Review Article

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Santalum Genus: phytochemical constituents, biological activities and health promoting-effects

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Abstract: *Santalum* genus belongs to the family of Santalaceae, widespread in India, Australia, Hawaii, Sri Lanka, and Indonesia, and valued as traditional medicine, rituals and modern bioactivities. Sandalwood is reported to possess a plethora of bioactive compounds such as essential oil and its components (α-santalol and β-santalol), phenolic compounds and fatty acids. These bioactives play important role in contributing towards biological activities and health-promoting effects in humans. Pre-clinical and clinical studies have shown the role of sandalwood

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extract as antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, neuroleptic, antihyperglycemic, antihyperlipidemic, and anticancer activities. Safety studies on sandalwood essential oil (EO) and its extracts have proven them as a safe ingredient to be utilized in health promotion. Phytoconstituents, bioactivities and traditional uses established sandalwood as one of the innovative materials for application in the pharma, food, and biomedical industry.

Keywords: bioactivities; clinical studies; essential oil; phytochemistry; safety; sandalwood.

1 Introduction

The genus *Santalum* is a woody flowering plant that belongs to the family Santalaceae commonly known as sandalwood. The members of the genus are generally trees or shrubs. The plant is obligate hemiparasite attaching itself by haustoria to establish contact with the host and extracts xylem sap for nutrients and water [1]. The family Santalaceae comprises 29 genera with around 400 species out of which 18 well-recognized species are under the genus *Santalum* [1–7] (Table 1).

Sandalwood is generally popular for its fragrant heartwood oil used by cosmetic industries for the production of perfume [13, 18–21]. The high demand for sandalwood oil and timber has resulted in drastic overharvesting; as a result, many taxa are now considered as rare, threatened or listed as endangered [22]. Moreover, one species *Santalum fernandezianum* Phil. from the Juan Fernandez Islands (South Pacific Ocean), has been reported extinct due to over-exploitation by human beings [23]. About 25 species belong to the genus *Santalum*, they are evergreen trees or shrubs characterized by a semi-parasitic lifestyle. They conduct photosynthesis; however, they take in water and inorganic nutrients by parasitizing on the roots of other plant species.

Plants of the genus *Santalum* are characterized by the production of EOs with many biological properties due to the high content of bioactive substances such as lignans, glycosides, triterpenoids, and sesquiterpenoids (α/β-santalol - the compound found in the largest amount). These bioactive compounds include antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, neuroleptic, antihyperglycemic, antihyperlipidemic, and anticancer activities.

Santalum genus has been known to possess many health benefits proved based on traditional uses and modern biological approaches through preclinical studies. Traditionally, *Santalum* genus has been used as an antipyretic, immune booster, antidiarrhea, and for treating cold and cough. Modern uses have shown their effect as antioxidant, anti-inflammatory, antibacterial,

Table 1: Section, recognized species, according to the International Union for Conservation of Nature (IUCN) category, common name and geographical distribution of *Santalum* species.

Taxonomic group/Section	Species and IUCN Red List Category	Common name	Geographical Occurrence	Reference
Section *Santalum* skottsb.	*S. album* L.	Indian sandalwood	Australia, Belgium, Cambodia, China, Germany, Great britain, Holand, India, Indonesia, Japan, Madagaskar, Malaysia, Norway, Spain, Srilanka, Switzerland, and the United States.	[3, 8, 9]
Section *Solenantha* Tuyama	*S. fernandezianum* Phil.	Freycinet sandalwood, or iliahi	Hawaiian islands (O'ahu, Moloka'i)	[10, 11]
	S. haleakalae Hillebr.	Haleakala sandalwood or iliahi	Hawaiian islands (Maui)	[11, 12]
	S. pyrularium A. Gray	Hawaiian sandalwood or iliahi	Hawaiian islands (Kaua'i)	[3, 5, 13, 14]
Section *Hawaiiensia* skottsb.	*S. ellipticum* Gaudich.	Coastal sandalwood or 'Iliahialo'e	Hawaiian islands	[3, 11, 12]
	S. paniculatum Hook. & Arn.	Hawai'i	Hawaiian islands	[3, 11]
Section *Polynesica* skottsb.	*S. fernandezianum* F.Phil.	Chile sandalwood	Juan fernandez islands	[3]
Genus *Eucarya* T.Mitch.	*S. acuminatum* (R.Br.) A.DC.	Desert Quandong, native Peach	Australia	[15–17]

antifungal, antiviral, neuroleptic, antihyperglycemic, antihyperlipidemic, and anticancer activities. One of the most important parameters considered for the application of plant extracts in the biomedical field is its safety. The safety aspects of EO components have been studied by various researchers and it is concluded that extracts from *Santalum* genus are fairly safe to be used as health-promoting effects. The current review is the first of its kind that gives a snapshot of the *Santalum* genus concerning its traditional uses, bioactive components, bioactivities (*in vitro*, *in vivo* and clinical trials), and its safety aspects while using it as a health-promoting agent in humans.

2 Review methodology

Available information on the genus *Santalum*, its biological properties, and its potential mechanisms of action was collected by searching the following databases: PubMed/Medline, Web of Science and ScienceDirect. The following MeSH terms were used: "Santalum/growth & development", "Santalum/chemistry", "Plant Oils/isolation & purification", "Animals", "Apoptosis/drug effects", "Carcinogenesis/drug effects", "Cell Cycle Checkpoints/drug effects", "Humans", "Mice", "Plant Extracts/chemistry", "Plant Extracts/therapeutic use", "Plant Oils/therapeutic use", "Antioxidants/metabolism".

The study included research articles and reviews published in extenso, written in English language in scientific journals, book chapters and books with information about *Santalum* genum and sandalwood. Editorials/letters to publishers, case reports, conference abstracts, studies that included homeopathic preparations were excluded. The PlantList database was used to verify the taxonomy and provide information on the classification and distribution of *Santalum* subspecies [24, 25].

3 Botany

Santalum is widely distributed to semi-arid areas from Indonesia in the West to Juan Fernandez Islands (Chile) in the East and from Hawaiian Archipelago in the North to New Zealand in the South [8] (Figure 1). The major production places of the plant are shown in Table 1.

