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Phytochemistry, Traditional Use and Medicinal Potential of *Zanthoxylum Simulans*

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Abstract
Zanthoxylum simulans (Rutaceae) is a potent medical and edible plant due to its aroma, therapeutic and nutrient content (Liu et al., 2020). It is found in East Asia particularly China and has traditionally been used in the treatment of different kinds of malaise including digestive dysfunction, inflammatory conditions and pain-related disorders in addition to that of an edible spice and flavouring agent in local foods (Wang et al., 2015). A wide ethnomedicinal significance has influenced scientists to show more interest in its chemical composition and biological activities. This review aims to provide an update, summary, and critical assessment of the evidence that is currently available about the phytochemistry, customary uses and pharmacological potential of Z. simulans. With phytochemical investigations, a variety of bioactive compounds have been found, including alkylamides, flavonoids, essential oils, coumarins, and lignans, many of which have been shown to possess highly potent antioxidant, anti-inflammatory, antimicrobial, and neuroprotective properties (Chen et al., 2018; Jiang et al., 2019). Pharmacological studies have theorized the pharmaceutical potential of Z. simulans in the treatment of metabolic conditions, cardiovascular health, and brain disorders with a number of compounds showing structure-activity associations that could be used in drug development. Although preclinical research offers promising perspectives, there is still a lot of gap in research in the area, which mostly concerns the unification of the extraction procedures, extensive clinical verification, and safety characterization. The filling of these gaps could help establish Z. simulans in evidence-based herbal medicine and functional food formulations. In general, this review reveals the therapeutic versatility of Z. simulans and shows the research avenues that should be pursued to utilize its bioactive roles in contemporary health care.

Keywords: *Zanthoxylum simulans* , phytochemistry, traditional medicine, therapeutic potential, bioactive compounds, sanshools, essential oils, flavonoids, antioxidant activity, anti-inflammatory effects.

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1. Introduction
1.1 About the Genus *Zanthoxylum*
The family of Rutaceae has more than 200 species in the genus Zanthoxylum and is widely distributed mainly around tropical and sub-tropical areas worldwide (Khan et al., 2019). Members of this genus exhibit considerable medicinal and aromatic value, due to the presence of bioactive molecules such as alkylamides, essential oils, flavonoids, etc. The family Rutaceae itself is of economic importance, with genus like Citrus, Murraya, and Ruta extensively utilized in the traditional medicine systems in Asia (India and China), Africa and South America (Singh & Sharma, 2020).
The Chinese prickly ash or Sichuan pepper (*Zanthoxylum simulans*) is native to East Asia and an excellent example of one of the species as the plant is actively used in cooking and is also therapeutically significant (Li et al., 2016). Although the genus is spread across the globe, Z. simulans has strong ethnobotanical relevance especially in Asian medicinal systems and hence a suitable candidate to a concise phytochemical and pharmacological survey

1.2 Taxonomy of *Z. simulans*

Kingdom: Plantae
Phylum: Magnoliophyta
Class: Magnoliopsida
Subclass: Rosidae
Order: Sapindales
Family: Rutaceae

Genus: Zanthoxylum

Zanthoxylum simulans is a deciduous shrub or small tree growing 3–7 m in height with spiny branches, pinnately compound leaves and aromatic fruit husks containing unique sanshool compounds resulting in its numbing taste (Wu & Raven 2008). It grows best in temperate to subtropical climates and the soil needs to be well-drained, so that it does not become waterlogged.

***Zanthoxylum simulans* tree with ripe fruits (Image Source: Rangkhani Gabisa, in Baglung District, Dhaulagiri Zone, Nepal)**

Dried seeds of *Zanthoxylum simulans* used as a spice

Z. simulans is mainly distributed in China (in the provinces of Sichuan, Hubei and Shaanxi), but its range also includes Japan, Korea and some areas of Southeast Asia (Zhang et al., 2021). In much of the countryside, besides its traditional application as a culinary condiment, it is grown like medicinal plant into local health care practices. Its amenability to cultivation has also allowed this plant to be grown in botanical gardens and spice farms on other continents.

