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Chapter

An Overview of Genus *Zanthoxylum* with Special Reference to Its Herbal Significance and Application

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Abstract

The plants of genus *Zanthoxylum* are effectually utilized in conventional and present-day medicine system to fight many diseases and disorders like pain, seizures, inflammation, cancer, liver and heart malady. Many of its plants—trees and shrubs, are citrus in nature, with curative antimicrobial, antihelminthic, antipyretic, and antiviral activities. More than 100 of its plant species have been identified and recorded for their potential as an herb in modern pharmacopeia. The species of this genus also have potent ethno-pharmacological significance. Many medicinal secondary metabolites like terpenoids, flavonoids, and alkaloids have also been profiled in many *Zanthoxylum* species. Additionally, fruit of many of the species is also significantly utilized as a major spice under the name "Sichuan pepper" in many countries like China and India. Thus, this unique blend of herb and spice characteristic of the genus needs a detailed description. This chapter highlights the major significant discoveries in the recent decade in this genus, which can add a step in the way of development of herbal medicines. Documentation of such medicinal plants may aid in derivation of plant-based medicines, which is the demand of the hour.

Keywords: cancer, herb, herbal, Sichuan pepper, *Zanthoxylum*

1. Introduction

Herbal or phyto-based medicines are in the mainstream of present pharmacological world [1]. Nearly two-thirds of the medicines throughout the world is plant based, the rest being the conventional ones [2]. The main reasons behind the preference of herbal drugs over the synthetic ones are that they have negligible side effects, are cost-effective, and easily available [3]. Also, the knowledge of herbal sources has led to the formation of base for many modern medicines. Some examples mentioned by Vickers and Zellman [4] are aspirin taken from willow bark, digoxin from foxglove, and morphine from opium poppy. Many researchers have also stated the development of resistance to allopathic drugs after a long medicament leading to becoming ineffective [5]. Thus, a documentation of medicinal plants and its herbal aspect becomes the first step toward a "botanical healing."

2. *Zanthoxylum* genus

Zanthoxylum genus, belonging to family Rutaceae, comprises of aromatic, therapeutic deciduous shrubs and tree species [6]. Most of the plants in this genus are characterized by the presence of a strong lemon like odor, and prickly spines in the world [7]. The plant is mostly found in the South and Southeast Asian regions at an altitude of 1300–2500 m [7–9]. It is a plant of the warm temperate climate [10]. The benefits of this genus vary from healing common problems like toothache, gum problems, stomach ache, cough, cold, fever, dyspepsia, expulsion of roundworms, and in the treatment of fatal disease like cancer [11–16]. It is an anti-inflammatory, antinociceptive, antifertility, adipogenic, hepatoprotective agent; it also has the special ability to improve speaking power, reducing rheumatism, arthritis, asthma, skin diseases, abdominal pain, anorexia, ataxia, and purifying the blood [12, 15, 17–24]. The plant has phytomolecules that display insecticidal, antiparasitic, nematicidal, larvicidal, and fungicidal activities [13, 15, 25–29].

3. *Zanthoxylum* as herbal medicine in ancient pharmacology

Several species under *Zanthoxylum* genus have been used by various regions of the world since ancient times for benefits of mankind and their live stocks [5, 30, 31]. *Z. liebmannianum* bark is used for removal of parasites in Mexico [32]. For malaria, *Z. rhoifolium,* [33, 34] and *Z. acutifolium* [5] have been preferred from this genus. Nyishi tribe of India utilizes *Z. armatum* fruit, seed and bark in a traditional "Honyur" mix to treat stomach disorder, fever, and cholera, respectively [10]. *Z. chiloperene* var. angustifolium Engl. is also known as an antiparasitic agent in Paraguay [35]. *Z. integrifolium* bark is utilized by YaMei and Lanyu indigenous tribes of Taiwan, to treat dyspepsia and fever [5]. Freitas et al. [36] has reported antitumor and colitis-relief in *Z. rhoifolium* Lam. *Z. monophyllum* has found a place in the Venezulan medicine for treating jaundice, and ophthalmia [5]. Roots of *Z. zanthoxyloides* have been used to treat sickle cell anemia [37]. *Z. alatum* has been used for treatment of diabetes, toothaches, and abnormal cell growth [38].