The well-recognized species are broadly grouped into four categories viz. Indian sandalwood (*Santalum album* L.), Australian sandalwood (*Santalum acuminatum* (R. Br.) A. DC.), Hawaiian sandalwood (*Santalum ellipticum* Gaudich., *Santalum freycinetianum* F. Phil., *Santalum haleakalae* Hillebr., *Santalum paniculatum* Hook. & Arn., and *Santalum pyrularium* A. Gray), and Pacific Islands sandalwood (*S. fernandezianum* Phil.).

A taxonomic grouping in *Santalum* is purely based on morphological characters. It has been reported that Section *Santalum* is described as reddish corollas that are longer than wide and partly superior ovaries [12, 26, 27]. Based on smaller ovaries, longer perianth tubes and absence of hairs to the filament [28] separated the two Hawaiian members (*S. freycinetianum* and *S. haleakalae*) from the section

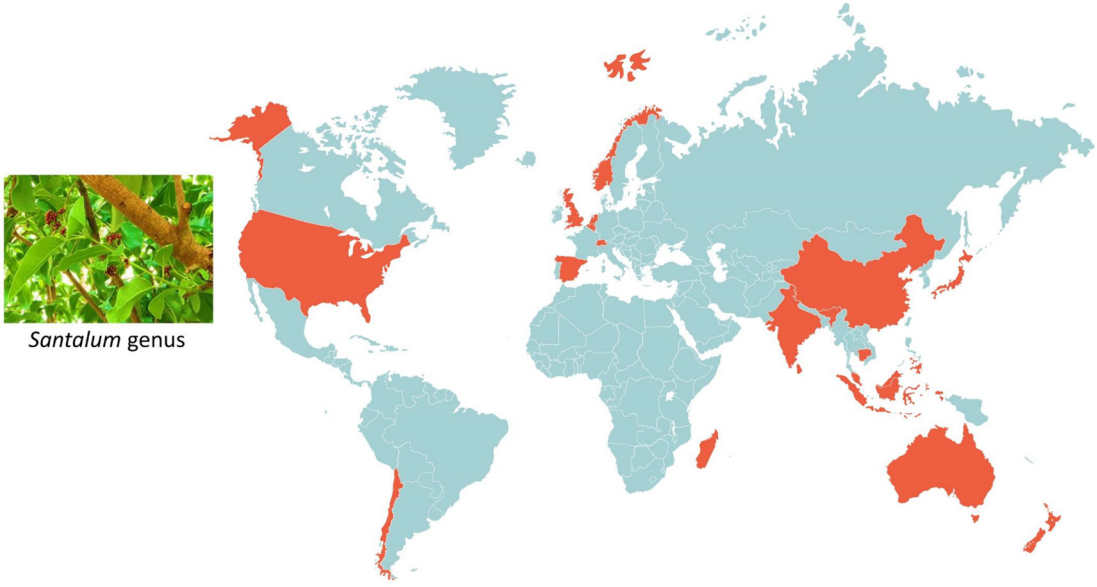

Figure 1: Geographical distribution of *Santalum* genus.

Santalum into the endemic section *Solenantha*. The characteristic features of the section *Hawaiiensia* are explained as having white, brown, orange or green corollas that are as wide as long and inferior ovaries [12, 26, 27].

Section *Polynesica* is similar in appearance to the section *Hawaiiensia* but with partly superior ovaries [26]. A molecular phylogenetic study reveals that the sectional classification of *Santalum* needs revision [3]. Skottsberg [26, 29] suggested that sections *Hawaiiensia* and *Polynesica* were closely related based on morphological characters and section *Polynesica* was treated as a synonym of section *Hawaiiensia* by [30]. But molecular phylogenetic analysis indicates that sections *Hawaiiensia* and *Polynesica* are not close to one another rather related to other taxa of section *Santalum* and should not be united taxonomically [3]. Revisionary studies based on molecular data considered six species of *Santalum* in Hawaii, whereas previously there were only four recognized species [5]. Hawaiian species are considered to be a result of two colonization processes which comprises four species within red-flowered section *Solenantha* (i.e., *S. freycinetianum*, *S. haleakalae*, and *S. pyrularium*); and two species within white-flowered section *Hawaiiensia* (i.e., *S. ellipticum*, and *S. paniculatum*) [14].

General features of the genus *Santalum* are evergreen trees or shrubs; leaves opposite rarely alternate, sometimes in whorls, glabrous or sometimes glaucous, ovate, obovate or lanceolate, coriaceous [31]. Flowers cymose panicle, axillary or in the terminal, tetra or pentamerous, hermaphrodite; bracts small. Perianth-tube campanulate to conical or ovoid, adnate to the base of the ovary; stamens 4-5, dorsifixed, filament slender, short, anthers ovate; 4-lobed; style long, stigma 2-4 lobed; ovary inferior or partly inferior; ovules 2-3. Flowers produce sweet to a week or no fragrance. Fruit globose to sub-globose drupe, annulate on the top by the deciduous perianth; seed subglobose; albumen copious. Morphological differences of some important species are summarized in Table 2.

4 Traditional uses

The close-grained heartwood of *Santalum* is used for ornamental and carving work. *Santalum* fruits are edible and the seeds contain fatty oil which is suitable for the manufacture of paint. Incense sticks are made of powdered heartwood and are used in houses and temples. In addition, powered heartwood is ground into a paste and used as a cosmetic [35]. *Santalum* genus is mentioned in Indian mythology, folklore, scripture, and the oldest literature (for example, Vinaya Pitaka (400–300 BC) and Milinda Pahna (200 BC)) and also in the epic Ramayana and Mahabharata. The ancient Egyptians used *Santalum* plants oil for embalming the dead and in the ritual burning to venerate the gods. In certain communities among the Hindus it is traditional to put a piece of sandalwood in the funeral pyre. A beige-coloured paste obtained from sandalwood is put in on the forehead and other body parts, especially by devotees of God Krishna (Vaishnavites) and for ritual bathing of Hindu gods [36]. In Zoroastrian temples, *Santalum* burns in sacred lights to soothe the problems of all mankind. It is used by Jews, Buddhists, Hindus, as well as almost all other belief systems for its huge variety in attributes [35].

5 Bioactive composition

5.1 Essential oil, terpenes, and derivatives

After 30 years of growth with a natural condition, oil is collected from the heartwood of sandalwood. The yield of the oil depends on the age of the tree; an old mature tree gives an oil yield between 2.5–6%; the colour of the heartwood, individual tree understudy, location within the tree, and the environment of growth of the tree. Sandalwood oil consists of main terpenoids: mono- and sesquiterpenes and their oxygenated derivatives (mostly the alcohols, ketones, and aldehydes) and also some fatty acids, and phenylpropanoids chemical compounds [37–39] (Figure 2).