1.3 Rationale for Review

Although Z. simulans has a long history of applications as a folk medicine and food source, it has no cohesive body of scientific literature to establish the phytochemical diversity, ethnomedicinal applications, and pharmacological potential. Current literature zones in on single compounds or a particular pharmacological activity and fails to give an inclusive picture of the benefits of the plant as a whole (Patel et al., 2020).

With the increasingly global interest in plant-derived medicines, especially folk medicines, one must recount the bioactive substances of Z. simulans, summarize the mechanism of action, and describe the potential of the agents applied in modern medicine (Chen et al., 2018). In addition, pursuing Z. simulans is justified from the point of view of fundamental science and business because of the growing interest in natural antioxidants, antimicrobial substances, and ingredients for functional foods (Liu et al., 2020).

1.4 Objectives

The primary objectives of this review are as follows:

1. **Summarize phytochemical constituents** – To list and discuss the accumulated information about the bioactive compounds isolated so far with a specific reference to alkylamides, flavonoids, essential oils, coumarins, and lignans, isolated in Z. simulans.
2. **Document ethnomedicinal uses** - To record traditional applications across different cultures, with emphasis on Chinese and other East Asian medical systems.
3. **Evaluate pharmacological activities** - To evaluate in vitro, in vivo, and limited clinical data regarding its antimicrobial, anti-inflammatory, antioxidant, neuroprotective, and other possible therapeutic effect.
4. **Identify research gaps-** To indicate the shortcomings of existing studies, such as the necessity of uniform methods of extraction, clinical confirmation, and characterization of toxicology.

2. Conventional uses and Ethnomedical Significance

2.1 Historical Uses in Traditional Chinese Medicine (TCM)

According to the Traditional Chinese Medicine (TCM) system, *Zanthoxylum simulans* has a centuries old history with citations in classical works on Materia Medica like the Bencao Gangmu (Compendium of Materia Medica) authored by Li Shizhen during the Ming Dynasty (Li et al., 2016). Referred to by the Chinese as Huajiao, this plant is categorized as acrid and warm in nature and is related to the meridians of the spleen and stomach. It is also traditionally used to reduce abdominal pain, relive cold and promote blood circulation. Abdominal disorders, gastric pain, diarrhea accompanied by cold, and loss of appetite have all been treated using the dried fruit husks in decoctions and in combination with body tonics, including Zingiber officinale (ginger) and Cinnamomum cassia (cinnamon bark) (Liu et al., 2020). This versatility of Z. simulans as used in the Traditional Chinese Medicine (TCM) has shown positive response against inflammation (Chen et al., 2018). The standard combination of Z. simulans is with other aromatic herbs to enhance warming, circulation stimulating and pathogen destroying effects.

2.2 Regional Folk Medicine Practices

Besides, formal TCM, Z. simulans is also popular in local and folk medicines in the Chinese countryside. The dried fruit husks are used to relieve toothache in many provinces by either chewing directly or as a tea. This is substantiated by the fact that it was found to demonstrate antimicrobial activity against oral pathogens (Wang et al., 2015). In certain mountainous populations, decoction of the bark of the plant is used as an antidote against skin infections, boils, and insect bites, and may reflect the traditional perception of the plant as diaphoretic and disinfectant.

It also has long culinary uses, especially in Sichuanese cuisine, where it is prized for its characteristic and distinctive tingling and numbing effect brought on by sanshool alkylamide (Feng et al., 2017). This culinary use is regarded by folk medicine to not merely be a flavor enhancer, but also a digestive aid supposed to provoke the secretion of saliva and gastric juice. The consumption of Z. simulans as part of everyday meals can be considered a special branch of dietary intervention and has remained in line with ancient Chinese dietary ideologies that considered food and medicine as one (Hu et al., 2018).

2.3 Cross-cultural Uses

Consumption of Z. simulans is not targeted at China alone as the tradition is used in the neighboring areas where the plant or a similar species is grown. It is also referred to as Sansho which is common in Japan, having both purposes as a spice as well as a herbal remedy. In Japanese Kampo medicine, fruit husks are processed into prescriptions for gastrointestinal conditions and topical pain relievers (Kawasaki et al., 2016). Z. simulans and other species are part of folk medicine in Korea to treat common colds, skin disease, and parasitic infection (Park et al., 2020).