4. *Zanthoxylum* as herbal medicine in modern pharmacology

4.1 Anticancerous activity

Z. leprieurii and *Z. zanthoxyloides* inhibits cancerous activity of leukemia (HL60) and (MCF7) breast cancer cell line [39]. It also shows moderate anticancerous activity (MCF-7), liver (WRL-68), prostrate (PC-3) and colon ($CACO_2$) carcinoma cell lines [37]. In another study, methanolic extract (ME) of the pericarp of *Z. armatum* revealed the presence of compounds ZP-amide A, C, D, E, hydroxyl α and β sanshool, and Timuramide A, B, C and D [9]. All these compounds inhibited the growth of mouse glioma cells that were deficient of tumor suppressor genes NF1 homolog-Nf1, whereas only few compounds showed activity against cell lacking Trp 53—the genes responsible for encoding tumor suppressor gene p53, at a concentration that is nontoxic to the nontumor cells. *Z. alatum* Roxb. stem bark petroleum ether extract (PE) possesses various anticancerous lignans, namely sesamin, kobusin, and 4′0 demethyl magnolin [38]. Out of which 4′0 demethyl magnolin, which is a novel compound, gave the best anticancerous output against lungs (A549) and pancreatic (MIA-PaCa) cancer cell lines, in comparison to the standard docetaxel. *Z. armatum* dried

root ethyl acetate extract (EAE) (a good antioxidant) and its two components flavonoids, apigenin and kaempferol-7-O-glucoside, also possess an anticancerous trait against A-549, MIA-PaCa, MCF-7, and $CACO_2$ cancer colon cell lines [40]. In an extensive study, the ME of leaf of *Z. armatum* induced apoptosis in cervical cancer cell lines (HeLA) at IC_{50} (60 μg/mL) through Caspase 3-independent and extracellular signal-regulated kinases (ERK)-dependent mitogen-activated protein kinases (MAPK) apoptosis pathways [41]. Karmakar et al. [42] demonstrated that at an IC_{50} value of 102.30 μg/mL, the ME of the leaves of *Z. armatum* exhibited toxicity against Ehrlich Ascites cancer cells. The toxic effect was attributed to the presence of phenol and flavonoid compounds in the plant extract. Karmakar et al. [43] stated that the ME of leaves of this plant are capable of apoptosis by regulation of bcl-2/bax protein expressions and DNA damage in cancer cells and determined the presence of flavonoids, rutin, myricetin, and quercetin in the methanolic extract as potent anticancerous phytochemicals. Zanthonitrile [{4-[(3-Methyl-2-buten-1-yl) oxy] phenyl}acetonitrile] isolated from the leaves of the plant eluted by hexane: ethyl acetate solvent has a cytotoxic effect on Ehrlich Ascites Cancer cells with an IC_{50} value of 57.28 μg/mL [44]. Aqueous extract (AE) of *Z. piperitum* De Candolle fruit induces c-Jun N-terminal kinase autophagic cell death in colorectal (DLD-1), hepatocarcinoma (HepG2), and $CACO_2$ cancer cell lines but not in A549, MCF7, and colon (WiDr) cells [45]. Alam et al. [46] demonstrated that ME and crude saponins from leaves, fruit, and bark of *Z. armatum* have a potential of exerting a cytotoxic effect on breast (MDA-MB-468, MCF-71) and colorectal cancer (Caco-21) cell lines using the mechanism of apoptosis. Another compound Tambulin, a flavonoid isolated from the fruit exhibited antiproliferative action on certain cancer cell lines like MCF-7, WRL-68, COLO-205, MDAMB-231, with an IC_{50} ranging from 37.96 to 48.7 μg/mL [45]. Three compounds isolated from *Z. zanthoxyloides* fruits ME, hesperidin, skimmianine, and sesamine, possess anticancerous activity up to some level against A549, MCF7, and PC3 cell lines [47]. Pang et al. [48] confirms the anti-proliferative activity of seed oil of *Z. bungeanum* Maxim. on melanoma (A375) cells by arresting G1 phase and inducing apoptosis. Component analysis revealed the presence of unsaturated fatty acid in the seed oil. The EAE fraction of the fruit of *Z. acanthopodium* has been found effective for breast cancer cell line (T47D) toxicity [49]. Another isolated compound scoparone, a coumarin from the fruit of *Z. leprieurii*, at an IC_{50} of 44.93 μg/mL can be used to design anticancerous agents against human HepG2, with the least amount of toxicity to normal Chang liver cell lines [49]. Fruit of *Z. acanthopodium* in n-hexane fraction is also, effectively anticancerous toward T47D cell line [50]. The possible mechanism for this is cell cycle inhibition, apoptosis induction, and downregulation of cyclin D1 activity. Geranyl acetate is present in the highest percentage in the effective fruit n-fraction.

