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TUMBURU (*ZANTHOXYLUM ARMATUM* DC.) AS A POTENTIAL NATURAL REMEDY FOR TOBACCO CHEWING ADDICTION: A PHYTOPHARMACOLOGICAL PERSPECTIVE

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ABSTRACT

Tobacco addiction remains one of the leading global health challenges worldwide, responsible for over 8 million deaths annually. Chewing tobacco is a deeply entrenched habit affecting worldwide more than 300 million people with particularly high prevalence in south asia and southeast-asia. Despite the extensive awareness campaigns and the well documented health risks, the addictive nature of nicotine creates a formidable barrier to quitting. Unlike smoking, smokeless tobacco delivers nicotine and an array of carcinogens directly to the oral mucosa, triggering leukoplakia, periodontal disease and ultimately oral cancers. Tobacco addiction is primarily driven by nicotine, a psychoactive substance that creates physical and psychological dependence which makes it difficult for the person to break free from the insatiable cravings. Tobacco has become a coping mechanism for a person's anxiety and stress. The long-term use of smokeless tobacco results in addiction which further on poses health hazards on an individual. From the origin in the America to the global spread, there is no such safe level of exposure to tobacco. The modern-day challenges of health regulations continue to evolve as the society balances

between the interests of public health, economic considerations and freedom of an individual. This article reviews the scientifically validate data of *Zanthoxylum armatum* that can provide an acceptable aid for tobacco chewing cessation. This review examines the mechanisms and phytopharmacology of *Tumburu* that helps an individual in quitting tobacco for not only for the physical health but also for mental and social well-being. It reviews *Zanthoxylum armatum's* traditional ethnobotanical knowledge, phytochemical profile and preclinical research outcomes. It also provides valuable insights for individuals to learn about the health risks associated with chewing tobacco that can reinforce the decision to quit addiction. The efforts to combat tobacco-free life is essential to decrease the long-term harmful effects and to make healthy choices in life.

KEYWORDS: Tobacco, addiction, *Ayurveda*, *Zanthoxylum armatum*, *Tumburu*, nicotine.

INTRODUCTION

The World Health Organization (WHO) classifies tobacco addiction as a chronic condition driven by nicotine dependence, which creates a complex cycle of physical and psychological dependence. It is a global health hazard prevailing all over the world accounting for over 8 million deaths annually.[1] The journey to quitting tobacco remains difficult for individuals fighting against the relentless grip of nicotine. Around 80% of the 1.3 billion tobacco users reside in low- and middle-income nations, which aggravates a nation's economy and health problems. In 2020, 22.3% of the global population consumed tobacco of which 36.7% were men and 7.8% were women.[1] On an average, tobacco users lose almost 15 years from their life expectancy.[2] India is termed as the second largest tobacco producing nation[3] and the second largest consumer of tobacco worldwide.[1] Smokeless tobacco products like *Khaini*, *Gutka*, *Jarda*, *pan masala* etc., contributes to this major problem as they are easily available at a very low price in India. Tobacco, being one of the *Sthavara Vanaspatika visha* when accumulated into the body over for a long period of time even in low doses causes harm when the concentration in different tissues reaches high level due to their cumulative effect and acts as a *dushi visha* (slow poison) in the body.[4] Ayurvedic terminology as *Vyasana*, *mada*, *madakari* etc.[5] can be associated with the term addiction. *Vyasana* which refers to an attachment towards indulging in desires, delusions or illusions often tied with the consumption of substances. It signifies a strong inclination towards satisfaction for particular things. The word *Mada* typically refers to as intoxication and *madakari* can be termed as substances which intoxicates. According to the GATS 2 (Global adult tobacco survey second)

which was carried out during August 2016 - February 2017 revealed that 28.6% (266.8 million) of adults in India aged 15 and above, use tobacco in some form or another. About 24.9% adults (232.4 million) are daily users and 3.7% (34.4 million) are occasional users of which 42.4% are men and 14.2% are women. Every tenth adult in India (10.7%) currently smokes tobacco, every fifth adult (21.4%) in India uses smokeless tobacco and about 3.2 crore adults use both the forms of tobacco. Among these, the use of smokeless tobacco was seen in 29.6% men and 12.8% women.[6] Commercially, *Nicotiana tabacum* and *N. rustica* are the two commonly cultivated species in India out of the 79 Nicotiana species found worldwide.[7]

