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Restorative Efficiency of Bursera Simaruba-Isolated Phytonutrients for the Therapy of Various Diseases

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ABSTRACT

In pursuit of new medicinal compounds in traditional medicinal plants growing in America (south, north, central part), Bursera Simaruba is one such potential medicinal tree. Phytochemical analysis of methanolic extraction of the bark and leaf hexane extract of the plant has triggered the isolation of quite a few phytoconstituents. The whole plant of B. Simaruba is rich in resins, lignans, terpenes, steroids etc. The various parts of the plant are renowned for their inhibitory action towards many bacteria, virus, fungi and protozoa. It also shows antioxidant activity and is proven to cause programmed cell death (apoptosis). It also shows action against inflammation. It is mainly being researched for its anti-cancer activity. Finally, the plant is known in folk medicine for its use as anti-snake venom treatment. Regulatory aspects of use and formulation of herbal medicines and alternative medicines around the world and their legal status respect to their countries is an important aspect. The present review includes possibilities and insights through potential studies into herbal formulation as well as the regulatory aspects for herbal medicines around world.

Keywords: Bursera simaruba, herbal medicines, herbal formulation, phytoconstituents, regulatory aspects, medicinal plant

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INTRODUCTION

Bursera simaruba (L) sarg; belonging to the genus Bursera and family Burseraceae has around fifty vernacular names regionally. It is a large semi evergreen tree. Some of the common names are: Gumbo limbo[1], incense tree, almacigo, Mexican White Birch, Red Birch, Indian White Birch, yala-guito [46] etc., [2][3]and is native to the range of: Brazil, Colombia, Venezuela, Guyana in south America; Caribbean to Florida[4] in the north; Panama to Guatemala in central part of the America.[2] B. Simaruba is used in various traditional medicinal practices because of the presence of higher concentration of resins as shown in the Fig 1. Some of the essential oils, steroids, lignans and terpenes can be found in the resins of the plant[5]. B. simaruba plants can be characterised by the appearance of ducts that have secretory properties in stems and leaf, which gives the resins, oleoresins, gum-oleoresins with properties of yielding balsam. The balsamic properties of resins obtained from the bark accounts for the easy kindling of the wood. [6]

It's a belief among the Mayans that the plants possess healing properties. It is used in traditional medicine in the treatment of psoriasis, eczema, nosebleed, skin fungus, headache, stomachache. It is also used to predict rains by its flowering pattern[2][7]. The branches of B. Simaruba is typically used as "working" fences by the Yucatec people [8].The resin is used in making of varnishes and are used as gum Arabic substitution. Resin is also a natural insect repellent. B. Simaruba is used to make incense, thus the name incense tree.

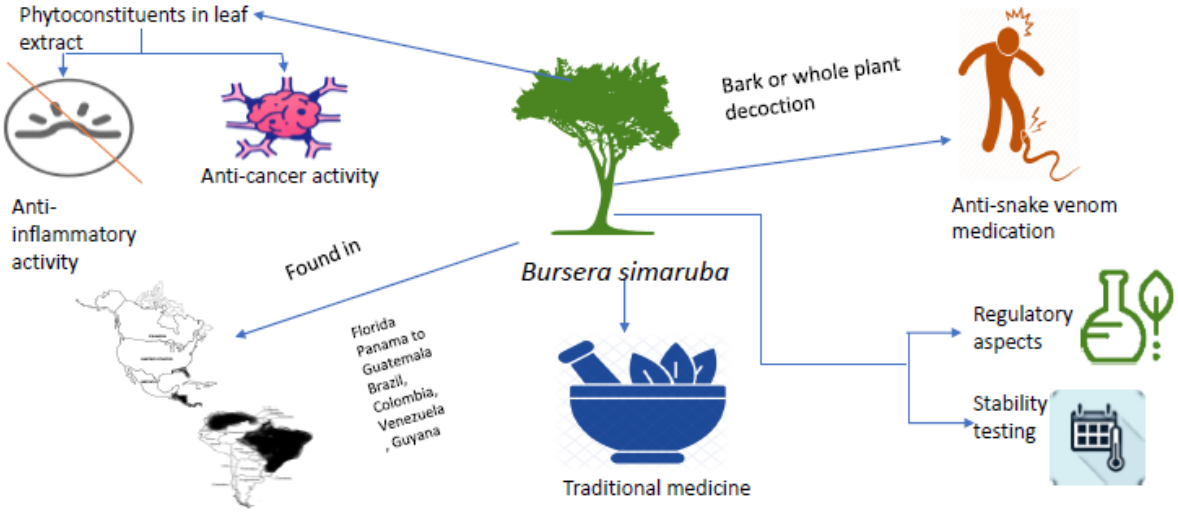


Figure 1: Application of Bursera Simaruba in various traditional medicinal

Synonyms of Bursera simaruba

Although not used anymore, some of the formerly used synonyms of B. Simaruba are: *Bursera elaphrium, B. pistacia* [1] [9]