4.2 Neuroprotectant activity

Nakamura et al. [51] has reported that *Z. bungeanum* could reduce scopolamine-induced dementia. Gx-50, an isolate of *Z. bungeanum* could also aid in Alzheimer's disease, PE of the same plant can act as an antidepressant [52]. This compound gx-50 has the ability to cross blood–brain barrier and stop the degradation of nerve cells. Qinbunamide isolated from pericarp of *Z. bungeanum* can activate the nerve growth factor to further activate neurite outgrowth at 20 μM concentration [53]. Three alkaloids berberine, chelerythrine, and columbamine isolated from chloroform extract of *Z. schreberi* inhibit cholinesterase and butyrylcholinesterase [51]. As these enzymes are responsible for breakdown of acetyl choline, their inhibition

leads to increase in number of nerve messengers, especially helpful in case of Alzheimer's and myasthenia gravis.

4.3 Antiparasitic activity

Z. chiloperone leaves EO and one of its major component canthin-6-one, showed an inhibition of parasitic activity of *Trypanosoma cruzi* at 10 mg/kg of oral and subcutaneous dose in comparison to standard benznidazole (dose 50 mg/kg) [35]. ME of *Z. armatum* seeds, at a concentration of 50 mg/mL induced paralysis in *Pheretima posthuma* (test model) in lesser time than the reference drug piperazine citrate (10 mg/mL) [54]. *Z. armatum* methanolic leaves extract at the concentrations of 250–1000 μg/mL showed a moderate trypanocidal activity on blood parasite found both in humans and animals—*Trypanosoma evansi* in an *in vitro* condition utilizing mice cells as a model [28]. Hexane bark extract of *Z. heitzii* acts as an inhibitor of *P. falciparum* at an IC_{50} 0.050 μg/mL [55]. Dihydronitidine one of the major components of the extract also acts as an antimalarial compound at an IC_{50} value of 0.0089 μg/mL [55]. In another investigation, anti-leishmanial activity was seen in crude extract and its hexane fraction of *Z. armatum* fruit against *Leishmania major* [46]. The essential oil (EO) of *Z. monophyllum* leaves also possess acute toxicity against larvae of *Anopheles subpictus* (LC_{50} 41.50 μg/mL), *Aedes albopictus* (LC_{50} 45.35 μg/mL), and *Culex tritaeniorhynchus* (LC_{50} 49.01 μg/mL). Among its two major compounds Germacrene D-4-ol has better efficiency than α-Cadinol [56]. Also, The EO, along with Germacrene D-4-ol, and α-Cadinol, EO has very low toxicity against *Gambusia affinis,* an eradicator of malarial larvae. Costa et al. [57], has reported antiparasitic activity of three noval compounds (5,7,8-trimethoxy coumarin, syringaresinol, and dictamine, isolated from the ethanol extract (EE) of roots of *Z. tingoassuiba* against *Leishmania amazonensis* and *Trypanosoma cruzi*, similar to positive control benznidazole and amphotericin. The larval stage of *Schistosoma haematobium*, a bladder cancer causing parasite can be successfully eliminated by acridone compound arborinine, isolated from fruit of *Z. leprieurii* at an IC_{50} value of 6.98 μg/mL [57].