THE CYCLE OF TOBACCO ADDICTION

Addiction refers to a condition that arises from the repetitive administration of a drug on a periodic or continuous basis[8] due to psychological or physical dependence. It is characterized by the consumption of drug or substance at dose levels and under circumstances significantly increase the potential for harm, regardless of whether it is intended for therapeutic, pleasurable or physician-prescribed purposes. The primary addictive alkaloid in tobacco is nicotine which causes the brain's mesolimbic reward system to stimulate and release dopamine. This reinforces the cycle of dependency by producing a sense of pleasure and relaxation in the body. With continued use, individuals develop a tolerance to nicotine, needing larger amounts to experience the same effects. Withdrawal symptoms further entrench the habit, making quitting challenging. Nicotine is a cardiac poison which is cardiotoxin in nature and affects mainly the mechanism of heart. Alkaloid nicotine is present in all the parts of the plant (especially in its leaves). It first stimulates & then represses the vagal and autonomic ganglia and then the cerebral and spinal centres. Nicotine addiction involves the brain's nerve cells and neurotransmitters like acetylcholine. Nicotinic receptors are activated by nicotine and activates the nicotinic acetylcholine receptors (nAChRs) in the central nervous system leading to increased activity which then can affect the mood, appetite, memory, learning etc. Later on, it affects the normal functioning of the CNS. The addiction is therefore brought on by this reliance on nicotine for regular functioning. It stimulates the release of dopamine; a neurotransmitter linked to feelings of pleasure and makes an individual feel good.[9]

Chewing tobacco contains nicotine, carcinogens (Tobacco-specific nitrosamines, Polycyclic Aromatic Hydrocarbons) and other harmful substances (mostly heavy metals as cadmium,

uranium and polonium) that impacts the different systems of the body.[10] Nicotine gets absorbed directly through the mucous membranes of the mouth, entering the bloodstream which leads to the activation of nicotinic acetylcholine receptors and stimulating the dopamine release and causing a pleasurable sensation. As the time passes, this creates dependence and addiction which are characterized by cravings and withdrawal symptoms when nicotine level drops. Chewing tobacco contains about more than 28 cancer causing agents including benzopyrene.[11] Another species, *Nicotiana rustica* commonly referred to as Aztec tobacco contains significantly higher nicotine levels, with its leaves holding up to 9% compared to the 1-3% found in *N. tabacum*. Tamil Nadu, West Bengal, Bihar, Assam and Uttar Pradesh are the primary growing regions for chewing and snuff tobacco, according to ICAR-CTRI (Central Tobacco Research Institute). Since *N. rustica* requires cooler climate, its cultivation is confined mainly to the northern and north-eastern areas of the country, i.e., U.P., West Bengal, Bihar and Assam.[12,13] Tobacco leaf comprises of alkaloids mainly Nicotine, Nornicotine, Anatabine, Anabasine, Cotinine, Myosmine. The potent one is the nicotine. Nicotine absorption generally occurs through the oral cavity which then gets in contact with other internal organs.[14]

HARMFUL EFFECTS

In *Ayurveda*, tobacco is first described by the name *Tamakhu*[15] by *Aacharya Yogratnakara* in the 17th century. Its synonyms being *Tamraparna, Tambaku.*[15,16] etc. It has been classified under the category of *Visha* (poison) i.e. cardiac poison due to its highly toxic nature and addictive properties which disrupts the balance of the *Tridoshas* (*Vata*, *Pitta* and *Kapha*) and leads to various diseases. Some of the *ayurvedic* texts as *Yogratnakar* have mentioned the harmful effects of *Tamakhu* as *Madapittabhramakaram* (causing *Mada, Pitta* and *Bhrama*), *Drishtimandhyakaram* (which diminishes eyesight) and if taken in smoked form causes cardiac debility and male infertility (*Hridishukrahrit*).[15] *Shaligram Nighantu* has mentioned it to be *Madak, Bhramak* and *Dhrishtimadhyakar.*[16] One of the chewing tobacco related mortalities in India is the high incidence of oral cancers. Due to the continuous use of smokeless tobacco products, it can lead to amblyopia, pre-cancerous lesions and other oral mucosal lesions such as leucoplakia, erythroplakia, verrucous hyperplasia, oral submucous fibrosis, Inflammation of buccal and gingival mucosa and dental decay and caries. Other adverse health consequences can be esophageal cancer, lung cancer, pancreatic cancer, cervical cancer, hypertension, heart disease, stroke, diabetes, insulin resistance, gestational