The bark extract of *S. album* contains mainly santalol (90%) [40, 41], exo-norbicycloekasantalal, β-santalic, teresantalic, nortricycloekasantalic, bicycloekasantalic, dihydro-β-santalic acids, urs-12-en-3b-il-palmitate, β -sitosterol, (+)epi- β-santalol, (-) β-santalol, (-)trans-β-santalol, α-santalol (52%), β-santalol (23%), epi-β-santalene, cis-lanceol, cis-nuciferol, β-, epi-β-teresantalic acid, β-, epi-β-norekasantalic acid, β-, epi-β-ekasantalic acid, α-santalic acid, 11-keto-dihydro- α -santalic acid, bisabolenols A, B, C, D and E, tricycloekasan-talol, α- and β-santalenes, trans-α -bergamotene, α-curcumone, nuciferol. The bark extract of *S. album* includes l-allohydroxiproline, betulinic acid, β-sitosterol, and fatty acids. The bark extract of *S. album* contains betulinic acid (0.05%), β -sitosterol, glucose, fructose, and sucrose [38, 40]. Although including a low amount of trans-β-santalol, cis-lanceol hydrocarbons, α-santalene, β-santalene, α-bergamotene, epi-β-santalene, as α-curcumene, β-curcumene, γ-curcumene, β-bisabolene and α-bisabolol; cis-α-santalol (53%), cis-β-santalol (23%), α-trans-bergamotol, epi-cis-β-santalol sesquiterpene alcohols are the major components of the sandalwood oil [42–46].

Table 2: Contrasting morphological characters of important *Santalum* species.

Category	Species	Size	Leaves	Flower	Fruit	Reference
Indian sandalwood	*S. album* L.	Small to the medium-size tree with slender drooping branches	Opposite, lanceolate to ovate; acute to obtuse at base, entire; apex acute to acuminate; pale green to lush green	Initially, straw yellow coloured and gradually turn to deep purplish or brown	Green to purplish–black; succulent	[8, 9, 31, 32]
Australian sandalwood	*S. acuminatum* (R. Br.) A. DC.	A shrubby small tree	Opposite, more or less lanceolate; pale green to olive-green; acute apex	Small, creamy white or greenish-white	Globose, green turning to orange–red to bright, glossy red; persistent tepal scar	[15, 16, 33]
Hawaiian sandalwood	*S. ellipticum* Gaudich.	Shrub to small tree	Elliptic to orbicular, ovate, or obovate; leathery to succulent; glaucous; dull, greyish green	Greenish in bud but tinged with brown, orange, or salmon after opening; produce a sweet fragrance; flower as long as wide	Purple to black drupes, with a distinctive apical receptacular ring	[11, 34]
	S. paniculatum Hook. & Arn.	Shrub or tree	Ovate, obovate or elliptic; upper surfaces glossy and lower surface dull; yellowish orange to bluish or olive green.	Greenish in bud but tinged with brown, orange, or salmon after opening; produce a sweet fragrance; flowers as long as wide	Purple to black with a distinctive apical receptacular ring.	[11, 34]
	S. freycinetianum F. Phil.	Shrub to tree	Narrowly elliptic, oblong, to narrowly ovate; acute to rounded apex; bit glaucous; green	Light pink turning deep pink with maturity (rarely with white interiors); produce a weak fragrance; flowers longer than wide	Reddish–purple to almost black with a distinctive sub-apical receptacular ring	[5, 10, 11]
	S. haleakalae Hillebr.	Small tree	Ovate, obovate, or orbicular; stiff to coriaceous surfaces; olive green	Deep pink to red throughout, or with white to pink interiors; produce a weak fragrance; flowers longer than wide	Black or purplish–black with a distinctive sub-apical receptacular ring.	[5, 11]
	S. pyrularium A. Gray	Small tree or shrubby tree	Opposite; elliptic, ovate, to oblong; glaucous abaxially not much paler on abaxial surface; acute to obtuse apices; medium to dark green	Cream to purple throughout, greenish with the purple interior, or greenish-white turning red with age	Red, elliptic, with subapical ring	[5]

5.1.1 Extraction of the *Santalum* Oil

EO is one of the important components of an important component of sandalwood and its isolation from sandalwood depends on the methods of extraction. The EO of the sandalwood is widely used in the fragrance industry due to having a strong aroma and has various biological activities such as: anticancer, antiviral, antidiarrheal, cytotoxic activities, among others [47]. The different extraction methods can be applied to the *Santalum* during oil extraction. Therefore, the composition and amount of the fragrance and volatile compounds found in oil may vary dependent on the extraction methods. The conventional steam distillation and hydrodistillation methods are performed under high temperatures (around 100 °C) which can often result in loss of volatile compounds and changes in the odour [48–50]. Maceration or Soxhlet type solvent extraction are other techniques that have some the drawbacks such as large volume of solvent usage, exposure to hazardous and flammable liquid organic solvents, and environmental issues [51]. Therefore, the use of some solvent-free "green methods" during the extraction of EO has gained prominence in recent years. Microwave-assisted extraction, subcritical CO_2 (SC–CO_2)