4.4 Antimicrobial activity

Bark EE of *Z. fagara*, *Z. elephantiasis,* and *Z. martinicense* presented antifungal activity against fungi prevalent in domestic animals—*Aspergillus flavus*, *A. niger*, *Candida albicans*, *Saccharomyces cerevisiae*, *Microsporum canis*, *Trichophyton mentagrophytes* [31]. Though, it was unable to inhibit bacteria like *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, and *Psuedomonas aeruginosa* [31]. Lipophilic leaf of *Z. armatum* extract was found effective against *Alternaria alternata* and *Curvularia lunata* [58]. The EE of the whole *Z. armatum* plant proved to be effective against *S. aureus* (7 mm zone of inhibition), *Bacillus subtilis* (23 mm the biggest zone of inhibition), *B. cereus* (6 mm zone of inhibition), and *B. thuringiensis* (1 mm zone of inhibition) [25]. Barkatullah et al. [18] reported a maximum inhibition of *Micrococcus luteus*, *Pasteurella multocida*, *E. coli,* and *B. subtilis* by the application of *Z. armatum* leaf EE. *Z. leprieurii* and *Z. xanthoxyloides* EO decreased the effective time required to deactivate 7log cfu/mL of *Salmonella enteritidis* [59]. Oxychelerythrine, a benzophenanthridine alkaloid extracted from the ME of roots of *Z. capense* Thunb. altered the sensitivity of *S. aureus* ATCC 6538 to tested antibiotics (erythromycin, oxacillin, and tetracycline) in a positive way by twofold [60]. According to Alam and Saqib [46], n-hexane, chloroform, and aqueous-methanol fraction of *Z. armatum* fruits are a potent antifungal source, especially against *Trichophyton longifusus*, *Microsporum canis*,

A. flavus, *Fusarium solani*. The presence of alkaloids may be the reason behind such activity. Chen et al. [61] has found antimicrobial activity in the leaves extract of *Z. bungeanum* Maxim. against *E. coli. K. pneumonia, P. aeruginosa, S. enteritidis, Listeria monocytogenes, C. albicans*. Mirza et al. [62] observed that *Z. armatum* aqueous leaves extract-derived copper oxide nanomaterials (100 μl) was more sensitive in all bacterial strains tested (*S. aureus, Streptococcus mutans, Streptococcus pyrogenes, Staphylococcus epidermidis, B. cereus, Corynebacterium xerosis, E. coli, K. pneumonia, P. aeruginosa,* and *Proteus vulgaris*) in comparison to its source plant extract (100 μl).

Potent tuberculosis plant: ME of *Z. leprieurii* at minimum inhibitory concentrations (MIC) of 47.5, 75.3 and 125.0 μg/mL inhibited rifampicin-resistant and isoniazid-resistant strains of *Mycobacterium tuberculosis,* respectively [63]. Hydroxy-1,3-dimethoxy-10-methyl-9-acridone, 1-hydroxy-3-methoxy-10-methyl-9-acridone, and 3-hydroxy-1, 5,6-trimethoxy-9-acridone isolated from the plant also exhibited potent inhibition of resistant strains [63].

4.5 Antiviral activity

Z. coreanum root extract at an IC_{50} of 1.0 μg/mL inhibited porcine epidemic diarrhea virus growth [5]. Moreover *Z. planispinum* also exhibited the similar activity at an IC_{50} of 6.4 and 7.5 μg/mL respectively. Patino et al. [5] also reported the anti-HIV activity of *Z. ailanthoides*, *Z. integrifoliolum,* and *Z. scandens*.