Medicinal plants as a natural source -Traditional usage

The idea of using medicinal plants for treatment purposes was born at the same time as the birth of humankind itself. The earliest documented evidence for usage of herbs as medicines goes back to a time of 5000 years ago; Nagpur, India. [10] The 'Atharva veda', which is a sacred book of Indian origin can be considered the encyclopaedia for traditional herbal medicines, as it contains a very detailed explanation about medicinal science at that time [11][12]. Many works about the herbal medicine, which are of Chinese origin are also available today[13][14]. In holy books such as the holy bible[15], data about usage of aromatic herbs during treatment and rituals is available[16]. Today, the uses, adverse effects, formulations, indications of herbal medicines are being recorded in various pharmacopoeias. B. Simaruba is used in the treatment of various diseases like cancer, inflammation and is even used as an antidote against snakebites.

Herbal lignan phytoconstituents active against cancer

In plants, lignans among many other compounds are known to show potent anti-cancer activity.B. Simaruba is known to have a type of lignan called 5´-desmethoxyyatein, which has the structure similar to kusunokinin which is a lignan found in plant source [17–19] , which is a well-known synthetic compound to show anti-cancer activity.

5´-desmethoxyyatein in B. Simaruba is believed to show anti-cancer activity against the human HT1080 fibrosarcoma cell lines. [20] [8]5'-desmethoxyyatein is mainly believed to constrain activin receptor 2 (ACTVR2), prostaglandin G/H synthase 2, human epidermal growth factor receptor 2 (HER-2), janus kinase 3 (JAK3), protein kinase C (PKC), heat shock protein 90-beta (Hsp90-beta), transforming growth factor receptor I (TGF-β receptor I), androgen receptor and NF-kappa-B-inducing kinase (NIK) proteins, hence showing anti-cancer activity via growth inhibition, initiation of cell cycle arrest at G2/M phase and apoptosis induction of cancer cell lines. [21][22]

Herbal peltanin phytoconstituents active against inflammation

Currently, various steroidal and non-steroidal drugs are being used to treat inflammation, but the potential availability of alternative novel medicines like plant-based medicines pose an interesting approach for tackling this problem. Various plant parts and their extracts have been screened, of which the hexane extract from the leaves of B. Simaruba has shown a promising result towards the anti-inflammatory action against an adjuvant carrageenan induced paw oedema, in comparison with a standard drug [6]. methyl-β-peltatin A, which is present in the hexane extract obtained from the leaves of B. Simaruba is considered to be one of the active principles in the hexane extract is accountable for the anti-inflammatory function of B. Simaruba.

As of now, the standard methyl-β-peltatin A is known to inhibit the inflammation in a time, as well as dose dependant way. Methyl-β-peltatin A is also known to show potent cytotoxic activity. The standard as of now, the mechanism by which methyl-peltatin A shows anti-inflammatory activity is yet to be researched on. [2].

Herbal terpenoids phytoconstituents active against snake bite

Every year, many deaths occur due to non-availability of antivenom therapy on time[23][24]. Due to the possibility of hypersensitivity towards serum therapy [25], alternative medicines which are comparatively safe are desired. asL-amino acid oxidases (LAAOs), snake venom serine proteinases (SVSPs), phospholipases A_2 (PLA_2s), acetylcholinesterase (AChE), nucleotidases, *snake venom* hyaluronidases (SVHs) and *Snake-venom* metalloproteinases (SVMPs), are some of the most typical snake venom toxins[26–28] [29]. The bark and even the whole plant of B. Simaruba is used in many of south American countries as a medication for snake bites since long ago[30] [19].