The plant has been a cooking ingredient in Southeast Asia, particularly in northern Vietnam and Laos, where its taste has been used to add flavour to meat and soups as well as serving medical functions, such as the treatment of stomach cramps and fungal skin diseases (Nguyen et al., 2019). Timur or Sichuan pepper has also various uses in Nepal. Cross-cultural ethnobotany indicates that there is unity in the basis behind medicinals in Eastern and Southeast Asian practices between warming the body, digestion and alleviating pain although there is variation in their preparation.

2.4 Part-wise Utilization

The medicinal Uses of Z. simulans do not solely abide with its fruit husks; almost every portion of this plant has been used in the traditional practice

- Fruit Husks: This is the most common section which contains abundant volatile oils and alkylamides and used to treat digestive problems, pain, and culinary enhancement as seasoning (Hu et al., 2018).

- Seeds: The isolated away hulls are applied in folk medicine to promote of urinary outflow and edema (Wang et al., 2015).
- Leaves: Topically applied crushed fresh leaves are administered on insect bite and wounds because of its antiseptic property (Liu et al., 2020).
- Bark: Extracts of the stem bark are used as a rheumatic pain remedy, for skin disorder treatment and also as a tonic. It is speculated that the factors in the bark have anti-inflammatory and anti-microbiological activity (Chen et al., 2018).
- Roots: The roots extracts are used in the treatment of chronic wounds infected by microbes and as toothache remedy in some folk traditions (Li et al., 2016).

3. Phytochemistry of *Zanthoxylum simulans*

3.1 Major Classes of Compounds

Alkaloids

Alkylamides are found abundantly in *Zanthoxylum simulans* with the most characteristic compounds known as sanshools that produce its characteristic sensation of tasting tingling and numbing (Jiang et al., 2019). Hydroxy-alpha-sanshool, beta-sanshool and gamma-sanshool are amide alkaloids that have somatosensory neuron targets and exert effects on mechanosensitive ion channel activation, including TRPV1 and TRPA1 (Kawasaki et al., 2016). The activity is not only relevant to the culinary sensory effects but certain of the analgesic and anti-inflammatory properties of the plant. Also, Z. simulans contains benzophenanthridine alkaloids including chelerythrine and sanguinarine (Li et al., 2016). They are highly antimicrobial, antifungal and anticancerous and their mechanisms of activity involve the DNA intercalation and inhibition of protein kinases (Jiang et al., 2019). These bioactive alkaloids are useful and render the plant to be utilized traditionally within the curative methods of infections and inflammatory disorders.

Flavonoids

The second relevant category of phytochemicals in Z. simulans are the flavonoids. The most common ones are Quercetin, kaempferol, and glycoside derivatives (Luo et al., 2021). It has been established that these polyphenolic compounds can have excellent antioxidant capacity and this has been attributed to their capacity to donate hydrogen atom or electron to scavenge reactive oxygen species (ROS) (Liu et al., 2020). In the In- vitro experiments, it was established that a quercetin and kaempferol derived from Z. simulans slows the course of lipid peroxidation, reduced the content of nitric oxide, and reduced the formation of pro-inflammatory cytokines (Zhao et al., 2018)

Essential Oils

The essential oil profile of Z. simulans is dominated by monoterpenes and sesquiterpenes; specifically, limonene, linalool, citronellal, and β-myrcene and β-caryophyllene (Feng et al., 2017). Limonene is associated with anti-inflammatory properties, gastric protection as well as antibacterial effects, and linalool is reported to be utilized as a sedative, an analgesic, and even as antibacterial aid (Chen et al., 2018). Citronellal has shown insect-repelling effect, and are conventionally been used as topical applications. It has also been noted that the chemical composition of the essential oils varies in terms of area, part, and maturity of the plant (Zhou et al., 2020).

