressor helps in maintaining required pressure, microwave produces required temperature and condenser regulates temperature. Pressure mediates the diffusion of essential oils from wood slices into the distillation chamber. Application of pressure is essential to extract the essential oil because of its high density. The content of oil attained from Sandalwood powder using various extraction approaches varied from 43 to 84% (Hettiarachchi et al. 2010).

GC-sniffing technique (GC-Olfactometry) was useful in identifying the most powerful odorous volatile chemicals of Sandalwood oil, including α-santalol, β-santalol, α-santalene, α-bergamotol, epi-β-santalol and spirosantalol (Nikiforov et al. 1988). All these chemo-constituents have very high importance in aromatic industries. Numerous silica gel column chromatography based separations also have witnessed the presence of oxygenated compounds (96.6%) and hydrocarbons (3.4%) in the oil.

Sandalwood oil distilled from the heartwood of trees grown in the South China Botanical Garden, Guangzhou, China (Zhu et al. 1993) possesses with α-santalol (22.0%), α-santalol isomers (7.7%), β-santalol (1.9%), β-santalol isomers (5.5%), epi-β-santalene (2.3%), α-santalene (1.5%), β-santalene (1.8%), and *cis*-α-santalol (11.7%). Brunke et al. (1995, 1997) identified few more chemical constituents from the East Indian Sandalwood oil, such as cyclosantalol (1.6%), epi-cyclosantalol (1.2%), minor amounts of (<0.01%) of dihydroalbene, acetyldihydroalbene and epi-cyclosantalic acid.

Wei et al. (2000) stated that heartwood size increases when the branches are damaged due to wind currents. The chemical constituents of the Sandalwood oil obtained from the 25 years old tree were shown to have epi-β-santalene (0.12%), α-santalol (43.09%), α-santalene (0.08%), β-santalol (22.5%), β-santalene (0.25%), (Z)-*trans*-α-bergamotol (9.44%), curcumene (0.05%), nuciferol (9.65%), epi-β-santalol (3.66%) and (Z)-lanceol (0.51%). Gowda et al. (2006) revealed that

the heartwoods of 30 years-old trees hold about 5% oil, although the 12–15 years-old trees heartwoods possess oil content in the range of 3.5–4.0%. Further, the profitable viability was explored for introducing Sandalwood farms, and anticipated that the monetary profit would be very rewarding after 15 years.

Chen and Lin (2001) examined the variation in the volume of various chemical constituents in the Sandalwood oil obtained by various methods of extraction. Their results revealed the occurrence of α-santalol (30.7–41.5%), β - santalol (22.62–26.8%), α-santalene (0.08–0.65%), β-santalene (0.04–1.42%), epi β-santalol (3.94–6.75%), epi β -santalene (0.16–0.89%), curcumenol (0.09–0.33%), nuciferol (2.08–2.47%) and lenceol (0.46–0.88%).

Braun et al. (2003) estimated the chemical constituents present in the Sandalwood oil available in the Germany market. The chemical substances present in the oil included α-santalol (1.9%), β- santalol (0.6), α-santalene (0.7%), β- santalene (1.2%), epi β- sanatalol (3.5%), epi β-santalene (0.8%), epi-cyclosantalol (0.3%), dihydrosantalol (0.6%), trans α-santalol (0.4%), cis β-santalol (19.8%), trans β-santalol (1.5%), santene (0.2%), α- cedrene (0.1%), α-santene (0.7%), trans α-bergamotene (0.2%), trans β-bergamotene (0.17%), γ-curcumene (0.1%), cyclosantalol (0.4%), α-bergamotol (0.2%), epi-cyclosantalol (0.3%), α-bisabolol (0.2%), trans α- begamotol (6.4%), cis α- bergamotol (0.2%), fokienol (0.5%), Z-nuciferol (3.4%), Z-lanceol (1.4%), E-nuciferol (0.1%) and spirosantalol (0.9%). Some more chemicals, such as epi sesquithujene, E- α-bisabolene, E- β-farnesene, cis α-bergamotene, β-alaskene, α-alaskene, E- γ-bisabolene and (Z) γ -bisabolene were also present in very trace amounts (0.1%). Chiral compound exploration of the β-bisabolols exposed that the main stereo isomer was (6R, 7R) - β- bisbolol and the remaining forms are enantiomers.

Kusuma and Mahfud (2018) analysed the Sandalwood oil extracted through microwave air-hydrodistillation and microwave-assisted hydrodistillation approaches. Their study showed that the oil quality fulfils with the standard oil quality, which was confirmed based on the occurrence of the major volatiles, such as α- and β-santalol, α-bergamotol, α-santalene, cis-lanceol, α-curcumene and α-bergamotene. As the standards set by the International Organization for Standardization for the total content of santalol (50–70%) can be achieved, microwave-assisted hydrodistillation and microwave air-hydrodistillation approaches are suitable for obtaining Sandalwood oil in large scale to meet the international standards. The microwave air-hydrodistillation technique proved to be more efficient than the microwave hydrodistillation in terms of both quantity and quality of the essential oil. Microwave hydrodistillation yielded 37 compounds, whereas 43 chemical substances were extracted through microwave air-hydrodistillation method. Further, Kusuma and Mahfud (2018) suggested that the usage of airflow in the microwave-assisted air-hydrodistillation augments the diffusion of heavyweight fractions of essential oils from the wood slices. Their data supports that microwave air-hydrodistillation method is superior over to microwave hydrodistillation as the heavier fraction of essential oils is completely recovered from the wood slices. Sandalwood oil obtained using microwave hydrodistillation had only two heavyweight fractions (MW $\geq$ 222.37). While, the oil derived using