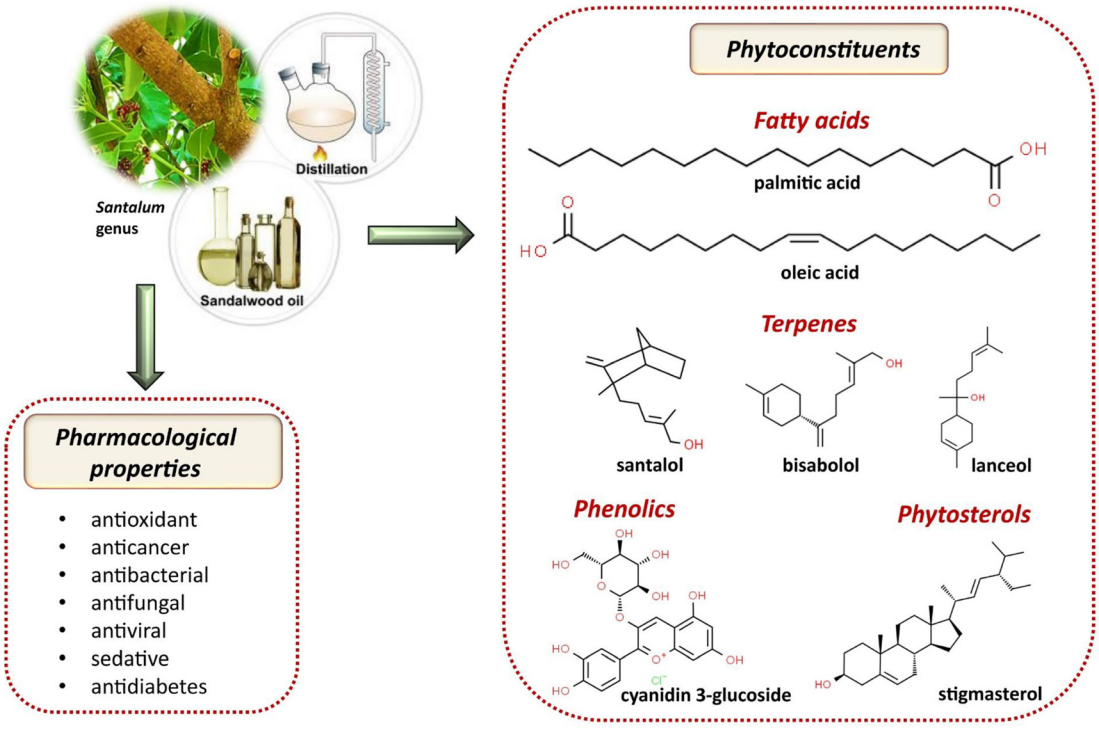

Figure 2: Illustrative scheme with the most important bioactive constituents of *Santalum* essential oil and their pharmacological properties.

extraction and some other combined novel technologies, such as microwave-assisted hydrodistillation method, are preferred due to having higher selectivity and extraction yield, need for less time for analysis and not posing environmental and safety concerns [52, 53].

Kusuma and Mahfud [52] objected to looking into the effects of the newly employed microwave air-hydrodistillation method for extraction of EOs and comparison with classical microwave hydrodistillation method. Results of this research showed that additional airflow to the microwave hydrodistillation can help obtain the sandalwood oil in higher yield directly proportional with air flow rate. The compound composition of microwave air-hydro distilled sandalwood oil is larger than another method concerning identification 43 compounds whereas 37 compounds are recorded in microwave hydrodistillation. Microwave air-hydrodistillation provides better aroma/fragrance quality than microwave hydrodistillation extracts [52].

Nautiyal [54] mentioned that extraction yield and quality affect the trade of sandalwood oil. It was also highlighted that heartwood preparation and the extraction method have an influence on α- and β-santalol levels in the obtained oil. In the study, eight different extraction methods which are SC–CO_2, ethyl alcohol, benzene, diethyl ether, toluene, steam distillation, hydrodistillation, and alkaline-hydro distillation are examined. The highest yield is obtained from SC–CO_2 extraction, 3.83 grams per liter (g/L). In the analysis of extracted sandalwood oil for α- and β-santalol levels were examined through gas chromatography (GC). The most efficient extraction methods are SC–CO_2, ethyl alcohol, and steam distillation; they include nearly 84% total α- and β- santalol. Hydrodistillation is the least efficient in terms of having α:β- santalol ratio, 3:1, whereas SC–CO_2, ethyl alcohol, and steam distillation had 1.9:1. Furthermore, Nautiyal [54] stated that organoleptic characteristics are affected by the levels of α- and β-santalol, besides other compounds. Pleasant sandalwood oil extracts are found via SC–CO_2 extraction, hydro, alkaline-hydro, and steam distillation. Furthermore, Nautiyal [55] extracted sandalwood (*S. album*) oil via SC–CO_2 at 200 bar and 28 °C under two conditions, and the fractionation of the extract was analyzed continuously. Extractions by steam distillation, hydro distillation, Soxhlet extraction were conducted for comparison. The results showed that SC–CO_2 extraction is much more effective in terms of the physical properties of oil than commercial sandalwood oil [55].

Over the last 25 years, about 65,000 chemical structures of the terpenoids and over 7,000 sesquiterpenes (C15) have been reported in previous studies [56]. The EO of the *S. album* tree is composed of the mixture of sesquiterpenes

i.e., α-santalol, β-santalol, epi-β-santalol, α-trans-bergamotol, α-bisabolol, lanceol, sesquisabinene hydrate, and farnesol [57]. According to the literature research, α-santalol and β-santalol (Figure 3) which are the main sesquiterpene alcohol compounds found in sandalwood oil are known to indicate biological activities against the skin and prostate cancer and malaria [58]. In the same context, GC analysis of *S. album* oil shows that Z-α-santalol and Z-β-santalol are found with proportions 41–55% and 16–24%, respectively according to the standard [52]; identified some of the sesquiterpenes and monoterpenols, such as α-santalol, β-santalol, α-bergamotol, and cis-lanceol.

According to this chromatographic analysis, santalol levels below these specifications can be related to extraction from undeveloped heartwood, adulteration with synthetic or semi-synthetic substitutes, or substitution with EOs from other species [42].

Mohankumar et al. [59] conducted a study on the heartwood of *S. album* EO concerning antioxidant and stress modulatory efficacy. The traditional steam distillation method is preferred for *S. album* oil extraction and the oil chemical profile identified by the GC–MS technique. *Santalum album* oil has at least 19 main components, accounting for 96.81% of the total content. The main compounds of *S. album* oil followed the order as α-santalol with 41.77% > β-santalol with 18.02% > (Z)-α-trans-bergamotol (8.50%) > (Z)-lanceol (6.57%) > epi-β-santalol (5.78%), cis-nuciferol (3.21%) > docosahexaenoic acid (2.54%) > β-trans-santalol (2.24%) > β-costol (1.41%) > β-santalene (1.24%) > (Z)-β-curcumen-12-ol (1.02%). Besides all components, the pleasant odour of *S. album* oil was contributed by α- and β-santalol.

Subasinghe et al. [60] investigate the Indian sandalwood (*S. album*) EO content and composition in Sri Lanka. Two naturally grown trees heartwoods are studied for comparing the oil properties. The maceration method is applied overnight with deionized water. One of the three the oil yield was measured at 15 cm below ground and found with the highest yield of EO whereas other trees showed a yield varying from 1.46 to 3.35 % w/w.