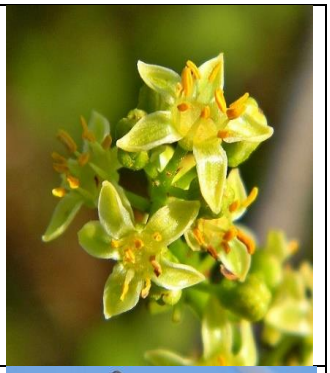
Plant constituents like terpenoids show protein binding and enzyme inhibiting properties. Especially, the terpene α-pinene present in the plant is known to show good neutralizing effects. [31] The possible mechanism of antivenom action of B. Simaruba could be that the terpenoids that are present mainly in shoots, leaves and flowers, shows inhibitory action against snake venom phospholipase A2 (PLA2) which is seen in the venom of Viper and Cobra. [32] the other plant of Burseraceae family that is used against snake bite is India is the seeds of *Boswellia serrata* Roxb. ex Colebr [33], bark, fruit extracts of *Garuzapinnata*[34] etc,.

Bursera simaruba tree description with their phytoconstituents

This tree can be commonly found in the dried groves. Its bark is reddish, which can be peeled in very thin strips, to reveal greyish under bark[35,36]. On crushing, the leaves are fragrant[37][38]. The fruits are edible. The plant is resistant to draught and can be grown in various types of soils such as heavy, medium or light (clay, loamy or sandy) soils. Given that the plant is not self- fertile, the flowers are pollinated by insects. The tree can be grown in low to no shade areas. The main fruiting time is March-April. [1] Table 1 below shows the description, chemical constituents and therapeutic applications.

Table 1: description, chemical constituents and therapeutic applications of plant parts of B. Simaruba

B. Simaruba plant parts	Description	Chemical constituent	Therapeutic applications	diagram
a) General description Height Spread Crown uniformity Crown shape Diameter of the trunk Density of the crown Rate of growth The tree textures	7.62m to 12.19m 7.62m to 12.19m Outline is irregular Round 20-80 cm. Open Middling Middling	Long-chain fatty acids (FA), Lignans, Terpenes, methyl esters of FA, flavonoids, sucrose, phenolic acids.	An effective topical cream can be made by using the raw material. The unprocessed plant matter is mixed with Aloe barbadensis miller, E vitamin and calendula (Calendula officinalis)or cortisone, to get the cream for topical application.[2]	
b) Leaves Arrangement of leaves Leaf type Leaflet margin Leaflet shape Leaflet venation Type of leaf and tenacity Length of blade in leaflet Leaf colour Fall colour Fall characteristic	Alternate Odd pinnately compound Entire Entire (elliptical) Ovate. Banchidodrome; pinnate Semievergreen leaflets 2 to 4 inches Green No fall colour change Not strikingly visible.	α pinene Myrcene β pinene	In traditional Yucatecan medicine to soothe the dermatitis caused by the resin of ***Metopiumhzunei*** Uacq.) Urban (Anacardiaceae) [3].	

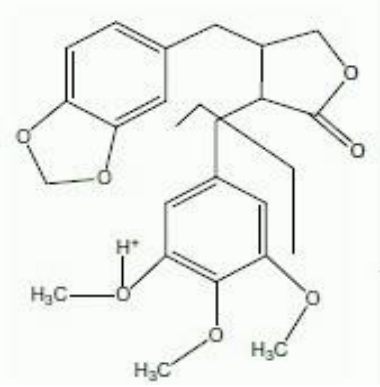
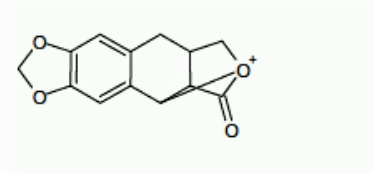
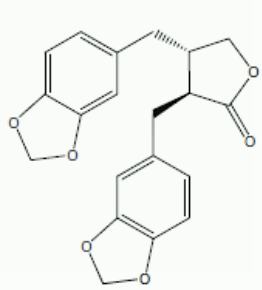
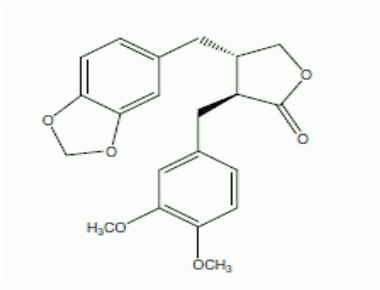
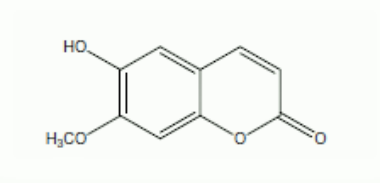
c)Flowers Colour Characteristics	Green Unobtrusive and not striking; flowering is observed in spring	Terpenes.	Inhibitory action against snake venom.	
d) Fruit Shape of the friut Fruit length Fruit covering Colour Characteristics of fruit	Oval 0.5 to 1 inch Fleshy Fruit Red Doesn't evoke the wildlife interest; not obtrusive. problem of littering is not sufficiently great.	Glaucarubinone Glaucarubalol, Glaucarubin	Is known to be used by Mayans for the treatment of snakebites, skin mycoses, fever, and diarrhoea, infections, endocrine system disorders, cellular tissue disorders, circulatory and various other disorders.	
e) Trunk and branches Bark Branch Pruning Trunk Trainability	On mechanical impact, easily harmed and are thin. Drooping can be observed as the tree develops. Needed for developing strong structure. Very showy. Trunk can be trained to be grown with many other trunks or it can be grown with a single trunk.	Isolimonene Viridiflorol β caryophyllene b-selinene	To treat sores, measles, rashes, insect bites, burns. When taken internally, by drinking the infusion of the bark like tea, it acts against UTI, pain, sun stroke, insect bites, measles.	 