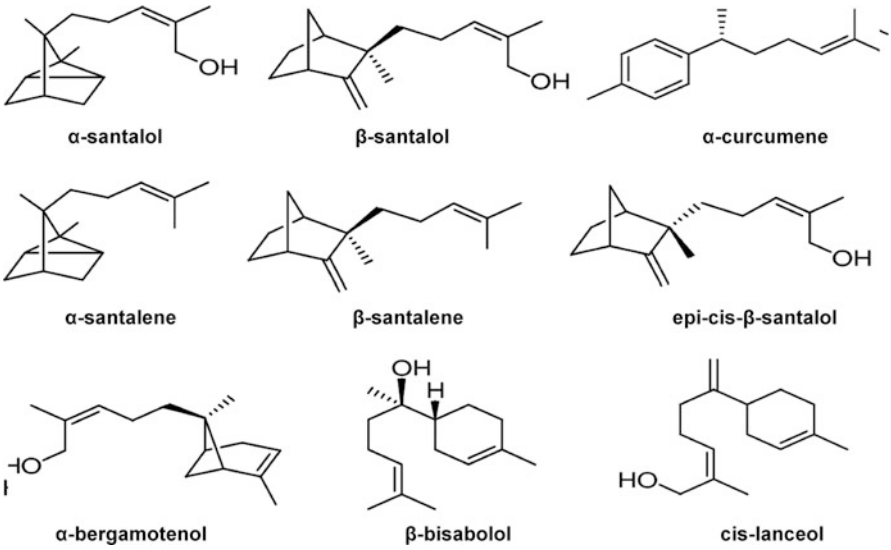

Fig. 5.1 The major volatile compounds stated from Sandalwood oil (drawn by author)

microwave air-hydrodistillation possessed seven heavyweight fractions (MW $\geq$ 222.37). Most of these heavy weight fractions belong to the oxygenated terpenes. These heavy fractions of essential oils give the characteristic aroma and fragrance to the Sandalwood oil. Overall, it has been established that oxygenated terpenes occurring in Sandalwood oil attained by microwave air-hydrodistillation present superior quality of the oil.

Gas Chromatographic examination (GC) showed the presence of peak areas for chief components, such as α-santalol, β-santalol, β-santalene and α-santalene in the first hour (Nautiyal 2014). Later in the second hour, peak areas for α- and β-santalene, α- and β-santalol were noticed. The peak areas for α- and β-santalene, α- and β-santalol were found in the third hour of extraction. Finally, in the fourth hour, peak areas for α- and β-santalene, α- and β-santalol were recorded. Noteworthy to mention that high quantities of α-and β-santalol were recorded in the second hour. A total of 35 volatile compounds were identified and quantified using GC-MS (Gas Chromatography-Mass Spectrometry) method. The data showed a chemically varied sesquiterpenoids, sesquiterpene, alcohols, alkanes, and fatty acids were witnessed. The foremost components were α-santalol (33–35%), β-santalol (17–18%), β-santalene (1.1–2.3%), α-santalene (0.56–1.6%), epi-β-santalene (0.8–1.6%), epi-β-santalol (2.2–3.5%) and α-bergamotol (4.0–7.7%) (Bisht and Hemanthraj 2014). Some of the volatile constituents are depicted in Fig. 5.1.

Immersion of Sandalwood pieces in ice-cold water for 3 days, prior to hydrodistillation enhances the production of Sandalwood oil (Nautiyal 2014). The oil was pale-yellow in colour having a pleasant aroma, and the oil yield was about 1.71%. Even after the softening of Sandalwood chips for a lengthy period, it was problematic for the vapour to penetrate through vessels, medullar ray cell, wood

parenchyma and fibres comprising essential oil. Conversely, un-pulverized wood slices give little quantity of oil. GC examination indicated the occurrence of higher quantities of α-santalol (48.38%) and β-santalol (28.73%), in addition to lower levels of α- and β-santalene. Alkaline water was used to charge the Sandalwood coarse powder, and used for hydrodistillation to recover 2.68% of oil. The result showed the yield of α-santalene (4.25%), β-santalene (3.01%), α-santalol (41.90%) and β-santalol (19.89%). The use of alkaline/neutral media reduces the development of artefacts all through distillation. However, the acidic media may promote the transformation of heat-sensitive monoterpenes (Nautiyal 2014, 2019).

Due to the scarcity and unavailability of good quality of Sandalwood trees the cost of the Sandalwood oil is increasing year by year. To meet the market demands scientists are searching for alternative production through synthetic methods (Shvets and Dimoglo 1998; Bajgrowicz and Frater 2000). Buchbauer et al. (1992, 1997, 2001) attempted to synthesize santalol derivatives with comparable olfactory activity.

5.4 Pharmacology of Sandalwood

5.4.1 Anti-Microbial Activities

5.4.1.1 Antiviral Activity

The antiviral properties of Sandalwood have been established through various biological studies. Sandalwood oil has been revealed to be used in preventing and treating skin blemishes, warts and other viral-prompted tumours on the skin (Haque and Haque 2000, 2002). The traditional Indian medical system, Ayurveda and Chinese Traditional Medicine have mentioned about the antiviral potency of Sandalwood oil (Chattopadhyay et al. 2009). Sandalwood oil exhibits the potential antiviral property against Herpes simplex virus 1 and 2 under in vitro studies in a concentration dependent way by inhibiting replication process. Furthermore, it was presumed that Sandalwood oil protects the cells via modulation sulphydryl groups and liver's glutathione S-transferase (GST) (Benencia and Courreges 1999). Schnitzler et al. (2007) reported that the Sandalwood oil suppresses the replication of HSV virus Type 19, and β-santalol showed anti-influenza activity against H3N2 virus. Sandalwood oil exhibited in vitro inhibitory effects against HSV-2 in infected Cellosaurus (RC-37) cell lines. The Sandalwood oil prevents viral particle's adsorption onto the host cell by inhibiting the interactions of virus and host cell, non-specifically (Koch et al. 2008). The chief constituents of Sandalwood oil, i.e., α- and β-santalols and their synthetic derivatives are employed in treating warts and Molluscum contagiosum, a skin infection. They have also considered to cure HIV and other RNA viral diseases. Constituents of Sandalwood oil also showed curative properties against psoriasis, eczematic rashes, skin dryness, skin allergies, seborrhoea and basic acne lesion on the face (de Groot and Schmidt 2017). In addition to these, Sandalwood oil and chemical derivatives of santalols are reported to be very effective against cold sores, affected by HSV (Singh and Nulu 2010).