4.6 Antioxidant activity

Oxypeucedanin, a coumarin compound present in ME of roots of *Z. flavum* Vahi., possesses significant antioxidant activity with an IC_{50} value of 8.3 μg/mL in a dichloro-dihydro-fluorescein diacetate (DCFH-DA) assay [32]. Z. *armatum* fruit EE showed promising activity as a natural source of antioxidants [64]. According to their study, the bioactive compound responsible for such quenching action is flavonoids, especially quercetin. Moreover, the EE of its stem bark tested via 2,2′-diphenyl picrylhydrazyl (DPPH) free radical scavenging activity exhibited significant antioxidant activities [23]. DPPH radical scavenging activity was obtained in the sequence of ME of stems (IC_{50} 54.6 ± 2.9 μg/mL) > dichloromethane extract of stems (IC_{50} 4.7 ± 117.5 μg/mL) > EO of fruits (IC_{50} 5764.7 ± 6.5 μg/mL) of plant *Z. limonella* Alston [65]. Singh et al. [65] reported that the EO from the seeds of *Z. armatum* was a potent antioxidant. Ethyl acetate fraction and aqueous fraction of *Z. bungeanum* showed potent DPPH, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging abilities and ferric-reducing antioxidant power (FRAP) [66]. The EO and its constituent oleoresins showed moderate antioxidant activity when evaluated by DPPH radical scavenging, Fe^{2+} chelating, ferric thiocyanate method, and different lipid peroxidation assays. Leaves extract of *Z. bungeanum* maxim "You Huajiao" variety from China possess DPPH and ABTS radical scavenging activity. It also possesses the reducing potent power (FRAP) [61]. A compound Ombuin isolated from the fruit of *Z. armatum* possessed antioxidant capacity [67]. Two new sesquiterpenoid glycosides, dihydrophaseic acid 4′-O-[6″-O-(4‴-hydroxy-3‴, 5‴-dimethoxy) benzoyl)]-b-D-glucopyranoside and dihydrophaseic acid 4′-O-[6″-O-(3‴-methoxy4‴-hydroxy) benzoyl)]-b-D-glucopyranoside, isolated from the ethanolic extract of stems of *Z. armatum* showed moderate scavenging activity in DPPH free radical assay with IC_{50} values of 241 and 264 μM, respectively [68]. Aqueous extract of leaves of *Z. armatum* and copper oxide nanoparticles derived from it were less effective in DPPH radical scavenging activity in comparison to L-ascorbic [40].

4.7 Anti-inflammatory activity

The crude extract of *Z. armatum* reduced thermal pain significantly at the concentrations of 100 and 400 mg/kg body weight in case of intraperitoneal (i.p.), in comparison to 30 mg/kg body weight i.p. of standard anti-inflammatory drug phenacetin [69]. Also, its root extract exhibited analgesic activity when compared to standard drug indomethacin (40 mg/kg body weight i.p.) [69]. The anti-inflammatory activity of EE of the stem bark of *Z. armatum* against paw edema in Wistar rats has also been observed by Sati et al. [23]. Thus, *Z. armatum* may be helpful in the treatment of pain and inflammation symptoms. Eight lignans that may be responsible for this curative quality, namely eudesmin, horsfieldin, fargesin, kobusin, sesamin, asarinin, planispine A, and pinoresinol-di-3,3-dimethylallyl, were recognized by HPLC analysis in its EE of stem and root [70]. Nine terpenylated coumarins, namely 7-[(E)30,70-dimethyl-60-oxo-20,70-octadienyl]oxy-coumarin, schinilenol, schinindiol, collinin, 7-[(E)-70-hydroxy-30,70-dimethy-locta-20,50-dienyloxy]-coumarin, 8-methoxyanisocoumarin, 7-(60R-hydroxy-30,70-dimethyl-20E,70-octadienyloxy)coumarin, (E)-4-methyl-6-(coumarin-70-yloxy)hex-4-enal, and aurapten, along with a 4-quinolone alkaloid and integrifoliodiol, isolated from the leaves of *Z. schinifolium* by α-glucosidase inhibitory effect showed anti-inflammatory activity [71]. EO from fruits of *Z. coreanum* Nakai inhibited both the IgE-antigen complex and IL4 production in RBL-2H3 mast cells showing anti-inflammatory activity [60]. 2α-methyl-2β-ethylene-3β-isopropyl-cyclohexan-1β, 3α-diol and phenol-O-β-D-arabinopyranosyl-4′-(3″,7″,11″,15″-tetramethyl) hexadecan-1″-oate noval compound isolated from the methanolic extract of *Z. armatum* fruit exhibited anti-inflammatory activity by inhibiting pro-inflammatory cytokines like TNF-α and IL-6 in peritoneal macrophages at the concentration of 5 and 10 μg/mL [72].