age/pre-term birth, fetal growth restriction, congenital defects, erectile dysfunction, infertility, inflammatory bowel disease, macular degeneration etc.[17,18]

CESSATION MEASURES

Most approved treatments for tobacco addicts work by manipulating and targeting nicotinic receptors to regulate nicotine intake. However, the effectiveness of these receptor-based therapies remains limited, indicating a clear need for better options. Current cessation strategies as nicotine replacement therapies (gum, patch), varenicline, bupropion, behavioral counseling show modest success. Nicotine gum reduces cravings but still propagates habitual chewing, while pharmacotherapies can carry side effects, cost barriers and social stigma of negative perception, shame and isolation. Relapse rates remain high as quitters resume chewing. Clearly, novel research and treatment are needed to address both the biochemical grip of nicotine and the compulsive habit of chewing. To advance the development of more effective anti-addiction therapies, a deeper understanding of the neural mechanisms involved in nicotine addiction is critical. In this regard, the herb *Tumburu*, commonly known as Zanthoxylum armatum, has emerged as a natural remedy aimed at addressing the habit of chewing and supporting its cessation to enhance overall health outcomes.

Zanthoxylum armatum commonly called as *Tejovati* (toothache tree) and the fruit known to be as *Tumburu* belongs to the Rutaceae family. The thorny shrub is traditionally used in *Ayurveda*, Tibetan and *Nepali* medicine as its various parts particularly the fruit pericarp, seeds, bark and leaves are utilized for their therapeutic significance and helps in the vitiation of Vata and Kapha doshas. Its pungent pericarps, containing alkylamides are known to produce a tingling, numbing effect (a kind of local anesthesia) when kept in mouth or chewed. Alkylamides extracted from the fruit cause a strong tingling sensation in the mouth.[19] To investigate the peripheral mechanism behind this effect, a study was carried out in which extracellular nerve activity was recorded from the lingual nerve of rats. The primary pungent compound, hydroxy-α-sanshool (HO-α-S), altered the levels of spontaneous activity in cool-sensitive fibers as well as inducing activity in tactile fibers, cold nociceptors and silent fibers that were insensitive to innocuous thermal or tactile stimuli.[19] This analyses that Zanthoxylum alkylamides cause tingling and anesthetic effects in sensory neurons. The tingling and numbing effects of alkylamides may help reduce the urge to chew tobacco and sensory reinforcement associated with chewing tobacco. By modulating sensory neuron activity, they could serve as a natural substitute to cravings. Thus, it could act as a natural

sensory substitute, supporting tobacco cessation efforts through both physical and neurochemical pathways.

BOTANICAL PROFILE AND DISTRIBUTION

Zanthoxylum armatum DC. is a thorny shrub or small tree up to 5 m tall, native to the Himalayan foothills (India, Nepal, Bhutan) and parts of southwestern China. Leaves are pinnate, bearing 7–15 lanceolate, spiny-edged leaflets; flowers are yellow-green, arranged in clusters; fruits are reddish aromatic fruits containing black seeds enveloped by an aromatic pericarp. Bark of the plant is known as *Tejovati* and fruits are known as *Tumburu*.[20] Fruit is sub globose, ovoid and red in colour. Fruit appears like black pepper and their mouth is cracked showing black seeds inside. It is mainly found in the valleys of the Himalayas at an altitude of 1000 to 2100 m. In the Khasi Hills at elevations ranging from 600 to 1800 meters and in the hill ranges of peninsular India. In Ayurveda, the dried fruit pericarp (*Tumburu phal*) is classified as dry, pungent, *Ushna* and *Laghu* with *Kapha* - *Vata shamak* properties. Practitioners recommend chewing the pericarp for treating toothache, sore throat, oral care and halitosis. Its bark decoction is used for rheumatism and circulatory disorders.