Haque and Coury (2017) evaluated the efficiency of Sandalwood oil in unproblematic management of cutaneous viral warts affected by Human Papilloma Virus (HPV), and presented a case study. They subjected the Sandalwood oil externally twice a day for 12 weeks. Among ten patients tested eight patients (80%) were completely recovered from HPV. They considered wart size, severity, healing time, side effects for evaluation. All the ten patients failed to show any side effects, such as erythema, skin irritation, itching, scarring or peeling of skin, and discomfort. Thus, Sandalwood oil can be suggested for a person with HPV as it is an effective and unproblematic curative method.

5.4.1.2 Antibacterial Activity

In an early study, tannins present in the stem bark of Sandalwood tree were reported to exhibit inhibitory property against *Staphylococcus aureus* (Shankaranaryana 1986). Likewise, many investigations were carried out to investigate the antibacterial activities of Sandalwood oil, and most of these studies have indicated the effective inhibitory activities of Sandalwood oil against several bacterial pathogens (Beylier and Givandan 1979; Jirovetz et al. 2006; Kumar et al. 2015). Chaurasia (1978) reported a higher anti-microbial activity of Sandalwood oil against *Escherichia coli* and *Bacillus mycoides*. Viollon and Chaumont (1994) evaluated 26 essential oils for their anti-microbial activity against axillary microflora, and found that Sandalwood oil and its synthetic analogues showed the best results. A study by Warneke et al. (2009) reported that Methicillin resistant *S. aureus* can be inhibited effectively by using Sandalwood oil. Purified α- and β-santalol compounds and crude extracts of Sandalwood oil exhibit anti-microbial property against a gram-negative bacterium, *Helicobacter pylori,* which is responsible for peptic ulcers (Ochi et al. 2005). Methanol extract of Sandalwood was reported to be active against *B. subtilis*, *Salmonella typhi, S. aureus* and *Pseudomonas aeruginosa,* and highly active against fungus *Candida albicans* (Bakkiyaraj and Pandiaraj 2011). Simanjuntak (2003) carried out experiments on the anti-microbial activity of different constituents of Sandalwood oil, such as α-santalol, β-santalol and epi-β-santalene, and found that α-santalol and β-santalol as the effective constituents against *S. aureus* and *S. typhimurium,* however epi-β-santalene also showed good results against *S. typhimurium*. Jirovitz et al. (2006) reported that santalols exhibited anti-microbial activity against yeast, gram positive bacteria at higher concentrations, whereas at lower concentrations, they were effective against gram-negative bacteria. Misra and Dey (2012a) showed that the crude phytoextracts of immature tree shoots and in vitro shoots exhibited antibacterial activities against 13 bacterial strains, including *Klebsiella aerogenes*, *P. aeruginosa*, *P. fluorescens*, *Acinetobacter calcoaceticus*, *E. coli*, *Citrobacter freundii*, *B. subtilis*, *Alcaligenes faecalis*, *S. typhimurium*, *Arthrobacter nicotianae*, *Enterobacter cloacae*, *Micrococcus flavus* and *S. aureus*.

5.4.1.3 Antifungal Activity

Chourasia and Tirumala (1987) reported the antifungal properties of Sandalwood oil against pathogenic fungi, such as *Trichophyton rubrum, T. mentagrophytes* and *Microsporum canis*, however inefficient against *Aspergillus niger*, *A. fumigatus*

and *Candida albicans*. Chaumont and Bardey (1989) reported that Sandalwood oil is having antifungal property against *M. canis, T. mentagrophytes* and *T. rubrum*. Sandalwood oil exhibited anti-dermatophytic activity against *M. canis, T. rubrum* and *T. mentagrophytes* (Simanjuntak 2003). Warneke et al. (2009) reported that Sandalwood oil is an effective antifungal agent against *Candida* species that are resistant to antifungals. Many fungal dermatophytes and yeasts, including *Microsporum, Trichophyton* and *Candida* species were effectively inhibited by the Sandalwood oil (Inouye et al. 2010; Nardoni et al. 2015; Moy and Levenson 2017). Lately, antifungal activity of Sandalwood oil against *C. albicans, Aspergillus niger* and *Cryptococcus neoformans* was reported by Powers et al. (2018).

5.4.2 Anti-Oxidant Efficacy

Anti-oxidant property of Sandalwood has been reported by several researchers. It has been tested in vitro for its promising controlling influence on nitric oxide (NO) levels by the use of NO donor, sodium nitroprusside. Sandalwood extract showed significant NO scavenging activity in a dose-dependent way (Jagetia and Baliga 2004). Other studies also have evidenced the NO scavenging activity and 2,2-diphenyl-1-picrylhydrazyl (DPPH) anti-oxidant activity (Patrick and Timothy 2002; Jagetia and Baliga 2004). Khan et al. (2014) reported that Sandalwood can protect cardiac tissue from oxidative stress induced cell injury and lipid peroxidation, and also interferes with doxorubicin (DOX)-induced inflammatory in cardiac tissue.