Another study examines the phytochemical analysis and antibacterial efficiency of extracts of *S. album* in preclinical studies. *In vitro* extracts contain callus, somatic embryo, and seedlings; non-oil-yielding young and oil-yielding matured trees are included *in vivo* part. Combined dichloromethane and methanol are used for the 18 h maceration method. Seedlings have the highest amount of sesquiterpenoids with 51.4 mg/g, and the old tree has the least (8.07 mg/g). Monoterpenoids compound content range changes between 3.1 and 4.5 mg/g, except young tree leave extract that has the highest content with 9.5 mg/L [61].

The volatile oil from *S. album* wood and of *Boswellia sacra* Flueck, (syn. *Boswellia carteri* Birdw.) the resin obtained by SC–CO_2 extraction and the effects of extraction conditions on the composition is analyzed in the study of [37]. In general, oxygenated sesquiterpenes dominate the composition of the oil with a 90% ratio and hydrocarbon sesquiterpenes follow these compounds around 5%. According to the results, the best operative conditions is obtained working at 120 bar and 45 °C with the 0.658 g/mL density of CO_2 in the extraction vessels for both matrices.

Another research was conducted on EO composition from roots of *S. album* [62]. Samples were kept in ethyl ether at 48 h for extracting the oil from the root bark. *Santalum album* root heartwood had 10.3% in fresh weight oil yield. Fifty-three different chemical compounds are detected by GC-MS; moreover, β-santalol and α- santalol were included in the ethanolic extract at the highest level with 19.6 and 16%.

In the study of Jones et al. [63]; the yield of the oil from 22 *S. album* trees was evaluated with the use of core sampling at two different heights (30 cm and 100 cm ground level). The results showed that the total concentration of sesquiterpene hydrocarbons is found in a slightly higher proportion in samples. On the other hand, the ratio of α-santalol and β-santalol is lower generally at 100 cm above ground level.

In recent years, procurement of sandalwood resources and their biologically active compounds such as EO or terpenoids have been decreased due to the devastating of the natural stocks and habitats. Therefore, some of the strategies like the heterologous expression, plant cell cultures and plant cell bioreactors have gained prominence to promote the synthesis of sandalwood terpenoids [47, 64].

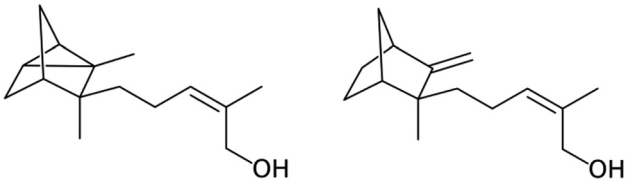

Figure 3: Structure of α-santalol and β-santalol.

5.2 Fatty acids

The identification of fatty acid in the oil is generally performed using gas chromatography/mass spectrometry (GC-MS) [65–67]. Zhang et al. [68] examined the 60 compounds from the pericarp-derived volatile oil of *S. album*

with different extraction methods. Colourless EOs are obtained in 2.6 and 5% yield by hydrolyzation and n-hexane extraction and analyzed by GC and GC-MS. Fatty acids, especially palmitic and oleic acids, dominated the total extracted oil with 40–70% depending on the extraction method. *Santalum album* berries proximate analysis, and *in vitro* activities of these compounds have been done by Sri Harsha et al. [69]. Soxhlet method with hexane is used for taking off the oil. The oil that contains a higher amount of oleic acid (45.4%) and palmitic acid (32.5%) is measured 1.5 g/100 g fresh weight. Berries have a very low amount of α-tocopherol when compared to other berry tocopherol content.

5.3 Phenolics and saponins

Santalum album berries phenolic content is found 310 mg gallic acid equivalents (GAE)/100 g fresh weight in methanolic extract of berries. Acidified methanolic extract of *S. album* berries anthocyanin level is measured 0.21% in fresh weight, and the anthocyanin is confirmed as cyanidin 3-glucoside [69]. Various extract of *S. album* has antioxidant activity and a significant role in fighting against free radicals. Kaur et al. [70] reported that the methanolic extract of this strain indicates higher phenolic fractions than other extracts. Besides, cyanidin-3-glucoside is one of the anthocyanin pigments that show antioxidant properties and nutritional potential in *S. album*.

Like *S. album* callus, somatic embryo, and seedlings (*in vitro*); non-oil-yielding young and oil-yielding matured trees (*in vivo*) phenolic results, a similar result is shown in saponin content, *in viv*o extracts with 31.6 and 43.6 mg/g show higher saponin content than *in vitro* extract (9.4 and 17.1 mg/g) [61]. Phytoconstituents and antioxidant activity were analyzed *in vitro* grown callus cultures of *S. album*. The yield of the extract for a dichloromethane–methanol (1:1) solvent mixture was found as 4.3%. The results uncover the abundance of phenolic extracts (18.2 μg). Other major phytoconstituents are found in the extract as terpenoids (16.4 μg/mg), saponins (9.4 μg/mg) and flavan-3-ols (7.0 μg/mg) [71].

Chintamani and Dikshit [72] investigated the antioxidant potential and secondary metabolite of the fruit pulp and the kernels of the *S. album*. As a result of the GC-MS analysis, phenols that have been found in the free form are detected in the acetonitrile extract of fruit kernel and sterol derivatives such as cholest-4-en-3 one compound is recorded mostly in the dichloromethane extract of fruit pulp and. Besides, pyrazine amide and acetamide-2-cyano were obtained as a major constituent of the kernel with the extraction in the methanol and acetonitrile, respectively.

5.4 Phytosterols

β-Sitosterol is found in the *S. album* combined hexane and isopropanol solvent extract (85.35 mg/100 g oil) and *S. album* supercritical CO_2 extract (88.9 mg/100 g oil) at the highest level. Stigmasterol and δ-5-avenasterol amounts are quite higher than other types of chemical compounds [73].