Figure: *Zanthoxylum armatum* fruit (*Tumburu*).

VERNACULAR NAMES

English name - Prickly Ash

Ayurvedic name - *Tejovati, Tumburu* (fruit)

Hindi name - *Tejphal, Nepali dhaniya*

Oriya name – *Tundopoda*

Bengali name - *Gaira, Tambul*

Manipuri - *Mukthrubi*

Nepali name - *Timur, Nepali* pepper

BOTANICAL NAME

Zanthoxylum aramatum D.C

Zanthoxylum alatum Roxb.

FAMILY – Rutaceae

RASA PANCHAK

- ***Rasa*** *– Katu, Tikta, Madhura (Raj Nighantu)*
- ***Guna****– Laghu, Tikshna, Ruksha, Vidahi*
- ***Virya*** *– Ushna*
- ***Vipaka*** *– Katu*
- ***Doshakarma*** *– Kapha - Vata Shamak*

Part used – Fruit (2-3 gm) and stem bark (10-20 gm) (API – VOL. 2, VOL. 4).[21]

Flowering – March – May, **Fruiting** - July - October

In Ayurvedic texts, *Tumburu* is said to be ***Hridhya***, *Dantashodhak, Mukhavairasyahara*, ***Hridya-dhourbalyahar*** and indicated in *Mukha roga's*. It has been indicated in different *Samhita's* and *Nighantu's*. The indications are given in the table I and II –

Table I: Indications In *Samhita's.*

S.NO.	*SAMHITA*	REFERENCES	INDICATIONS
1.	*Charak Samhita*[22]	*Phal varga, Sutrasthana* 2/3, *Vimansthana* 8/142,143, *Chikitsa sthana* 8/137,26/188,26/195, *Siddhi sthana* 9/18	***Shirovirechana dravya****, Katu skanda, Tikta skanda In* ***shirashula****,* ***mukhavairasya****,* ***mukha roga****,* ***danta roga****,* ***apatantraka***
2.	*Sushruta Samhita*[23]	*Chikitsa sthana* 5/21,24/8	***Apatantraka, dantashodhana***
3.	*Ashtang Hridya*[24]	*Chikitsa sthana* 14/17,21/36, 21/59 *Uttar tantra* 22/99	***Apasmara, hridya roga****,* ***vatavyadhi, muka danta vikaar***

4.	*Ashtang Samgraha*[25]	*Sutrasthana* 18/23	*Katu skanda*
5.	*Bhela Samhita*[26]	*Hinguwadi yoga*	***Apatantraka, hridyaroga***

Table II: INDICATIONS IN NIGHANTU'S.

S.NO.	*NIGHANTU*	*RASA*	*GUNA*	*VARGA/* REFERENCES	INDICATIONS
1.	*Bhavprakash Nighantu*[27]	*Katu, Tikta*	*Laghu, ruksha, Tikshna, vidahi*	*Haritakyadivarga Shloka num.- 114,115 (Pg.no. - 56,57)*	***Netra roga, shiroroga**, guruta, pliharoga, **danta shool***
2.	*Dhanvantari Nighantu*	*Katu*	*Tikshna*	*Shatpushpadivarga Shloka num.- 42,43 (pg.no. - 77)*	***Apatantraka, udar roga, Agni deepak, shoolhar***
3.	*Kaiyadev Nighantu*[28]	*Katu, Tikta*	*Ruksha, Tikshna, Laghu*	*Aushadhivarga Shloka num.- 1374,1375 (pg. no. – 255)*	***Hridya, apatantraka, netra roga, shiro ruja, pleeha roga, udar roga***
4.	*Raj Nighantu*	***Madhura**, Katu, Tikta*	-	*Amraadivarga Shloka num. – 185 (pg. no. – 378)*	***Jatragni pradipta***
5.	*Priya Nighantu*	*Katu*	*Tikshna*	*Haritakyadivarga Shloka num. – 57 (pg. no. - 15)*	***Mukha roga, Lalasravi***
6.	*Nighantu Adarsha*	*Katu, Tikta*	*Tikshna*	*Beejpurkadivarga Pg. no. – 245 – 247*	***Shirovirechana***
7.	*Shaligram Nighantu*	*Madhur, Katu, Tikta*	*Laghu, ruksha, Tikshna, vidahi*	*Haritakyadivarga Page no. – 118-119*	***Deepana, netra roga, shiro roga**, guruta*
8.	*Guna Ratnamala*	*Katu, Tikta*	*Ruksha, laghu, Tikshna, vidahi*	*Haritakyadivarga Page no. – 52,53*	***Hridya**, **netra roga**, **shiro ruja**, pleeha vridhi*
9.	*Dravyaguna-priyavrat sharma*	*Katu, Tikta*	*Laghu, ruksha, Tikshna*	*Pg. no. - 327- 329*	***Dantashodhan, Deepan-pachan**, Yakritudtejaka, **Hridyotejaka**, **Mukha danta roga, Vatavyadhi, Apatantraka, Hridya dhourbalyahar***