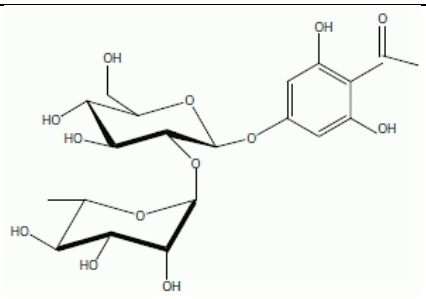
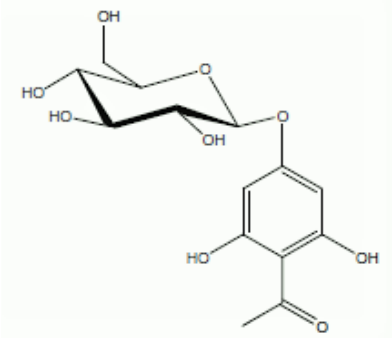
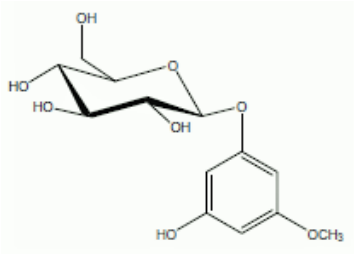
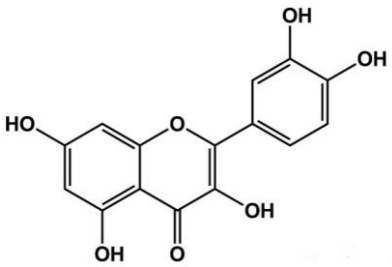
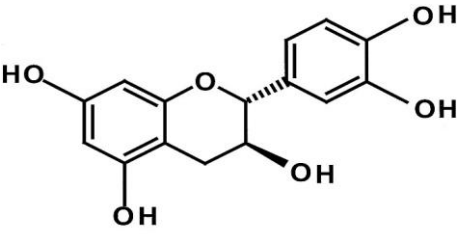
f) Root Liftability Invasive potential	Surface roots can lift sidewalks. Little	Amarolide Gimarolide Chaparrinone 2,12-didemethylquassin holacantone	In mayan culture, the roots, along with other parts of the plant is used for its anti-inflammatory, analgesic, antibacterial, and antifungal capabilities. [1][32]	
g) Resins	Fragrant	α pinene Germacrene D[33] α copaene	Diaphoretic Diuretic Purgative Vulnerary Against yellow fever	
h) Seeds	A single seed of 5-6mm diameter is enclosed inside a three-valved fruit, which is a capsule.	Glaucarubolone , Glaucarubalo[l] [34]	Known to inhibit cell proliferation.	