Pedpati et al. (2012) reported that cyanidin-3-glucoside, an anthocyanin pigment occurring in Sandalwood was reported to be anti-oxidant in nature, and hence nutritionally vital. In a comparative study done by Mishra and Dey (2012b), it has been revealed that even in vitro grown callus cells show significant anti-oxidant property. Banerjee et al. (1993) reported that Sandalwood oil administration to the adult male Swiss albino mice increases the acid-soluble sulphydryl (SH) levels and GST activity in the liver, suggesting the possible chemo-preventive action of Sandalwood oil. The methanol extracts of Sandalwood showed DPPH and hydroxyl radicals scavenging activities, in addition to acetyl cholinesterase inhibitory activity in albino mice. Hence, it is a potent curative agent against neurological disorder, such as dementia, age-related memory loss and Alzheimer's-related depression. Misra and Dey (2013b) reported that Sandalwood oil and its chief compound, α-santalol exhibit anti-oxidant and anti-hyperglycaemic activities in d-galactose and alloxan-mediated oxidative stresses prompted diabetic Swiss albino mice.

5.4.3 Anti-Inflammatory Activity

Santalols, the major constituents in Sandalwood oil have been testified for their significant anti-inflammatory property (Sindhu et al. 2010; Rajsmita and Keshavamurthy 2019). Sandalwood disclosed significant anti-inflammatory and

anti-ulcer properties in the carrageenan-induced paw edema, cotton pellet-stimulated granuloma, as well as pylorus ligation-encouraged ulcer. These research findings suggest the need to include in the list plants, which cures inflammatory disorders like ulcers in the Indian traditional medicines. Saneja et al. (2009) employed methanolic extract of heartwood to test the anti-inflammatory, anti-oxidant, and analgesic activity in mice. Sharma et al. (2018) reported that East Indian Sandalwood oil is capable of suppressing lipopolysaccharides (LPS)-stimulated Nuclear Factor (NF)-kB activation, and subsequent chemokine and cytokine expressions by reducing transcription and activation of PDEs (Cyclic adenosine monophosphate phosphodiesterase). Hence, it can be suggestible that East Indian Sandalwood oil can cause pro-inflammatory inducements by hindering the capability of PDEs to hydrolyse cyclic adenosine monophosphate (cAMP), and consequently allowing for protein kinase A (PKA)-mediated attenuation of NF-kB activation. Moreover, α-santalol has also been found to have anti-inflammatory effects by altering the expression of various cytokines and chemokines. In addition to that both α and β-santalol have been reported to suppress arachidonic acid pathway mediated by lipopolysaccharides, thereby decreasing prostaglandin E2 and thromboxane B2. Sandalwood oil is reported to cure wide range of skin diseases, such as acne, psoriasis, eczema, common warts and Molluscum contagiosum (Moy and Levenson 2017). Having good anti-inflammatory properties East Indian Sandalwood oil has been advised to treat a number of inflammatory skin disorders like psoriasis and atopic dermatitis, possibly as a result of inhibition of phosphodiesterases (de Groot and Schmidt 2017; Bommareddy et al. 2019).

5.4.4 Hepatoprotective Activity

Hegde et al. (2014) reported that the hydro-alcoholic extract of the leaves of Sandalwood shows a noteworthy hepatoprotection against carbon tetrachloride (CCl_4) and paracetamol-induced hepatotoxicity in mice. The mechanisms involve decreasing of serum marker enzymes activities, lipid peroxidation, bilirubin oxidation, and significantly increasing the glutathione levels, catalase and superoxide dismutase in a dose-dependent manner. Observations on the loss of weight in the liver tissue and histopathological examinations further confirmed the hepatoprotective activity. The traditional drug, Khamira Gaozaban Ambari Jadwar Ood Saleeb Wala includes Sandalwood as a main ingredient, and is shown to have free radicals scavenging and hepatoprotective activities against CCl_4-induced toxicity in albino rats (Akhtar et al. 2013). Hepatoprotective activity was showed by lowering the serum glutamic oxaloacetic transaminase, serum alkaline phosphatase, glutamic pyruvic transaminase, bilirubin, total cholesterol and total proteins contents, and hepatoprotective nature was also ascribed to its anti-oxidant properties. Rao et al. (2014) reported that the hydro-alcoholic extract of the stems also exhibited a significant effect of hepatoprotective properties against paracetamol-prompted hepatotoxicity via diminishing the activities of serum marker enzymes and lipids oxidation. Kamalarajan et al. (2019) testified that chloroform extract of Sandalwood

possesses hepatoprotective and anti-oxidant activities by lowering the serum hepatic marker enzyme activities. The effective hepatoprotective and anti-oxidant response was noticed at 400 mg/kg/BW (Body Weight), which is equal to the response of the standard drug, silymarin.

5.4.5 Anticancer Activity

Zhang and Dwivedi (2011) reported that α-santalol possesses the chemo-preventive properties on TPA (12-O-tetradecanoylphorbol-13-acetate)-induced and DMBA (7,12-dimethylbenz(a)anthracene)-prompted skin cancer growth in mouse models, and also it prevented UVB-promoted skin cancer enlargements in SKH-1 hairless mouse model in a dose-dependent way. Investigations have revealed that α-santalol mediates its anti-carcinogenic property by inducing apoptosis by activating caspases along with the interference of cytochrome C enzyme release and mitochondrial membrane potential in A431 (epidermoid carcinoma) cell lines. Further, it can alter manifold cell cycle controlling proteins, and inhibit cell growth via inducing G2/M phase arresting in melanoma cells, i.e., UACC-62 and A431 (Dwivedi et al. 2006; Zhang and Dwivedi 2011). Dwivedi et al. (2003) reported that α-santalol, the chief constituent in Sandalwood oil hindered the papilloma growth in both strains (CD-1 and SENCAR) of mice. Further, Santha and Dwivedi (2015) reported the anticancer activity of the oil against chemically encouraged skin tumourigenesis in SENCAR and CD-1 mice, ultraviolet-B (UVB)-encouraged skin cancer formation in SKH-1 mice, and in vitro models of skin, breast and prostate cancer. The oil also arrests cell cycle and induces apoptosis in cancer cells. Kaur et al. (2005) reported that the α-santalol has been used for skin cancer chemoprevention in animal models of skin tumours. Further, they stated that α-santalol at lower concentrations, i.e., between 25 and 75μM may possibly encourage apoptosis mediated death in A431 (human epidermal carcinoma) cells via reducing the release of cytochrome C enzyme, damaging the mitochondrial potential, in addition to activation of caspases. In another investigation, topical application of α-santalol to the female nude mice strain, SKH-1 showed chemo-preventive effects, including reduced activity of ornithine decarboxylase (Dwivedi et al. 2006). Bommareddy et al. (2007) stated that α-santalol prevents UVB-induced skin tumours by inhibiting in vitro lipid peroxidation activity in liver and skin microsomes. Another study reports the anticancer property of α-santalol against breast cancer cells, namely MCF-7 and MDA-MB-231. The compound exhibited chemo-preventive activity via the cell cycle arresting at G2/M phase and induction of apoptosis (Santha et al. 2013). Arasada et al. (2008) reported that α-santalol significantly increases apoptosis related proteins (caspase 3 and 8) levels and tumour suppressor protein (p53) via an extrinsic pathways in UV-B-induced skin tumourigenesis model in SKH-1 mice. Alpha-santalol also prompts apoptotic activity in human prostate cancer cells by the activation of caspase 3 enzymes (Bommareddy et al. 2012, 2017). In another study, 2 aromatic glycosides, 6 new sesquiterpenoids and a number of neolignans were isolated from the heartwood chips of Sandalwood, and were shown to possess