PHARMACOLOGICAL & RESEARCH FINDINGS

The pharmacological and research findings highlight the documented biological activities and therapeutic potential based on experimental studies. These findings are derived from in-vitro, in-vivo and clinical research, showcasing actions such as antioxidant, anti-inflammatory, anxiolytic and neuroprotective effects. Active phytochemicals like alkaloids, flavonoids, terpenes or alkylamides are often identified as responsible for these effects with mechanisms

involving modulation of enzymes, receptors or signaling pathways. Such studies also help establish effective dose ranges, compare efficacy with standard drugs and provide a scientific basis for traditional medicinal uses. In this perspective, *Zanthoxylum armatum's* essential oils and alkaloids exhibit anxiolytic, anti-inflammatory, antioxidant and neuroprotective activities supported by pharmacological studies showing analgesic, anti-inflammatory and neuroprotective effects. These combined properties position Z. armatum as a multi-target potential phytomedicine to both alleviate withdrawal and substitute the habit of chewing without nicotine.

1. NEUROCOGNITIVE EFFECTS IN HUMANS[29]

A study investigated the effects of Zanthoxylum armatum (ZA) lipid extract on cognitive function, mood and cerebral blood flow in 82 healthy adults both male and female aged 30-55 yrs., using a double-blind, randomized, placebo-controlled design. In the trial, participants received either a single dose or 56 days of ZA lipid extract doses. On Day 1, acute improvements were observed in attention speed and visual processing tasks, although name-to-face recall accuracy declined. By Day 56, participants showed enhanced overall task performance speed, improved mental arithmetic (Serial 3s substractions) and reduced mental fatigue compared to the sunflower oil placebo. Near Infrared Spectroscopy (NIRS) revealed a reduced hemodynamic response in the prefrontal cortex during cognitive tasks, suggesting that ZA may enhance neural efficiency while improving cognitive performance.[29]

Nicotine users often report using tobacco to improve alertness and attention. The ZA study showed improved speed of attention and task performance, indicating that ZA could serve as a natural cognitive enhancer, potentially substituting nicotine's stimulating effects. Tobacco withdrawal commonly leads to irritability, mental fatigue and sadness/depression. ZA supplementation reduced mental fatigue and enhanced performance over time, suggesting a mood-supportive role during nicotine withdrawal. Reduced cerebral blood flow response with improved performance suggests greater neural efficiency, which might help restore normal brain function disrupted by chronic tobacco use.

2. NEUROPROTECTIVE & COGNITIVE EFFECTS IN ANIMAL MODEL[30]

The study evaluated the neuroprotective potential of *Zanthoxylum armatum* (ZA) extract against scopolamine-induced cognitive impairment, a model for memory loss. Ethanolic extracts of ZA fruits were prepared by cold maceration and bioactive compounds (β-sitosterol, stigmasterol and lupeol) were isolated and characterized. In silico docking showed

stigmasterol had the strongest binding affinity to acetylcholinesterase. Rats were administered the extract (100, 200, 400 mg/kg orally) prior to scopolamine to induce memory deficits. In-vivo testing in rats demonstrated that ZA extract significantly improved memory retention, reduced brain acetylcholinesterase activity and exhibited antioxidant properties. These findings suggest that ZA may enhance cognitive function through anticholinesterase and antioxidant mechanisms. The study identifies stigmasterol as a key acetylcholinesterase inhibiting phytochemical. By enhancing acetylcholine levels, it may help reduce nicotine cravings and support cognitive function during withdrawal. Its antioxidant effects can combat oxidative stress caused by tobacco use, while its neuroprotective action may aid in brain recovery. Together, these effects suggest ZA could serve as a natural supportive remedy during tobacco cessation.