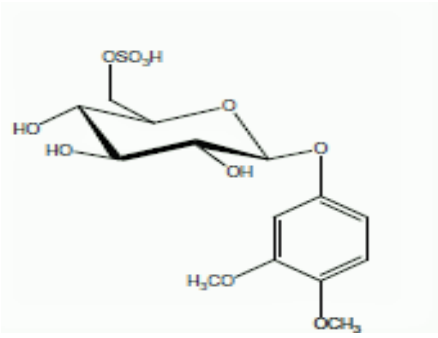
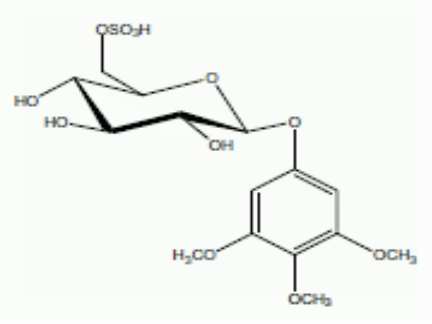
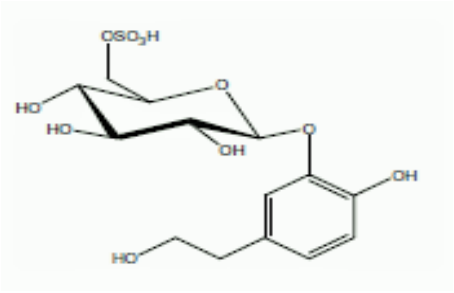
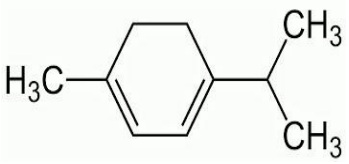
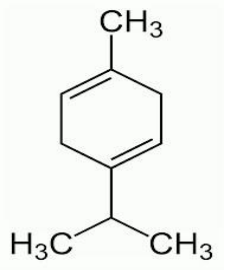
Chemical constituents

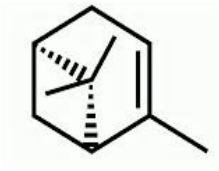
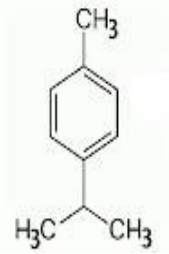
Phytochemicals present in B. Simaruba are known to show potent anti-cancer activity. It is necessary to isolate the particular chemical constituent responsible, in order to find the kinetic and dynamic properties as well as the mechanism of action of compound responsible for the activity in order to increase the therapeutic efficacy. The extraction from various parts of the plant is done by initially thoroughly air drying the plant part, then grinding it to a fine powder and then extracting it with a suitable solvent like hexane, ethanol etc., by percolation or any other suitable method according to specifications. Following extraction, evaporation of the solvent is done and the extract is dissolved in a suitable vehicle for further analysis[6] In a study, of the of B. Simaruba extracts obtained with methanol or hexane and the parts of the plant used for extraction being branches, bark and leaves proved the existence of 17 compounds. The methanol extract evaluation also showed an additional anti-radical activity [50]. The bark also contains lignans and some natural compounds. Essential oils can be found in leaves, flowers and fruits of the plant. Flowers also contains terpenes.[51] Table 2 below shows the various chemical phytoconstituents and their structures[38;52–58][59].

Table 2: compound name and structure of phytoconstituents present in B. Simaruba

Name of the compound	Structure
a) Phenolic components:	
• Yatein	
• β-peltatin-O-β-D-glucopyranoside	
• Hinokinin	
• Bursehernin	
• Scopoletin	

• Floroacetophenon-4-neohesperidoside	
• 4-acetil-3,5-dihydrossifenil-β-D-glucopyranoside	
• Picraquassioside D	
b) Flavonoids:	
• Quercertin	
• (+)-catechin	

c) Natural compounds:	
• 3,4-dimethoxyphenyl-1-O-b-D-(6-sulpho)-glucopyranoside	
• 3,4,5-trimetoxyphenyl 1-O-b-D-(6-sulpho)-glucopyranoside	
• 3,4-diidroxyphenylethanol-1-O-b-D-(6-sulpho)-glucopyranoside	
d) Essential oil components:	
• α-terpinene	
• γ-terpinene	

• α-pinene	
• *p*-cymene	

Studies showing indications of anti-cancer, anti-inflammatory, anti-snake venom, anti-hypertensive, anti-allergic and antioxidant activities of B. Simaruba