6 Pharmacological activities

6.1 Anticancer activity

Cancer is a population of cell cells with uncontrolled growth and multiplication [74–77]. Natural bioactive compounds help us with anti-inflammatory qualities to fight infections like bacterial, fungal and viral, but also with antioxidant properties with cancer [78–81]. Cytotoxicity is one of the biological activities that characterize sandalwood oil. Mishra et al. [82] in their study showed that new cyclic octapeptide cyclosaplin was cytotoxic against MDA-MB-231 that are human breast cancer cells. Its anticancer activity is based on inducing apoptosis in cells but also on suppression of viability of the cells (Figure 4). Different scientists from the world found that compounds from sandalwood have anticancer activities in many types of skin cancer and leukaemia cells [82–86]. Matsuo and Mimaki [83] found new neolignan and known lignans in sandalwood and this study, they showed that new neolignan was cytotoxic towards HL-60 cells, which are human promyelocytic leukaemia cells. In different work, Matsuo et al. [84] showed that cis-β-santalol and -β-santaldiol were cytotoxic against HL-60 human promyelocytic leukaemia cells by inducing apoptosis in them. According to Santha and Dwivedi [85]; α-santalol from sandalwood oil from *Santalum album* have anticancer properties, because it can induce apoptosis, have an anti-angiogenic effect and also antioxidant activity on various types of cancer cells.

6.2 Antibacterial, antifungal and antiviral activities

Antibacterial activities are another one that was found among compounds of sandalwood oil due to the content

of α/β-santalol and were active against *Salmonella typhimurium* and *Staphylococcus aureus* which are bacteria that cause well known and still threatening diseases throughout the whole world [39, 61, 87]. Epi-β-santalene was found to effective against *S. typhimurium* [88] (Figure 4).

In seeds of *Santalum album* there is a compound known as santalbic acid, which has antibacterial properties against gram-positive bacteria and antifungal effect on many types of pathogenic fungi [89]. Ochi et al. [90] found that crude organic fractions and sesquiterpenoids from sandalwood oil have antimicrobial activity against *Helicobacter pylori* which caused peptic ulcers and also can be the cause of gastric cancer. Vadnere et al. [91] purposed to conduct phytochemical analysis and antimicrobial screening of *S. album* seeds petroleum ether and ethanol extracts. *In vitro* antimicrobial activity of both extracts was analyzed using a disk diffusion method for *Bacillus subtilis, S. aureus, Pseudomonas aeruginosa, Escherichia coli* and *C. albicans*. The outcome of the investigations highlights the potential high efficacy of petroleum ether extract related to santalbic acid, which can function as an antimicrobial agent [91].

Different research showed that derivatives from *S. album* possess significant antifungal properties against species as *Microsporum canis*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* which is due to the inhibitory effect on mitosis [39, 87, 92]. Powers et al. [93] in their studies have shown that the most active, of the 60 EOs obtained from commercial sources against *Aspergillus niger, Candida albicans*, and *Cryptococcus neoformans*, both in terms of antifungal and cytotoxic activity, were the sandalwood species (*S. album, S. paniculatum*), rich in santalols.

Gupta and Chaphalkar [94] found that aqueous root extract of *S. album* has anti-inflammatory and antiviral activities because it inhibits proliferation, production of monocytes marker – CD14 and also inhibition of nitric oxide in their study on immunopharmalogical activities of it against hepatitis B virus surface antigen – HbsAg, and New Castle disease virus. Antiviral properties were also reported by other scientists in the study of *Herpes simplex* viruses type 1 and 2 [95]. The authors showed that antiviral activity is dose-dependent and didn't exist due to virucidal activity but rather because of the effect on the replication. Sandalwood oil has been also shown to be used against warts, skin blemishes, and other viral-induced tumours on the skin [96].

6.3 Antioxidant

Antioxidants are a group of compounds that protect the body from the chemical process called oxidation [97–99]. This process produces free radicals that attack cell membranes, and for this reason natural antioxidants are important for human health [100, 101]. Antioxidant efficacy is also a known property of sandalwood oil and methanolic extracts from the heartwood of *S. album* [102] but Misra and Dey [71] found it *in vitro* in callus extract of Sandalwood tree and their study showed that it is comparable. Also, antioxidative properties were found in anthocyanins pigment cyanidin-3-glucoside [69].

6.4 Other pharmacological activities

Diabetes is a disease that is widespread along with all the world and sandalwood oil is also found effective in

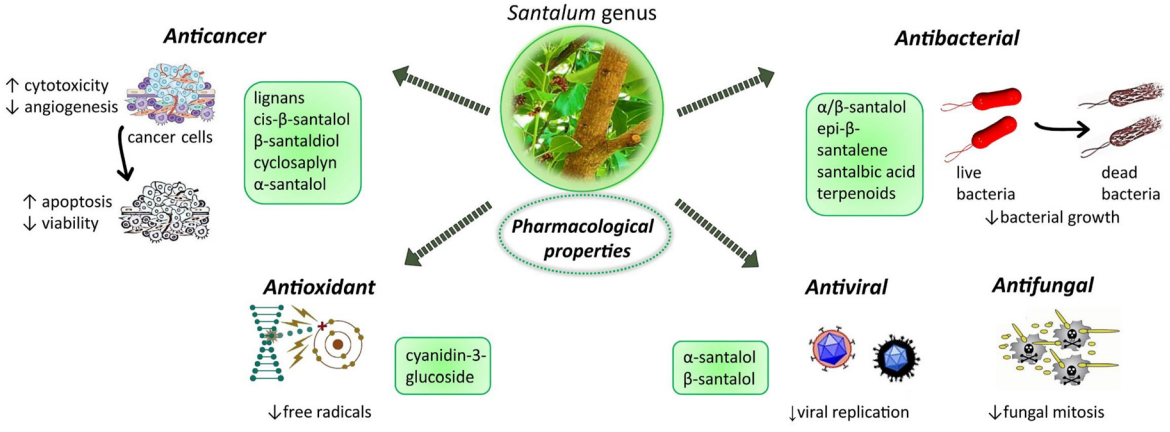

Figure 4: Illustrative scheme with the most representative pharmacological properties of *Santalum* genus and the correlation with bioactive compounds. Symbols: ↑ increase, ↓ decrease.

managing the complications of this disease [103]. Kulkarni et al. [104] found that it has antihyperglycemic and antihyperlipidemic activities in their studies with diabetic rats, because of the antihyperlipidemic properties it can also help with protecting the liver and also with cardiovascular diseases. Sandalwood extract was reported to inhibit the cardiac tissue damage via reduction of lipid peroxidation damage on the doxorubicin induced cardiotoxicity rat model and significant protective effect against induced myocardial infarction in albino rats in a dose-dependent manner [105].