3. ANTIOXIDANT & ANTIMICROBIAL ACTIVITY[31]

The study evaluated the antimicrobial and antioxidant properties of ZA fruit and seed extracts (methanolic, ethyl acetate and n-hexane) which were collected from three regions of Uttarakhand i.e. Bageshwar, Pithoragarh and Champawat district. Using the disc diffusion method, the extracts were tested against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *E. coli*. Fruit extracts, particularly methanolic ones, showed stronger antibacterial activity with *Staphylococcus aureus* being the most susceptible strain. Antioxidant activity, assessed through DPPH radical scavenging, was also highest in the methanolic extract. These findings suggest that Z. armatum possesses significant antibacterial and antioxidant potential, supporting its traditional use in treating infections and oxidative stress-related conditions.

Chronic tobacco chewing often leads to oral infections, gum diseases and oxidative stress in the oral cavity and body. The antibacterial activity against pathogens like *Staphylococcus aureus* suggests ZA could help prevent or treat oral and dental infections commonly seen in tobacco users. Additionally, its antioxidant properties may help reduce oxidative damage caused by prolonged tobacco exposure, supporting tissue repair and overall detoxification.

4. CYTOTOXICITY AND ANTITUMOR ACTIVITY[32,33]

The study was conducted to evaluate the acute toxicity, antipyretic, phytotoxic and cytotoxic activities of ethanolic and n-hexane extracts of ZA leaves and fruits. The extracts were found to be safe at doses up to 2000 mg/kg in animal models. Using Brewer's yeast-induced pyrexia in mice, both leaf (ZLE) and fruit (ZFE) ethanolic extracts showed significant antipyretic effects with the strongest fever reduction observed at the 3rd hour post-administration. The

fruit extracts exhibit slightly higher activities than leaf extracts. All extracts exhibited dose-dependent phytotoxic and cytotoxic potential, with maximum effectiveness at 1000 µg/ml.[32] The cytotoxic and phytotoxic properties suggest potential for anti-cancer activity, which is particularly relevant given the high risk of oral cancers in chronic tobacco chewers. Moreover, the plant's safety profile at high doses supports its use in longer-term herbal interventions. Together, these findings suggest that Z. armatum could aid in detoxification, reduce inflammation and possibly provide chemopreventive support.

A study investigated the essential oil (ZVO) of *Zanthoxylum armatum*, extracted by hydro-distillation and analyzed using GC-MS, which identified 34 compounds, with beta-linalool (53.05%) as the major constituent. ZVO exhibited strong antispasmodic activity by relaxing rabbit jejunum muscle contractions, both spontaneous and potassium chloride-induced. It also demonstrated antibacterial effects, particularly against M. luteus and B. subtilis, and showed concentration-dependent antifungal activity, with notable effects against M. canis, C. albicans, and C. glabrata. Additionally, ZVO showed cytotoxic and phytotoxic potential, indicating its broad-spectrum biological activity and therapeutic potential.[33] The essential oil (ZVO) rich in bioactive compounds like beta-linalool and D-limonene, may support tobacco chewing addiction management. Its antispasmodic activity could help relieve gastrointestinal discomfort and stress-related muscle tension often experienced during withdrawal. The antibacterial and antifungal properties may aid in preventing or treating oral infections, which are common in chronic tobacco chewers. Additionally, compounds like D-limonene and linalool are known for their anxiolytic and mood-stabilizing effects, which could help reduce cravings and ease withdrawal-related anxiety. Thus, ZVO may offer both physical and psychological support during tobacco cessation.