Coumarins and Lignans

The identified coumarin xanthyletin, imperatorin and bergapten in Z. simulans demonstrate antimicrobial, anticoagulant and anti-inflammatory activity (Hu et al., 2018). Z. simulans also include Lignans such as sesamin and asarinin that have been described to possess antioxidant, hepatoprotective and cardioprotective effects (Zhang et al., 2021). It is believd that the pharmacological benefits of Z. simulans in the traditional medical practice have its origin in the co-existence of these coumarins and lignans.

3.2 Analytical and Isolation Techniques

The effect of more contemporary advancements that have come along in the arena of analytical chemistry has resulted in an increased capability to determine and quantify the phytochemical contents of Z. simulans. Flavonoids, alkaloids and coumarins are commonly extracted and quantified by chromatographic analysis using High-Performance Liquid Chromatography (HPLC) coupled with rapid spectrum characterization by photodiode array (PDA) detection (Zhou et al., 2020).

The dominant method available to characterize essential oil is the Gas Chromatography-Mass Spectrometry (GC-MS) which provides both qualitative and quantitative information of volatile monoterpenes and sesquiterpenes in an extremely sensitive manner. Inventions on Solid-Phase Micro Extraction (SPME) methodologies prior to GC-MS have made SPME more sensitive to low-abundance volatile compounds, and since solvents used to dissolve samples usually cause interferences, SPME have helped to lessen that interference.

LC-MS/MS provides high-resolving separations and structural confirmation of alkaloids and flavonoid glycosides (Jiang et al., 2019). It has demonstrated efficiency in differentiation among sanshool derivatives and their isomers with very high probability of co-elution amid platforms that have been deployed in the context of traditional chromatography.

Alongside the traditional methods of identification, mentioned above, other methods such as Nuclear Magnetic Resonance (NMR) spectroscopy, Fourier Transformer Infrared Spectroscopy (FTIR) are also used to further identify molecular structures and functional groups once phytochemicals are isolated. Individual phytochemical components are most often purified by preparative column chromatography and Counter-Current Chromatography (CCC) prior to testing of their bioactivity.

3.3 Structure–Activity Relationship Insights

Structural characteristics of Z. simulans phytochemicals have close relationships with their bioactivities. An example where this is true is the case of Sanshool alkylamides, which possess conjugated double bonds and amide linkages that are needed to interact with TRP ion channels in order to produce analgesia along with tingling sensations (Kawasaki et al., 2016). Variations to chain length and level of unsaturation may considerably change their efficiency and receptor selectivity (Jiang et al., 2019).

Exemplary of the flavonoids is quercetin and kaempferol, which is differentiated by having hydroxyl groups on their aromatic rings, a fact that enhances their ability to act as hydrogen donors and, thus, increases free-radical scavenging potential (Zhao et al., 2018). Glycosylation also influences the physicochemical property, solubility and bioavailability through its place of occurrence that have direct effects on the pharmacokinetic profile of these compounds (Luo et al., 2021).

Monoterpenes form a group of the essential oil components that display structure-dependent antimicrobial effect. The occurrence of functionalized functional groups, i.e., hydroxyl and aldehyde ones, in compounds of the linalool and citronellal types enhances the destabilization of microbial cell membranes and, therefore, increases antibacterial activity (Feng et al., 2017).

Substituents in the benzopyrone skeleton determine pharmacological activity that occurs in the coumarins. Indicators can be methoxy functional dependencies made in certain rings that increase lipophilicity and allow passing through the membranes, which strengthens the antimicrobial activity (Hu et al., 2018). Sesamin, the lignin present in Z. simulans, has a biphenyl structure with the bridges of methylenedioxy groups, known to act as antioxidant and lipid-modulating agents (Zhang et al., 2021).

The identified structure activity relationships (SAR) gives useful insight in the possible creation of superior semi-synthetic derivatives with better impacts, selectivity, and safety. It too confirms the logic of ancient multi-compound herbal combinations, in which there might be potential synergy of effects among different types of phytochemicals.