antitumour promoting activity in Burkitt lymphoma (Raji) cells, activated with Epstein–Barr virus Early Antigen (EBV-EA). Further, in vivo investigation demonstrated its potential tumour suppression effects in mouse model (Kim et al. 2006). In addition to α-santalol, its derivatives established tumour-selective cell toxicity in human promyelocytic leukaemia (HL-60) cells and normal human diploid fibroblast cultures (Matsuo and Mimaki 2012). Two lignans isolated from the heartwood samples suggestively indicated apoptosis mediated anti-tumour in HL-60 (human promyelocytic leukaemia) cells and A549 (human lung adenocarcinoma) cells (Matsuo and Mimak 2010). The use of α-santalol between 10 and 40μM was shown to be efficient in inhibiting angiogenesis via interfering on vascular endothelial growth factors, which further trigger to inhibit the progression of prostate malignancy (Saraswati et al. 2013). Ortiz et al. (2016) performed the cell toxicity and genotoxicity of Sandalwood oil in MCF-10A and MCF-7 human breast cancer cells. Their findings showed that Sandalwood oil (6–8μg/mL) exhibits both cytotoxic and genotoxic activity in MCF-7 cell lines. However in MCF-10A cell line, only cytotoxicity was observed. It was also revealed that Sandalwood oil effectively initiated the DNA damage in MCF-7 cells. Powers et al. (2018) reported the cytotoxic property of Sandalwood oil against MCF-7 and MDA-MB-231 cancerous cell lines. Jain and Nair (2019) have reviewed in detail on the molecular pathways involved in the chemoprevention by sandalwood oil and α-santalol. Molecular pathways include the induction of apoptosis via caspase cascades pathway activation. In precise, α-santalol activates caspases and cleavage of poly (ADP-ribose) polymerase. Further, α-santalol could also elicit the mitochondria to discharge Cytochrome C into cytosol. It may suppress the intracellular signal transduction pathway, i.e., PI3K/Akt pathway (Bommareddy et al. 2015). It induces arresting of cell cycle at G2/M phase and apoptosis by upregulating the levels of p21 and p53, correspondingly. Sandalwood oil also prevents the release of cytokines and uplifts the synthesis of interleukins (IL-1β), causing the suppression of the downstream NF-κB pathway. Moreover, Sandalwood oil suppresses activator protein 1 (AP-1), and may also enhance IL-6 levels to exhibit anti-inflammatory action.

Palatty et al. (2014) studied the comparative effects of 2 commercial products, namely Johnson's baby oil (Johnson and Johnson Ltd., India) and Vicco® turmeric cream (VTC) of Vicco Laboratories Pvt. Ltd., India on 50 patients having neck and head tumour, requiring >60 Gy of remedial chemoradiotherapy or radiotherapy. Sandalwood oil is one of the main ingredients in VTC. They divided them in to two groups, and the first group was allocated with external application of Johnson's baby oil and the second group with VTC. After 2 weeks of radiotherapy, second group observed the reduced levels of Grade 3 dermatitis. It indicated that Sandalwood oil has the curative potential against Grade 3 dermatitis. Rao et al. (2017) stated that the certain benefit of VTC is due to having sandalwood oil and turmeric in preventing radio dermatitis in women undergoing curative radiotherapy for their breast cancer.

5.4.6 Anti-Hyperglycaemic and Anti-Hyperlipidaemia Effect

Petroleum ether fraction of Sandalwood when administered orally for a long duration showed anti-hyperlipidaemic and anti-hyperglycaemic effects in streptozotocin-mediated diabetic rats. A drastic decline in the blood glucose level was observed. Metformin treated group also presented a decreased blood glucose levels as against the increased levels in the diabetic control group. In addition to blood glucose, low density lipoprotein, total cholesterol and triglyceride levels were also reduced, and cardio-protective high density lipoprotein levels were increased in the treated rats. It was concluded that Sandalwood has the potential anti-hyperglycaemic and anti-hyperlipidaemic activities (Kulkarni et al. 2012).