Anti-cancer activity of B. Simaruba

It is established through many in vitro studies, that B. Simaruba contains phytochemicals that show potential anti-cancer activity. In 1992 picropolygamain was isolated, which indicated its activity in the assay of brine shrimp. On further evaluation with the use of 3 human tumour cell lines of breast, colon and lung and (MCF-7, HT-29 and A-549 respectively) in vitro, it could be concluded this compound shows cytotoxicity analogous to that of Adriamycin[8]. [20] In a research conducted by Muriel Sylvestre and co-workers., their research, which included the cancerous cell lines of the lungs and colon (A-549, DLD-1 respectively) for the study of the anticancer activity of the essential oil. *B. simaruba* leaf essential oil used against both cancerous cell lines gave desirable results according to the study conclusions. The possible phytochemical constituent responsible for this action could be α-humulene[37][61]. In another research which aimed to determine the inhibitory and cytotoxicity studies against various tumour cell lines of breast, cervix, mammary gland, skin, tongue, epithelium and epithelium squamous tissue suggested that methyl extract of B. Simaruba, among 16 other species showed excellent inhibition, IC50/CC50 values, and MIC values for breast and cervical cancer cell lines. Some of the phytochemicals extracted which show the in vitro anti-cancer activity can be seen in the table 3 below. [62]

Table 3: The anticancer activity studies of *B. Simaruba* crude extracts and the isolated phytochemicals.

Name of the study	Compound/ extract name	Cell lines	IC50/ ED50/ Potency/ zone of inhibition	References
In-vivo hollow fibre assay studies	picropolygamain	Breast, colon, lung (MCF-7, HT-29, A-549 Respectively)	1.1µg/ml	Maria Carla Marcotullio et al., 2018.
Evaluation of cytotoxic properties of essential oils from leaf extract	α-humulene	Carcinoma seen of human lung(A-549) and adenocarcinoma of human colon, (DLD-1).	for A-549, 42 ± 2 µg/mL andforDLD-1, 48 ± 2 µg/mL	Muriel Sylvestre et al., 2007.
To check IC50 and CC50.	Methanol extract	a) Adenocarcinoma of mammary gland, b) adenocarcinoma of cervix epithelium and c) breast [a) ATCC, Manassas, VA and HeLa (ATCCCCL-2); b)ATCC; c) (ATCC HTB-22) respectively]	96±2 (percentage inhibition) IC_{50}– 75 CC_{50}- >800	Rex G. Cates et al., 2014

Anti-inflammatory activity of B. simaruba

In a research [2]which considered hexane extract acquired from the leaves of B. Simaruba, with the intension of finding its effect towards inflammation, it was observed that against a paw oedema inflammation due to induced carrageenan in rats, the active ingredients from the extract showed strong anti-inflammatory activity[63][64].

In another similar research,[6] the result obtained is in accordance with the results obtained in prior research on the same., but in this research they were able to identify more phytoconstituents responsible for inhibitory action towards inflammation, which is represented in Table 4.

Table 4: The anti-inflammatory activity *B. Simaruba* crude extracts and the isolated phytochemicals.

Intention of the study	Extract used	Compound(s) accountable for anti-inflammatory activity	used route of administration	References
To find the anti-inflammatory effects of fractions and compounds of B. Simaruba	Leaf- hexane extract	methyl-β-peltatin A	Oral	B. Noguera et al., 2004
Bioassay of the *Bursera simaruba*(L.) Sarg. leaves to discover the constituents which shows action against inflammation.	Leaf- hexane extract	a) α-amyrin b) 24*S*-stigmast-5-en-3β-ol c) 4*S*-stigmast-5,22*E*-dien-3β-ol d) ergost-5-en-3β-ol e)3-methylene-7,11,15-trimethylhexadec-1-ene (neophytadiene)	Oral	M.E. Carretero et al., 2007
To find topical anti-inflammatory activity.	Bark hexane and chloroform extract	It has been hypothesized that Triterpenes, Steroids, Lignans could be responsible.	Topical	Sosa et al., 2002.[35]

simaruba as anti-snake venom medication

In the whole world, only seven percent of all species of snakes are venomous in nature. From various reviews about traditional treatments for snakebites, it is known that an approximate number of six hundred different species of plants belonging to more than one hundred families are used as antidotes against snake venom all over the world. In central America, simaruba is used as anti-snake venom medication. It is traditionally known among the people of Nicaragua to treat the side effects caused by snake bite. Plant material used for this purpose is bark and whole plant. A decoction is made from either the bark or the whole plant and given orally. A project which interviewed over 140 subjects, who were traditional practitioners at Belize, revealed that the B. Simaruba tree has over sixteen traditional uses, snakebite therapy being a most significant use[67] [68] The presence of terpenes, especially α-pinene is known to show a better inhibitory action against the enzymes present in the snake venom.[69][70]

Anti-hypertensive activity of simaruba

In an original research conducted by Gil Alfonso Magos-Guerrero et al,[71] on various medicinal plants native to Mexico which are used for traditional medicine, they got some interesting findings, them being: B. simaruba extract showed a cardiovascular profile categorised by chronotropic effects which are negative and hypotension which lasts long-term induced by single administration orally, and also showed the property of vasodilation that could potentially be protectant to endothelium[72–81].