4. Pharmacological and Therapeutic Potential

4.1 Antimicrobial and Antifungal Activities

Alkylamides, benzophenanthridine alkaloids and essential oils constitute three major groups of bioactive substances regularly associated with the antimicrobial activity of *Zanthoxylum simulans* under quantitative and structural indices. In vitro explanations have shown that both sanshool-rich extracts as well as extracts that are majority made up of chelerythrine have high inhibitory characteristics on Gram-positive bacteria including Staphylococcus aureus and Bacillus subtilis (Kim et al., 2016). At the mechanistic level, the compounds damage the integrity of the membrane, induce the escape of the intracellular contents, and simultaneously inhibit the synthesis of nucleic acids.

It has been evidenced that some of the essential oils, i.e., those enriched with limonene, linalool, and citronellal, have a broad-spectrum antibacterial effect, where their minimum inhibitory concentrations (MICs) are on the magnitude of 0.25-1.0 mg/mL against diverse disease-causing strains (Feng et al., 2017). Complementarily, antifungal studies report that methanolic extracts show an inhibitory effect on the growth of Candida albicans, Aspergillus niger, and Trichophyton rubrum that act mostly through the disruption of ergosterol synthesis and generation of oxidative stress. These results support the conventional use of Z. simulans in skin infection, wound healings and oral conditions.

4.2 Anti-inflammatory and Analgesic Properties

Z. simulans exert anti-inflammatory effects in a variety of biochemical pathways. Sanshool alkylamides bind enzymes cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) which explains the decrease of pro-inflammatory prostaglandins and leukotriene synthesis (Liu et al., 2017). Z. simulans extracts also caused significant inhibition of paw edema and inflammatory cell penetration when administered as an oral dose in models of carrageenan-induced paw edema in mice.

A comprehensive evidence base has shown that the bioactive plant chemicals quercetin and kaempferol exert an opposing action that controls inducible nitric oxide synthase (iNOS) in lipopolysaccharide (LPS)-stimulated macrophages, making its expression suppress the production of nitric oxide during inflammation (Zhao et al., 2018). Sanshool, the allegedly thermostable diterpene compound found in Sichuan pepper, has also demonstrably been able to influence transient receptor potential (TRP) channels and, in this manner, re-balance the nociception cascade, establishing a molecular underpinning to claims of culinary analgesia and ethnomedicinal use in the treatment of rheumatic illnesses and toothache (Kawasaki et al., 2016).

4.3 Antioxidant Effects

Prominent antioxidant activity is observed in flavonoid- and phenolic rich Z. simulans. The In - vitro analyses show that the neutralization of free radicals is strong and dose-dependent emanating with IC 50 values similar to those of

ascorbic acid through empirical radical scavenging of 22-diphenyl-1-picrylhydrazyl (DPPH) and ABTS (Xu et al., 2019).
Flavonoids, coumarins and lignans have the characteristic of antioxidants that include scavenging of reactive oxygen species (ROS) and Obstruction of lipid peroxidation which provides some protection to the cellular membranes against oxidative damage. In Vivo-based research on oxidative stress in animal models reveal that extracts of Z. simulans increase the activity of the endogenous antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), and also reduce malondialdehyde (MDA) levels (Luo et al., 2021). These findings testify to a prophylactic effect of the extract against chronic disorders associated with oxidative stress, such as cardiovascular and neurodegenerative diseases.

4.4 Cardiovascular and Metabolic Health
Based on critical observation, cardiovascular effects can be attributed to the vascular relaxation and lipid-lowering efficacy of Z. simulans. In the case of hypertensive rat models, aqueous extracts caused considerable reductions in systolic and diastolic blood pressure, attributed to the removal of endothelium-dependent nitric oxide release and barring of the Ca2 + channels in mechanism of action (Park et al., 2020).
On a metabolic level, the metabolism of the lipids is affected by the creation of sanshools and flavonoids, as they reduce the serum total cholesterol, triglycerides level, and even low-density lipoprotein cholesterol (LDL-C) as well as increase the high-density lipoprotein cholesterol (HDL-C) level (Liu et al., 2020). Such anti-obese effects were validated against the high-fat diet-induced obese mice model, where the treatment of Z. bungeanum extracts reduced body weight gain and reduced adipose tissue mass and improved insulin sensitivity (Chen et al., 2018). These metabolic effects go with its conventional application as a metabolic stimulator and an appetite controller.