5.4.7 Effects on Central Nervous System

Several research findings have stated that Sandalwood is an excellent memory enhancer (Jackson et al. 2009; Biradar et al. 2009). Studies on sedative effect have shown that inhalation of East Indian Sandalwood oil decreased the motility of mice to an extent of 40–78% compared with 0% control (Khanna et al. 2004). Battaglia (2007) reported that Sandalwood oil relaxes the nervous system and reduces psychological traumas such as insomnia, headache, tensions, anxiety and emotional aerosols. Sandalwood oil and aqueous extract are generally used as sedatives (Okugawa et al. 1995; Joshi et al. 2013). Santalols, the bioactive principles are reported to have depressant activity on central nervous system (CNS) and hence administered patients suffering from insomnia (Ohmori et al. 2007). It is very exciting to recognize that synthetic Sandalwood compounds and Sandalwood oil stimulate the olfactory receptor neurons (Bieri et al. 2004). In addition to these, neuroleptic property of different solvent extracts of heartwood has been reported in mice. Both α- and β-santalols suggestively increased the levels of 5-hydroxyindoleacetic acid, 3, 4-dihydroxyphenylacetic acid and homovanillic acid in the brain of mice, when administered through intragastric and intracerebroventricular routes. α-santalol acted as a strong dopamine D2 and serotonin 5 HT2A receptor binding antagonism (Okugawa et al. 1995). As an antipsychotic agent, α-santalol effects were similar to that of chlorpromazine (Okugawa et al. 2000). α-santalol promoted substantial physiological changes, including sedative and relaxing influences, whereas Sandalwood oil instigated physiological deactivation, however activated behavioural changes after transdermal absorption (Hongratanaworakit et al. 2004). Likewise, α-santalol was shown to exhibit a superior inhibitory activity on both cholinesterase and tyrosinase enzymes, and thus Sandalwood can be used as one of the potential candidates for treating Alzheimer's disease and preventing hyperpigmentation of the skin (Misra and Dey 2013a).

Mohankumar et al. (2018) examined the protective effects of East Indian Sandalwood oil, α- and β-santalol against proteotoxic (α-synuclein) and neurotoxic (6-OHDA/6-hydroxydopamine) stress conditions in a model organism,

Caenorhabditis elegans. Their results showed that East Indian Sandalwood oil and its bioactive compounds exerted superior anti-apoptotic and free radical scavenging activities by prolonging the life span, and prevented the reactive oxygen species production, and germ cell apoptosis in *C. elegans* intoxicated with 6-OHDA. Adding East Indian Sandalwood oil and α- and β-santalol curtailed the α-synuclein- and 6-OHDA-encouraged Parkinson's illness related pathological conditions and upgraded the physiological functions. Further, the gene expression studies have shown that East Indian Sandalwood oil, or α- and β-santalol arbitrated protecting effects involve ERK-MAPK signal pathway and mitochondrial electron transport chain, and not through DAF-2/DAF-16, the key genes that are involved in the genetic pathways, mediating endocrine signalling. In addition, East Indian Sandalwood oil, or α- and β-santalol selectively controls SKN-1 and its downstream targets that resist against neurotoxic and stresses. They have suggested geroprotective and neuroprotective mechanisms of East Indian Sandalwood oil, α- and β-santalol on *C. elegans* (Fig. 5.2).

5.4.8 Other Uses of Sandalwood

Khan et al. (2014) examined that the water extract of Sandalwood inhibits significantly the cardiac tissue damage against doxorubicin induced cardiotoxicity in rat model. Also, it showed significant protective effect against isoproterenol-stimulated myocardial infarction in Albino Wistar rats in a dose-dependent manner. The oral administration of the hydro-alcoholic extracts of Sandalwood was effectively tolerated both physical (stress) and chemical induced gastric ulceration in rats (Ahmed et al. 2013). The Sandalwood oil (at a dose of 200 mg/kg) revealed significant anti-pyretic effects against yeast-induced pyrexia in Albino rats (Desai and Hiremath 1991). Sandalwood oil was shown to exhibit superior repellent activity to the pest, *Varroa jacobsoni* (ectoparasitic mite) in honey bee colonies. Hence, it can be used as an acaricide. Also, Choi et al. (2006) described the modest property against *Lycoriella mali*, a mushroom-infesting fly. Sandalwood oil is used to cure major burns as it contains anti-septic properties (Bhowmik and Sampath Kumar 2011). It also impedes the prompt of the growth and development of leukocytes. Sandalwood oil acts as an expectorant and used in bronchial infections and cough. Sandalwood oil is effective in healing some neurotical problems, such as sciatica and lumbago. Sandalwood oil is utilized as a fragrant agent in several products, such as soaps, cosmetics and perfumes (Deite 1892). Sandalwood oil's tranquillizing effect makes it more helpful for meditation as it encourages a feeling of deep harmony. The application of Sandalwood oil raised systolic blood pressure, skin conductance level and pulse rate. In addition, it encouraged to attain higher levels of alertness and mood in humans. Sandalwood is also used as a sex tonic and aphrodisiac. It is also used as a decongestant, anti-infectious, anti-depressant agent (Coombs 1995). Sandalwood paste and oil are generally employed as cooling agents which dissipate heat from the body. And it also enhances beauty by making the skin glow. The scent of the essential oil has also been said to calm the mind and acts as a mood enhancer