For fever, allergies and itching

The bark and leaves of B. Simaruba are chopped and mixed with a mixture of equal amounts of rubbing alcohol and water or just water and is applied on the forehead. The young bark and leaves of B. Simaruba are macerated and is placed on the affected area.[47]

Antioxidant activity of B. simaruba

In an original research conducted by Moustapha BAH et al., it was established that B. Simaruba shows anti-oxidant properties, though the exact molecule responsible for the anti-oxidant activity is yet to be determined.[82] [83;84]

Regulatory aspects of use and formulation of Traditional alternative medicines and their legal status

Modern medicine is being developed in an exceptional pace all around the globe, but in developing countries like India, a large number of traditional medicines are still in use. In past few years, the trend in medicine world has changed considerably and herbal medicines and alternative medicines are considered as a new booming field of interest. The use of medicinal plants as drugs has been increased, but adequate research ensuring the safety and effectiveness of such drugs is not always being performed at the same pace of increasing demands. Therefore, it is necessary to conduct the research on the same and to establish the standard regulatory requirements for the usage of the herbal medicines.[85]

India:

In India, Ayurveda is in existence since long ago. The quantification of market for traditional drugs in India is a hard task as every traditional practitioner indulges in creating his/her own formulation and dispenses the same.

India is dominated by various patented and proprietary Ayurvedic products. [86] They are retailed over the counter. Even today, many people in India opt for this complimentary system of medicine for minor difficulties like diarrhoea, cough, cold and even some minor stomach problems. Ayurveda, with the empirical support from the modern medical science can become a good innovative research field to establish the safety and efficacy which could help establishing it on global level for optimised utilization of this complementary system of medicine.

Legal significance:

In the country of India, traditional medications come under the Drugs and Cosmetics Act, 1940 (D and C act, 1940). This act is about the regulation of importation, manufacture, circulation and retailing of drugs. According to this act, no drug from traditional (alternative) systems is allowed to be developed devoid of licence from State Drug Control Authorities. It is amended that all the patented and non-patented drug formulations prepared from herbal source should contain the source listen in official standard books of above systems. In order to coordinate pharmacopoeias for all the differen t traditional schemes, numerous co-
mmittees have been set up. The guidelines for safety and efficacy of herbal drugs with the intention of incorporating the same to D and C act was established in 1993 with the help of an expert committee appointed by the government of India. "Herbal drugs" are defined as the products in which a large number of active constituents in them are derived from a plant. The organization for herbal drugs is based on their availability in market and the herbal nature, which is as follows:

Group1: now in use for> five years

Group 2: in usage for < five years

Group 3: novel medicines.

The requirement for submission of data from clinical trials and toxicity studies depends on the market availability, nature of herbs and the chances of the plant potentially being poisonous. [87]

North America:

Canada:

In Canada, regulations for drugs of herbal origin is set, meaning there are distinct requirements for labelling, indications etc., which should be in accordance with Food and Drugs Act and Regulations. The Information Letter, which was issued by the Canadian Health Protection Branch in 87 specified the herbal drugs that should contain cautionary label, if it is potentially hazardous. [85] The formulations can be sold as drugs, cosmetics or foods by their specific properties. A specific identification number called Drug Identification number (DIN) is allotted for herbal formulations after their approval by providing necessary verified traditional uses, toxicological studies etc. [88]

The United states of America:

In the USA, the use of medicines from herbal source is less popular as the distribution of the same is limited to only health food stores and the pharmacists are not trained with the use of herbs intended for medicine.