5. CARDIOVASCULAR ACTIVITY[34]

The study explored the gut, airway and cardiovascular effects of crude extract of *Zanthoxylum armatum* to validate its traditional medicinal use. The extract showed concentration-dependent relaxation of smooth muscles in isolated rabbit jejunum, trachea and aorta particularly against high potassium-induced contractions indicating a calcium channel-blocking (Ca++) antagonist effect, similar to the action of verapamil. The crude extract of *Zanthoxylum armatum* (ZA) was found to suppress castor oil-induced diarrhea in mice and lower both the strength and frequency of heart contractions in guinea pig atria. These findings suggest that ZA has significant spasmolytic, antidiarrheal, bronchodilatory and vasodilatory

effects through calcium channel blockade, supporting its traditional use in gastrointestinal, respiratory and cardiovascular conditions.[34]

Tobacco is a known cardiac poison causing increased blood pressure, heart rate, vascular constriction and long-term damage to the heart. The cardiovascular findings of ZA suggest it may help counteract these effects through its vasodilatory and calcium channel-blocking properties which reduce vascular resistance and lower blood pressure. Its cardio-suppressive effects, comparable to those of verapamil, help protect the heart from nicotine-induced stress by reducing heart rate and workload. Combined with its antioxidant activity, Z. armatum gives support to cardiovascular recovery and protection.

6. PHYTOCHEMICAL PROFILE[35-39]

Phytochemically, Z. armatum is rich in a wide range of bioactive constituents, including lignans, alkaloids, sterols, coumarins, phenolic compounds, terpenoids, flavonoids, benzenoids, glycosides, amino acids, fatty acids and monoterpenes like linalool and limonene. Other key compounds include methyl cinnamate, linalyl acetate, geraniol, citral and sabinene. These constituents contribute to its anxiolytic, anti-inflammatory, antioxidant and neuroactive effects.[35]

The constituents are extracted from different parts of the plant i.e. from seed, leaves, fruit, root and bark. It consists of different alkaloids, flavonoids, saponin, tannins, steroids, terpenes, glycosides, carbohydrates, phenolic, proteins, essential oil and amino acids. The bark is particularly rich in lignans such as sesamin, fargesin, eudesmin, epieudesmin, pulvatide and alkaloids like magnoflorine and xanthoplanine, as well as triterpenoids including β-amyrin and amyrenone. The fruits contain flavonoids (e.g., tambulin and tambulol), linalool, limonene and essential oils composed of citral, sabinene, linalyl acetate, geraniol and methyl cinnamate. The oil extract from leaf comprises of linalyl acetate, acids, phenols, limonene, citronellal and tricosane. The wood contains magnoflorine and xanthoplanine.[36]

The essential oil present in ZA can cross the blood-brain barrier, influencing central nervous system activity while its alkaloids exhibit prolonged neuroprotective effects. These bioactive compounds vary with altitude, harvest season and processing necessitating standardization to ensure therapeutic consistency. Linalool (72%), limonene (6.2%), beta-phellandrene (5.3%)

and methyl cinnamate (12.2%) are the major constituents present in *Tumburu* (fruit pericarp)[37]

LINALOOL[38]

A study was investigated in male mice to evaluate whether linalool (monoterpene) could modulate the rewarding effects of nicotine using the nicotine induced conditioned place preference (CPP) model. Nicotine (0.5 mg/kg, intraperitoneally) was administered during the conditioning phase, while linalool (12.5, 25 and 50 mg/kg, I.P.) was given 30 minutes prior to nicotine exposure to test its impact on acquisition, extinction and relapse (reinstatement). The results showed that the highest dose of linalool (50 mg/kg) significantly inhibited the acquisition of nicotine preference ($p < 0.01$), accelerated the extinction phase ($p < 0.05$) and reduced relapse behavior at both 25 and 50 mg/kg doses ($p < 0.05$ and $p < 0.01$, respectively).[38] Linalool's effects were comparable to varenicline, a standard nicotine cessation drug. These findings suggest that linalool can reduce the rewarding effects of nicotine and may serve as a promising natural adjuvant in treating nicotine addiction.