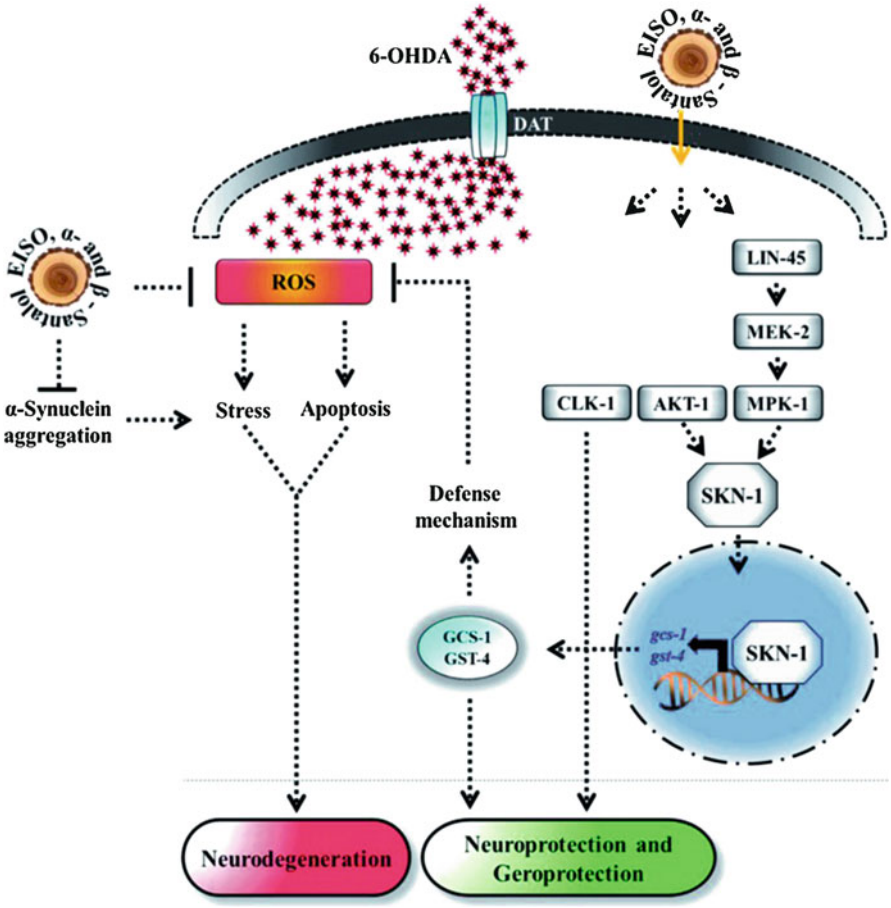

Fig. 5.2 The proposed neuroprotective and geroprotective mechanism of EISO and its active components on *C. elegans*. East Indian Sandalwood Oil (EISO) and santalol isomers likely acted through AKT-1 and ERK-MAPK mediated SKN-1 dependent pathway, which transactivates the stress-responsive genes *gcs-1* and *gst-4* that enhanced the tolerance to stress and extend the mean lifespan. The direct antioxidant activity, α-synuclein inhibitory potential, anti-apoptotic activity, and CLK-1 dependency of EISO, α- and β-santalol can also contribute for the reduction of neurodegeneration and longevity extension in *C. elegans* (Adapted from Mohankumar et al. 2018)

(Rajsmitha and Keshavamurthy 2019). Sandalwood oil is effective in treating liver and gallbladder complaints, dysentery, piles, inflammation of mouth and pharynx. It is used as a digestive and muscle relaxant. It also cures chronic colds and cough, scabies and urinary infections, expectorant, stimulant and carminative (Burdock and Carabin 2008). Application of Sandalwood oil is an effective remedy for acne and tinea. Research findings reported that Australian sandalwood oil was effective than tea tree oil to cure gonorrhoea when taken orally or external application. It acts as potent antibacterial agent against *Candida*. Also, the inhalation of Sandalwood oil

can help in calming and improving the respiratory system (Nautiyal 2019). Sandalwood oil has also shown a promise in human clinical trials for treatment of acne, psoriasis, eczema, common warts and *Molluscum contagiosum* (as reviewed by Moy and Levenson (2017)).

Sandalwood oil is commonly accepted as safe for the use as a flavouring ingredient in food by the Food and Drug Administration (FDA) of United States and Council of Europe (CoE 2000). It is also recognized by the Flavor and Extract Manufacturers Association, and the FDA also recognizes sandalwood oil as a natural flavouring agent (https://www.drugs.com/npp/sandalwood-oil.html; Kuriakoje et al. 2010). Sandalwood oil is employed as a natural flavouring agent in most of the food products, mainly frozen dairy desserts, alcoholic and non-alcoholic beverages, puddings, baked goods and confectioneries. Generally, the admitted levels of Sandalwood oil are below 0.001% (10 ppm). High levels of Sandalwood oil (98.89 ppm) are administered for hard candies. The maximum permitted levels of Sandalwood oil in foodstuffs are nearly at 90 ppm (Burdock and Carabin 2008).

5.5 Adulteration and Authentication of Sandalwood

The escalating demand for Sandalwood oil and non-availability of good quality trees keep rising the cost at an alarming rate. Hence, it became the most adulterated essential oil (Kuriakoje et al. 2010). As a result, the British Pharmaceutical Codex regulatory agencies are facing a severe problem to prevent the adulteration. Adulteration of Sandalwood oil leads to so many health complications. Addition of adulterants to the Sandalwood oil changes the composition of volatile chemoconstituents, physical properties, quality of the Sandalwood oil, and exhibits potential allergic reactions. Low grade essential oils from the other species of *Santalum*, castor oil, cedar wood oil are informed as the regular adulterants (Anonis 1998).

The Sandalwood oil can be blended by adding the essential oils obtained from different species of *Santalum* genus, other than the *S. album.* The essential oils that are generally mixed with the Sandalwood oil are copaiba (*Copaifera langsdori*) oil, amyris (*Amyris balsamifera*) oil and Atlas cedar (*Cedrus atlantica*) fractions (Nautiyal 2019). Artificial Sandalwood can be prepared by adding synthetic Sandalwood oil essence to the odourless essential oils. Another method of adulteration is the stretching, where odourless essential oils are mixed with the Sandalwood oil to increase the volume. Synthetic derivatives of β-santalol are commonly used as adulterants in Sandalwood oil.

Various synthetic chemical compounds derived from β-santalol are mixed with the actual Sandalwood tree. The production of synthetic Sandalwood oil is not a simple process. Adding the similar chemical compounds is not enough to make substitute for Sandalwood oil. So many synthetic essential oil manufacturers have been trying to bring the right substitute for the Sandalwood oil for many decades. The proposed substitute for Sandalwood oil must have all the qualities taste, odour, colour, etc. The available synthetic chemical compounds which are almost similar to Sandalwood oil are the α-campholenic aldehyde derivatives, originated from

α-pinene, a less expensive product expelled as a by-product in the paper manufacturing industry. The flavour of α-campholenic aldehyde derivatives is almost comparable to Sandalwood oil (Nautiyal 2019).