Legal significance:

In the USA; the Food, Drug and Cosmetic Act was introduced in the late 1930s, the Food and Drug Administration (FDA) deals with the regulation of any produces that declare to alleviate, treat, avert or cure any disease. Hence, the medicinal drugs should follow the same procedures as any chemical drugs for their allowance. In the USA, most of the natural products are controlled as foods or additives used in foods, even when they are being used as traditional medicines. If the herb is considered as "generally recognised as safe" (GRAS), it means that the product is free from misbranding and adulteration. Some herbs are also listed as "over the counter" by the FDA. [89–91]

Central America:

Nicaragua:

In 91, nursing schools in the country made efforts to study traditional herbal medicines, by developing basic academic materials about both popular and traditional medicine and introducing the same in schools. The Ministry of Health has included herbal products in the basic list of medicines that are to be made available in local health systems via community pharmacies. This is considered a significant step towards incorporating older forms of pharmaceutical products into Nicaragua's national health care system. [92]

South America:

Columbia:

The legal requirements for natural products and pharmaceutical formulations was issued by the Ministry of Health in July 1990. According to this, products with therapeutic uses are considered as medicines, herbal tea as food. A detailed requirement for the cultivation, collection, drying etc., of such medicinal plants has been given. A special license is required for manufacturing herbal medicines and such pharmaceutical preparations needs to be registered. The documents like process of manufacture, quality controls and in some cases, studies for toxicity, monographs, traditional use, adverse effects, dose, contra indications and bibliography are to be submitted. For a medicinal plant product, a certification that the plant is incorporated in the official list is needed. This registration is valid only for 10 years and is renewable. [85] [93-94]

Eastern Mediterranean:

Oman:

In 1995, a few general rules that are delimited by guidelines for import and use of traditional drugs were issued. Some of these requirements are:

- a certificate for free sale issued by the country of applicant and a certificate ensuring GMP is needed.
- label which includes active components, composition in terms of quantity, route of administration, manufacturing date and expiry date, number of the badge, and conditions for storage.
- the producer should present a scientific report proving the origin of each and ingredients, their effects pharmacologically and uses therapeutically, side effects, adverse reactions, precautions to be taken, effects of overdose and antidotes, and a list of countries where the product is being sold;
- an assurance proving that the product is free from corticosteroids and sex hormones, or impurities such as parts of any insect or other products. [85]

Europe:

The European Community has established an all-inclusive legislative grid to ease the movement of persons, capital, services and goods in the Community. Pharmaceutical products need an approval prior to marketing in the European market, which is in accordance Directives 65/65/EEC and 75/318/EEC. In Directive 91/507/EEC, the quality, safety and effectiveness documentations, along with the dossier, the expert reports and their specifications are pre-arranged. Article 39 paragraph 2 of

Directive 75/319/EEC postulates that all Member States shall inspect all goods on the market at the given time, with a time limit of 12 years, to decide if they meet the criteria of those directives.
Countries have adopted various approaches in phytomedi cine analysis. [85] [97- 106]

Stability studies of herbal medications:

Stability studies for herbal medicines is of prime importance as the whole plant is considered pharmacologically active. The main reason for the evaluation is to establish a safe storage period for the given herbal drug.[93]

Shelf-life determination:

Determining the shelf life is similar to chemical active pharmaceutical ingredients except for the fact that any unique nature of the herb is considered. A deviation of ±5% from the initial assay is agreeable. This can be extended beyond ±10% given there is agreeable reason. Variations like climate, harvesting conditions are to be taken into consideration, due to which a limit of ±10% is made acceptable for finished drug product. [93]

Stress testing:

This is to establish a pathway of degradation to the product under investigation. For drugs of herbal origin, accelerated and intermittent studies are not mandatory as the formulation is bound to fail beyond thirty-five degrees Celsius. Usually, the stability testing for herbal products is carried out at a temperature of twenty-five degrees Celsius, and the time point of three months is ignored meaning the test is carried out at half-yearly basis. [93]

5.3 Batches selection:

Batch selection is important as long-term testing requires drug substance, minimum 2 batches and product of the drug, 3 batches. This is almost impossible as different batches contain the herbs harvested at different time intervals, thus posing a potential biological variation.[94]

CONCLUSION AND FUTURE PROSPECTIVE

This review article is an overview of the botanical, chemical and pharmacological aspects of the plant Bursera Simaruba. WHO reported so far plant and their products are used for primary health care, 80% of people worldwide focus on herbal medicine? B. Simaruba plant extract obtained from methanol shows potential *in vitro* anti-cancer activity against tumour cell lines of lung, breast, and colon cancer and the leaf hexane extract of B. Simaruba has some phytochemicals which shows potential anti-inflammatory activity through oral and topical route of administration. It is a well- known anti-snake venom medicine in traditional treatment methods. Future research should therefore concentrate on the elaborate study of the phyto- constituents present in herbs to enhance safety and effectiveness in vaious pharmaceutical formulations.

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