LIMONENE[39]

This study investigated the effects of D-limonene on rats subjected to chronic restraint stress over 21 days, focusing on its impact on behavior and neuroinflammation. Rats treated with D-limonene showed improvements in behavioral tests, including increased sucrose preference (indicating reduced anhedonia), reduced anxiety-like behavior, and improved memory recognition compared to the stressed group. Biochemically, D-limonene elevated BDNF (a brain protein that supports nerve health) levels and reduced pro-inflammatory markers like IL-1β and caspase-1 in the hippocampus, suggesting a neuroprotective effect. D-limonene's effects were similar to fluoxetine, suggesting it has antidepressant-like properties. Overall, D-limonene demonstrated antidepressant-like and anti-inflammatory properties, mitigating stress-induced behavioral and cognitive impairments.[39]

Tobacco often leads to stress, depression, anhedonia (loss of pleasure), anxiety and cognitive decline. In this study, D-limonene reversed stress-induced depressive behaviors, improved mood and memory and reduced neuroinflammation by lowering levels of IL-1β and caspase-1, while increasing BDNF. These effects indicates that D-limonene may offer natural support in managing and protecting brain function during cessation.

The pre-clinical studies above establish proof of concept for Z. armatum's multi-mechanistic anti-addiction potential. By converging on reward modulation, anxiety relief, neuroprotection and behavioral substitution, ZA offers a holistic anti-addiction approach which can significantly help to decrease the craving intensity and improve nicotine withdrawal symptoms as irritability, anxiety, concentration, depression, appetite etc.

DISCUSSION

Tobacco addiction particularly through smokeless forms continues to pose a major public health hazard. The addictive nicotine, the key alkaloid in tobacco is driven by its action on nicotinic acetylcholine receptors (nAChRs), triggering the mesolimbic dopamine reward pathway. Chronic exposure leads to neuroadaptive changes that reinforce psychological and physiological dependence alongwith withdrawal symptoms such as irritability, cravings and cognitive dysfunction. In this context, *Tumburu* emerges as the herbal alternative. *Tumburu* shows significant potential in managing tobacco chewing addiction through a combination of pharmacological actions demonstrated across multiple studies. Its essential oils, rich in linalool and D-limonene, exhibit antidepressant, anxiolytic and neuroprotective effects helping to reduce withdrawal symptoms such as anxiety, stress, cognitive decline and depression. Linalool has been shown to attenuate nicotine's rewarding effects, accelerate extinction of nicotine-associated behavior and prevent relapse indicating direct anti-addictive potential. Additionally, Z. armatum displays acetylcholinesterase inhibitory activity, enhancing cognitive function and compensating for nicotine's effects on the cholinergic system. Its antioxidant and anti-inflammatory properties help mitigate oxidative damage caused by chronic tobacco use, while its antimicrobial activity supports oral health, often compromised in tobacco chewers. Furthermore, the plant's cardioprotective and vasodilatory effects may counteract nicotine-induced cardiovascular stress. Together, these properties suggest that *Zanthoxylum armatum* could serve as a comprehensive natural remedy to support tobacco cessation by addressing both physiological damage and psychological dependence.

CONCLUSION

This integrative review highlights the therapeutic potential of *Zanthoxylum armatum* as a multitarget herbal remedy for tobacco chewing addiction. The diverse pharmacological profile of ZA positions it as a valuable phytomedicine to both reduce withdrawal symptoms and interrupt the psychological habit loop of tobacco use, particularly in resource-limited settings. By alleviating both the physical consequences and psychological withdrawal

symptoms associated with cessation, ZA offers a holistic approach that aligns with both traditional medicinal use and modern therapeutic needs. Further clinical research and formulation development could pave the way for its integration into evidence-based strategies for tobacco de-addiction.

ZA represents pharmacologically its neuroactive, anxiolytic, anti-inflammatory and oral anesthetic properties combined with traditional ethnomedicinal usage justify further exploration in human clinical trials. The plant's traditional use and scientific data positions it as a nootropic agent worthy of further pharmacological investigation. A nootropic agent (also called a cognitive enhancer or smart drug) is a substance that improves brain function, particularly in areas such as memory, attention and learning. Future researches should focus on standardized extract protocols and more clinical trials targeting addictions specifically.

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