4.5 Neuroprotective Activities
There is preclinical data on the neuroprotective effect of Z. simulans, which indicates that it is useful in the alleviation of poor cognition and neuroinflammation. On a mouse model of memory impairment induced by administration of scopolamine, oral supplement of Z. simulans flavonoid-rich fractions increased the performance in memory tests including Morris water maze, showing an improved learning and spatial memory (Chen et al., 2021).
In neuroscience, findings show that such negative neurological events that occur during Alzheimer and Parkinson diseases can be inhibited by a particular pharmacological action. It has already been shown that Z. simulans stimulates neuroprotective effects through inhibitory effects on acetylcholinesterase (AChE) formation, up regulation of brain-derived neurotrophic factor (BDNF) and down regulation of pro-inflammatory cytokines like TNF-alpha and IL-6 in the brain (Zhao et al., 2018). In addition, the antioxidant flavonoid effects of Z. simulans protect neurones through the reduction of oxidative damage to neuronal membranes and mitochondria. The combination of all these findings suggests the potential of Z. simulans towards formulation of functional foods or supplements of neurodegenerative disorders.

4.6 Other Reported Bioactivities
Anticancer Potential
Among the alkaloids, the representatives of a benzophenanthridine (chelerythrine and sanguinarine) have been reported to demonstrate cytotoxic effects against the cancerous cell lines of human hepatocellular carcinoma (HepG2), breast cancer (MCF-7), and leukemia (HL-60) (Jiang et al., 2019). These mechanisms include imparting apoptosis through caspase activation, cell cycle stabilization on the G2/M phase and blocking NF-kB signaling.

Insecticidal Activities
Z. simulans essential oils are insecticidal and repellent; and this is mainly because of the citronellal, and limonene content. In the laboratory, there have been larvicidal effects and repellents effects against the common household pests against Aedes aegypti (Feng et al., 2017).

Skin Health
Novel investigations have assessed the therapeutic potentials of the topical preparations containing Z. simulans extracts, particularly with regard to their antimicrobial, anti-inflammatory, and antioxidative potentials. The experiments provide evidence of a reduction of bacterial burden in wounded areas, the augmentation of bacterial production of collagen as well as the fast rate of wound healing in animal models (Hu et al., 2018). Based on these results, it can be recommended that Z. simulans needs to be introduced into the conventional approach towards skin care and larger studies on the use of Z. simulans in cosmeceutical products need to be conducted.

5. Toxicology and Safety regulations
5.1 Acute and Chronic Toxicity
Toxicological testings of the Zanthoxylum simulans has been carried out predominantly on animals. In acute oral toxicity research in mice, seed extracts of ethanol had high relative safety ratio, and the lethal median dose (LD 50) was identified to produce low acute toxicity at more than 5g/kg body weight (Gao et al., 2018). At sub-lethal doses after a short-term exposure, there did not appear any significant behavioral changes, mortality as well as organ damage.

In mouse models, a 90 days study demonstrated that the daily dose of the medicine at 1 g/Kg per day did not result in any histopathological alteration with examination on the liver, kidney, nor the heart either at once or daily when evaluated orally (Liu et al, 2020). At higher doses, however, a mild gastrointestinal irritation characterized by diarrhea that was more likely secondary to the stimulatory effects of the bioactive sanshools on gastrointestinal smooth muscle was observed. Although they are typically MTD when administered at levels that allow them to be detected upon smelling, they showed low-level dermal irritation when applied as patch tests in animals, showcasing the necessity of a degree of dilution when applied as such given their possible application considerations at the topical level (Feng et al., 2017).

5.2 Safe Dosage Ranges

According to the general and worldwide-accepted standard of culinary consumption, as well as based on the medical practice, the moderate consumption of Z. simulans up to 56 g/day of dried husk per capita can be discussed as safe (Li et al., 2016). Decoction and extract decoction normally exist in the sphere of medicine with a dose of 2 to 10 g of dry plant matter per day per capita, which is divided into several times (Hu et al., 2018). Blends should be within concentrations of upto 0.5 percent to aid in the prevention of possible skin irritations when a topical essential oil is used.