Sedative activities are known as properties of derivatives from sandalwood [106–108]. Sandalwood oil is reported to produce a relaxing effect on the nerves and is used for headaches, insomnia and nervous tensions. Studies carried out by [109] observed that inhalation of sandalwood oil decreased the motility of mice to an extent of 40–78%. Also showed in their studies that a mild sedative effect occurred in female Swiss albino mice after inhaling sandalwood oil.

Okugawa et al. [107] showed an antipsychotic effect *in vitro* and *in vivo* on mice. In addition, α-santalol is a strong inhibitor of both tyrosinase and cholinesterase *in vivo*, and hence there is a great potential of the EO for use in the treatment of Alzheimer's disease [39].

The potential pharmacological property of *S. album* oil in infective skin conditions have been examined during a few clinical against a wide range of skin conditions. The therapeutic potential of *S. album* oil in dermatology is attributed to its antioxidant, anti-inflammatory and antimicrobial properties. Furthermore, *S. album* oil inhibits the hyper-proliferation of keratinocytes, which is problematic in eczema and psoriasis [110]. Dulal et al. [111] reported that sandalwood oil restores and rejuvenates ageing and wrinkled skin. Sandalwood oil has anti-inflammatory activity as well as emollient used in skincare.

All these pharmacological activities show the value of genus *Santalum* (Figure 4). Sandalwood or sandalwood oil can be used in medicine, cosmetology, and aromatherapy. These innovative materials can solve major issues or diseases such as diabetes, cardiovascular problems, infections of different types, cancer, and also help assist to maintain healthy and beautiful skin and a calm mind.

7 Health-promoting effects: clinical studies

Among all the *Santalum* species, the results of several preclinical studies on *S. album* revealed the vast variety of pharmaceutical properties of this valuable medicinal plant [61, 91, 94, 112]. Although there are promising *in vitro* and *in vivo* research results on *S. album* oil that shows the high potential capacity of *S. album* oil to treat skin cancer, to date there are limited human studies. Although the available information on sandalwood oil toxicity is limited, it is considered safe due its long history of oral use without any reported adverse effects.

Regarding skin safety, *S. album* oil has a good safety profile in terms of patch testing for contact dermatitis in both irritation and allergy. According to Burdock and Carabin [43]; undiluted *S. album* oil and 10% *S. album* oil are non-irritant. In five dermatology reports, some allergic reactions have been reported. Number of 12 out of 3,542 patients (0.34%) were sensitive to a 2% dilution of *S. album* oil, and in three reports, 69 of 5,595 patients (1.2%) exhibited sensitivity to a 10% dilution [113]. In a subsequent multicenter European study, 3 fragrance markers (FMs) (fragrance mix I, fragrance mix II, and Myroxylon pereirae) have been tested on consecutive patients to determine the frequency of positive patch-test reactions to EOs tested in the baseline. The result revealed that 656 of 48,956 dermatitis patients (1.38%) revealed positive reactions to 10% *S. album* oil [114].

Skin inflammation and irritation, known as radiodermatitis, are common side effects in radiation therapy for cancer patients [115]. Radio dermatitis is associated with oxidative stress and an increase in cytokines, including interleukin (IL)-1β, IL-6, and IL-8 [116]. In a study conducted by [117]; the effectiveness of a turmeric and sandalwood oil containing proprietary cream [Vicco® turmeric cream (VTC); Vicco Laboratories, Parel, India] on radiodermatitis in patients with head and neck cancer undergoing radiotherapy have been assessed. In this nine-week open-label clinical study, the degree of radiodermatitis of 46 cancer patients experiencing radiotherapy, significantly inhibited (24 patients) compared to baby oil (22 patients) applying Vicco® cream containing 16% turmeric extract and 0.5% *S. album* oil [117]. In a similar study, the same product (Vicco®) exhibited significantly delayed and moderated on 40 breast cancer patients (20 in each group) radiodermatitis in the sandalwood/turmeric group compared to the control group [118].

Based on four clinical trial projects on photoallergy testing, nine of 621 patients (1.45%) tested demonstrated positive effect to *S. album* oil at 2% [119–122]. It should be noted that photoallergy to EOs is very rare, and its clinical application was generally not established.

The potential clinical anti-inflammatory action of sandalwood oil was tested in a clinical trial performed in 50 patients with mild to moderate facial acne for 8 weeks. This

pilot study of a topical regimen treatment (foaming cleanser, serum, spot treatment, and mask) containing 0.5% salicylic acid and up to 2% *S. album* oil was conducted in teenage and adult subjects with mild to moderate facial acne [123]. For the eight-week treatment period, treatment was well tolerated by nearly all patients (42 of 47 participants (89.4%). Patients experienced an improvement when compared with baseline with notable reductions in lesion counts in patients with more severe or inflamed lesions, using the Global Aesthetic Improvement Scale (GAIS). There is no report of limitation of use of this regimen due to no adverse events [123].

According to the literature, it is assumed that *S. album* oil might have therapeutic benefits to psoriasis patients due to its anti-inflammatory, antiproliferative properties via inducing autophagy and cell death in proliferating keratinocytes [124–126]. A Phase 2 clinical trial results in patients with mild to moderate psoriasis illustrated that the topically applied 10% *S. album* oil serum administered twice a day for 28 days was well tolerated and alleviates mild to moderate psoriasis symptoms [127].

In a pilot study, undiluted *S. album* oil to common warts twice daily for 12 weeks has been applied to ten candidates with the age range from six to adult. The results showed that 10 of the 12 (80%) participants had complete resolution of all treated warts over their hands, feet, legs, or face, with the other two subjects experiencing moderate improvement. There was no report of skin irritation, redness, pain or other adverse symptoms [128].

8 Safety, adverse effects and therapeutic limitations

Due to the chemical composition of the sandalwood, its EO is most popularly used in folk medicine, cosmetics, pharmacy, as well as the food industry. The list of internal and external health problems, in which the oils of *Santalum* plants are used, contains inter alia general weakness, headache and stomach ache, common colds, bronchitis, skin diseases such as infectious sores, ulcers, acne, and rashes, heart ailments, fever, infection of the urinary tract, and inflammation of the mouth [129, 130].

Just as the positive effect of EOs depend on their chemical composition, their safety and side effects result from the main phytochemicals and as well as the synergistic action of compounds that are present in lower concentrations. The main components present in the sandalwood EOs, that should be taken into the consideration regarding the safety are α-santalol, β-santalol, β-santalene, Z-α-trans-bergamotol [43, 131].