Nowadays getting authentic pure Sandalwood oil is becoming very difficult as the demand is ever increasing. Hence, it gives a scope to adulterate with so many chemical compounds that may cause side effects. It is the primary responsibility of the perfumery industries, pharmaceutical companies and government authorities to check the adulterations of Sandalwood oil. Sandalwood oil producing companies must assign standard marking like hallmark for gold. There are several methods to test the purity of Sandalwood oil. Sandalwood oil adulteration can be easily detected by professionals or chemists through the application of advanced technology to analyse. Without having any machinery, a skilled person can recognize the pure Sandalwood oil, simply by its aroma (Nautiyal 2019).

The recommended levels of total free alcohols, calculated as santalols in the Sandalwood oil should not be lesser than 90% w/w. The validation of santalol content in Sandalwood oil by the described acetylation method generally lacks the specificity and accuracy (FCC 2003; Nautiyal 2019). Kuriakoje et al. (2010) identified the Sandalwood oil adulteration by using Near Infrared (NIR) analysis. In addition to this, they used multivariate calibration models like the partial least square regression and principal component regression as rapid analytical techniques. By using NIR spectroscopy with chemometric methods, even 1% of adulterants (low grade oils) in the Sandalwood oil can be effectively identified. Moreover, it is very simple, non-destructive, instant and rapid process.

The development of improved novel, rapid and non-destructive approaches is in the present day demand for determining the adulterants, instead of time-consuming old analytical techniques, which are not economical. Nautiyal (2011) evaluated the quality of Sandalwood oil using different techniques. The Sandalwood oil's quality depends on the international standards, (ISO 22759:2009) and (ISO-FDIS 3518:2001) for *S. spicatum* and *S. album*, respectively. Undeniably, all Sandalwood offered in the present market is not 100% genuine, and there is a scarcity of true *S. album* species. Mainly, santalol isomer is considered as the choice for Sandalwood oil quality evaluation, and the occurrence of $<$90% santalol content fulfils the quality. Routinely, GC study is the preferred analytical technique for assessing the essential oil quality (Nicolas et al. 2011; Nautiyal 2019).

The common Sandalwood adulterants found in Indian marketplace are the *Osyris wightiana* (Santalaceae), known as 'Nepal sandalwood' and *Erythroxylum monogynum* (Erythroxylaceae), known as 'Indian bastard sandal' (Anupama et al. 2012). The wood colour, grain and scent of Sandalwood and *O. wightiana* differ only slightly, thus making it difficult to distinguish them. The heartwood of *O. wightiana* is indistinctly aromatic, and used to adulterate Sandalwood (Shyaula 2012). The heartwood of *E. monogynum* possesses a pleasant scent and appears to be reddish-brown, and hence commonly used for adulteration (Oyen and Dung 1999). DNA barcoding can be used to identify the market adulterants of Sandalwood timberwood (Arun Suma et al. 2014). The typical DNA barcodes, i.e., chloroplast genomic sequences, such as the rbcL, trnH, −psbA and matK suggested by the

Consortium of Barcode of Life (COBOL) were investigated to differentiate wood adulterants of Sandalwood. SNPs (Single Nucleotide Polymorphisms) recognized with trnH, −psbA and rbcL sequences of *E. monogynum* and matK sequences of *O. wightiana* might be resourcefully exploited for detecting or checking Sandalwood adulterants.

5.6 Conclusions and Future Prospects

Sandalwood, a semi-parasitic tree is one of the most economically valued tree species, only after *Dalbergia melanoxylon* (African blackwood). Sandalwood oil, extracted from the tree heartwood is accepted as standards by the International Organization for Standardization (ISO). Sandalwood oil is majorly used as a flavouring for foodstuffs and liquid refreshments, and as a perfume in cosmetics, incense, ointments and detergents. In the traditional medicinal systems of the world, it has been used for treating numerous health issues. The essential oil constitutes nearly 90% santalols, i.e., α-santalol (up to 49%), β-santalol (up to 33%), α-trans-bergamotol (up to 5%) and epi-beta-santalol (up to 7%). Mainly, the santalols are accountable for the pleasing odour of Sandalwood, even though 2-furfuryl pyrrole might also add the effect.

Today, the oil is infrequently used pharmaceutically, however its extensive usage as a prevalent essence continues. Numerous in vitro and in vivo investigations have been performed to witness the medicinal values of Sandalwood and its essential oil. Sandalwood products possess anti-microbial activities, and found to be effective in inhibiting several drug-resistant microbial species. Both oil and its major compound, α-santalol exhibit chemo-preventive activities against many cancers. The molecular mechanisms of actions of such antitumour effects are credited to modifications in major cancer signalling pathways, including AP-1, MAPK, PI3K/Akt and β-catenin pathways, in addition to the caspases/PARP activation and p21 up-regulations. Further, α-santalol impedes cell proliferation via inducing G2/M phase cell cycle arrest. Further, investigations suggest that Sandalwood oil may be useful for treating ailments related to anxiety, central nervous system, cardio-metabolic risks, liver damages, etc. However, reliable clinical data concerning the usages of Sandalwood oil for the treatment of the above said health problems are limited, and hence requires more focus in this regard. In general, Sandalwood oil has a tolerable safety profile.

In recent times, Sandalwood adulteration is one of the major challenges as the demand for its products is rising in the world market. Some of the techniques such as DNA barcoding technique and NIR analysis can trace the adulterants of Sandalwood. However, future research should also consider in developing more such improved rapid analytical methods to complement the authentication of Sandalwood samples. Investigations, involving animal models should be encouraged to identify the toxicity and safety characteristics of Sandalwood and its compounds. Additionally, beneficial prospects of several novel bioactive compounds from Sandalwood using both in vitro and in vivo models must be explored in detail.

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