5.3 Regulatory Status

Z. simulans has a interesting status in China: it is included in the Chinese Pharmacopoeia as a medicinal plant, and at the same time is legalized in administrative documents as a food spice (National Pharmacopoeia Commission, 2020). Its dried husks and essential oils are established as flavoring agents in the internationally recognized standards of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) but its medicinal use is less well - defined (Wang et al., 2015). In the European Union and the United States it is permitted as a culinary herb/spice with no specific drug authorization, but preparations in dietary supplement form are marketed under general food safety laws.

6. Research Gaps, Challenges, and Future Directions

Despite the recent development in the phytochemical and pharmacological profiling of *Zanthoxylum simulans* , there still exists many gaps and loopholes that are thwarting the full integration of this plant in evidence-based modern medications. Lack of standardized extraction and processing methodologies is one of the big challenges. There is uncertainty in phytochemical profiles and bioactivity findings since various solvents, extraction durations, and plant parts are utilized in the current research studies (Patel et al., 2020). Lack of harmonized quality control procedures prohibits the obvious comparison of study results and consistency on commercial preparations of herbal measures. Regulation of reproducibility and quality of products would involve; elaboration of validated extraction procedures and phytochemical fingerprinting standards.

One more important limitation is the lack of large-scale, well-controlled clinical trials. Although many in vitro and in vivo studies endorse the antimicrobial, anti-inflammatory, antioxidant and neuroprotective properties of Z. simulans, human clinical evidence is limited and generally restricted to small pilot studies (Chen et al., 2018). Tough clinical experiments are greatly needed to prove efficacy, determine the most appropriate dosing schedules, and assess long-term safety amid various populations.

One more issue is sustainability, and in some areas, the wild Z. simulans are endangered by overharvesting and losing habitat (Singh & Sharma, 2020). It is vital to widen cultivation schemes, adopting sustainable extraction policies, and encouraging inference of conservation-oriented communities to maintain genetic variety and to replenish forever supply on medicinal and culinary products.

It is necessary to say that further study should be interdisciplinary, combining ethnobotanical information, sophisticated analytical methods, pharmacological experiment and ecological protection strategies. The scientific rigor of applications of Z. simulans would not only be enhanced by such approach, but also make its commercialization as part of herbal medicine, nutraceutical, and functional foods feasible and responsible to promote.

7. Conclusion.

Zanthoxylum simulans is a drug and food ingredient of great value and an ancient history of utility particularly in East Asian medicine. Its therapeutic uses are related to the promotion of digestive health, pain treatment, inflammation treatment, antimicrobial, and cooking, and, thus, demonstrate a profound entrenchment in the field of healthcare practice and nutrition (Li et al., 2016; Wang et al., 2015).

The bioactive compounds in the plant (sanshool alkylamides, benzophenanthridine alkaloids, flavonoids, essential oils, coumarins, and lignans) have been surveyed extensively pharmacologically (Jiang et al., 2019; Luo et al., 2021). The activity of many pharmacological effects depends on these molecules, including antibacterial effect, anti-inflammatory, antioxidant, neuroprotective and cardiometabolic health activities (Kim et al., 2016; Chen et al., 2018). High pharmacological potential is evident in Z. simulans with a broad pharmacological profile that suggests they have much potential to be introduced as analgesics, anti-microbials, and metabolic health supplements.

Looking at Z. simulans in functional foods terms, its duality as a spice and a medicinal plant makes it unique in that it can be able to be incorporated into health promoting foods. Such a promise, however, will be realised only through standardised extraction protocols, well-designed clinical trials, and sustainable sourcing strategies. The transdisciplinary research approach involving ethnobotany, phytochemistry, pharmacology, food science, and conservational biology are important in fully utilizing the medicinal and nutritional properties of this plant. Integration of native remedies with scientific evidence to determine its therapeutic applications can enable Z. simulans to transition beyond local solution to a globally available functional ingestible product and also promote data-driven healthcare innovation and biodiversity.

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