In the food industry, natural flavouring substances may be safely used in the products, meeting some criteria: must be used in the appropriate forms, in the minimum quantity required to produce their intended physical or technical effect, and following all the principles of the good manufacturing practice. Following this, the Food and Drug Administration (FDA) recommendation, a wide range of EO (clove, oregano, thyme, nutmeg, basil, mustard, and cinnamon) and components (linalool, thymol, eugenol, carvone, cinnamaldehyde, vanillin, carvacrol, citral) are classified as generally recognized as safe (GRAS) and have been accepted in the application in food products [132].

According to the FDA, *S. album* is an accepted natural flavouring substance and can be used in the food industry in any kind of product, without restrictions.

Although some limitations with the dosage of the *S. album* EOs are recommended. According to the data of Flavor and Extract Manufacturers Association (FEMA) published in the article of Burdock and Carabin [43] the maximum doses of sandalwood oil in alcoholic beverages should not exceed 0.77 ppm; in non-alcoholic beverages 1.96 ppm, hard candy 89.98 ppm, while in the case of baked products the maximum level is 9.72 ppm. Even though it is difficult to determine how much sandalwood EO is consumed with food by humans, National Academy of Sciences (NAS) data are estimated to 0.0074 mg/day or 0.000123 mg/kg/day sandalwood oil for 60 kg individual.

On the other hand, FEMA reported that these values are 0.0058 mg/day and 0.0001 mg/kg/day, while the mean consumption of foods containing the usual amount- PADI (Possible Average Daily Intake) - is estimated to 0.97 mg/person/day or 0.016 mg/kg/day of sandalwood oil [43]. In general, the information on the safety and adverse effects of the genus *Santalum* is extremely limited.

Even though the EOs are generally considered as safe, toxicological studies showed that some of them may be harmful to human health. Studies have been shown that different chemicals of EOs (menthol, carvone, limonene, citral, cinnamaldehyde, benzaldehyde, as well as methyl anthranilate, geranyl acetate, furfural, and eugneol) taken at high levels showed no carcinogenic effects [133]. Although low concentrations of EOs are usually devoid of mutagenicity and carcinogenicity, some single components or crude EOs may act as carcinogens. For example, estrogen-dependent malignancy can be induced by *Salvia sclarea* L. EOs, while estragole from *Artemisia dracunculus* L. shows carcinogenic potential in rodents. Following, psoralen (bergamia EOs) is photosensitive compound that

may induce DNA adduct formation and skin cancer, while methyleugenol (*Laurus nobilis* L.) and D-limonene (citrus EOs) is being known as carcinogenic in rodents [134].

The lethal dose (LD_{50}) of the sandalwood EOs was evaluated for rats (5.58 g/kg body weight) and rabbits (>5 g/kg BW, body weight). The LD_{50} was also estimated for the major constituent of the EOs, α-santalol and the values for rats were 3.8 g/kg BW, and for rabbits >5 g/kg BW. 3 mL/kg of α-bisabolol showed a reduction in fetal numbers in rats and rabbits, while 1 mL/kg showed no teratogenic effects [113].

Interestingly, studies on the effects of the inhaled sandalwood oil have shown that female Swiss exposed to the oil for 1 h shown 40% decreased motility, and in the blood of these animals, α- and β-santalols were present [43, 135]. Some studies with animal models suggest that sandalwood EO can irritate rabbit skin, but it seems that this oil has no such effect on human skin [113]. The results of studies showed that sandalwood EO is characterized by low sensitization potential. In the work of Paulsen and Andersen [136] of 318 patients responded that 10% of sandalwood EOs gave a positive effect.

At the same time, 2% concentration did not cause any negative effects on any of the respondents [136]. A total of 1.4% of all tested dentists and dental nurses responded to sandalwood oil in the case of the paper published by Kiecswierczyńska and Krecisz [137]. A total of 0.9% of patients (total of 1606 patients) responded to 10% sandalwood oil, at the same time 0.4% of patients responded to 2% concentration [138].

In the study with 641 patients with eczema, sandalwood oil had no response by any of the tested patients [139], while in the case of 422 patients with suspected contact allergy, 2.4% gave the positive response to sandalwood, and 3.1% to cinnamic alcohol [140]. Similar percentage results were obtained in the studies on the photoallergies' caused by sandalwood oil. 2.2% (3 of 138 patients) were positive to sandalwood oil reaction in the study conducted by Fotiades et al. [119] while 2 of 1050 probable photodermatitis patients (0.19%) in the study of Pigatto et al. [141].

In general sandalwood, EOs are recognized as nontoxic in the matter of phototoxicity, but the suggested maximum dose of the *S. album* EO is 2% [113]. The results of the study with 4266 Japanese people with cosmetic dermatitis showed that 57 (1.34%) was positive to 2% α-santalol. This suggests that the concentration of the sandalwood EOs should be lower for people of Japanese origin [113]. In general, the use of sandalwood oil in eczema, psoriasis, radiation dermatitis, and antifungal is reported in the literature, and the EOs is well tolerated with acceptable safety [142]. What is more, the major constituent of *S. album* EOs, α-santalol is being recognized as a chemopreventive effect with nontoxic side effects against normal cells [143].

9 Conclusions and future perspectives

The review highlighted the bioactive compounds present in the sandalwood and bioactivities of its extract proven by the *in vivo*, *in vitro* and clinical trials. The EO components such as α-santalol and β-santalol are considered important for evaluating the commercial value of the sandalwood. These components are responsible for most of the biological activities along with the soothing aroma of *Santalum* species. Traditional uses of the EO from sandalwood have been proven to be beneficial in treating somatic and other disorders such as common cold, fever, lung infection, and many types of inflammations. Antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, neuroleptic, antihyperglycemic, antihyperlipidemic, and anticancer activities of *Santalum* extracts have been recently proved through clinical trials. Recent scientific studies have not shown any adverse effect of consumption of sandalwood EO in *in vivo* trials. Hence, extracts from sandalwood are presently used in cosmetic products and as a flavouring agent in food items. More detailed studies are needed to decipher the exact molecular mechanism of the sandalwood extracts in improving human health. These molecular studies will also assist in delineating the more precise use of sandalwood extracts for human consumption. Exhaustive clinical studies are also needed to further promote the use of sandalwood ingredients in food and pharma application. Pharmaceutical formulation of the sandalwood extracts is another area that needs the attention of the scientific community to further improve the use of *Santalum* species in health promotion.

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