4.8 Antihyperglycemic activity

Z. armatum bark ME exhibits anti-hyperglycemic activity against streptozotocin-induced diabetic rats at 200 and 400 mg/kg concentration [73]. Stem bark AE of *Z. chalybeum* Engl. displayed anti-hyperglycemic activity at 10, 100, and 1000 mg/kg body weight concentration against streptozotocin-induced diabetic rats [74]. n-Butanol fraction of *Z. alatum* EE inhibits can inhibit protein tyrosine phosphatase-1B and stimulates glucose uptake in C2CL2 myotubes in streptozotocin-induced diabetic rats [75]. *Z. armatum* aqueous leaves extract the activity α amylase, and α and β glucosidase, thus, can act as an antidiabetic agent [75].

4.9 Insecticidal activity

Di-chloromethane extract of *Z. usambarense* bark displayed insecticidal activity against *Masca domestica* at 5000 g/ha, but its individual component could not produce any insecticidal results [70]. The EO contained sabinene, D-germacrene, β-mycrene, β-elemene and γ-elemene. The larvicidal potential of EO and its constituent from the seeds of *Z. armatum* were screened against three mosquito species, *Aedes aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus* [15]. Among these three species, *C. quinquefasciatus* showed the highest sensitivity at lowest concentration LC_{50} and LC_{95} at 49 and 146 ppm, respectively. However, linalool the most important constituent present at the maximum concentration (57%) in the EO failed to establish any significant larvicidal effect individually [15]. Hieu et al. [76] revealed that mixtures of *Z. armatum* seed oil (ZA-SO) and its constituents either alone (0.2 mg/cm^2) or as a binary mixture (0.01 + 0.99 mg/cm^2) with

Calophyllum inophyllum nut oil (CI-NO) can be potential repellents against stable fly, *Stomoxys calcitrans*. An aerosol of the mixture (ZA-SO-2.5% + CI-NO-2.5%) was also found effective as a repellent of stable fly. Among all its constituents tested, only methyl cinnamate exhibited a significant effect [77]. In a different study, three bioactive compounds—piperitone, myrtanol, and citronellal from *Z. armatum* seed oil were assessed for fumigant toxicity potency against stable fly with a simultaneous comparison of chlorpyrifos and dichlorvos, which are the organophosphorus insecticides [78]. The fumigant toxicity potential of seed oil and all three compounds according to the vapor phase assay was high with LC_{50} value 0.242–0.456 μg/cm^3, but their toxic level was five magnitudes below the organophosphorus insecticides, which reflects that *Z. armatum* may be further used as a bio-insecticide [78]. Additionally, constituents of EO-cuminaldehyde citronellal, neral, linalool, linalool oxide, terpinen-4-ol, 1,8-cineole, and piperitone induced a significant repellent behavior in the stable fly [76]. The *in vitro* insecticidal efficacy of the EE of the bark of the plant has been observed against mustard aphid *Lipaphis erysimi* at the concentrations of 0.5, 1.0, 1.5, and 2.0 mg/L [79]. After 24 h of spray at a concentration of 2.0 mg/L, 100% mortality of the aphid was there, proving that *Z. armatum* may be a good insecticide [79]. Nanoencapsulated EO of *Z. rhoifolium* leaves efficiently reduced the number of eggs and nymphs of *Bemisia tabaci* at 1–5% concentration [80]. Out of 32 constituents identified from the EE of *Z. armatum* twigs, 1,8-cineole piperitone, and limonene in particular were efficient as an insecticide against *Lasioderma serricorne* and *T. castaneum* [81]. While, in another study, the effect of *Z. armatum* leaves methanolic extract has been checked for antifeedant activity on the adults of "Red flour beetle"–*T. castaneum* [82]. Another study stated the effects of n-hexane, EE, and ME of leaves of *Z. armatum* on *Plutella xylostella*, diamondback moth [83]. In this investigation, the n-hexane fraction exhibited the best larvicidal activity at an LC_{50} value of 2988.6 ppm. Moreover, two compounds, particularly 2-undecanone and 2-tridecanone identified from the n-hexane fraction of leaf extract of *Z. armatum* through GC–MS analysis, which may be responsible for the larvicidal activity [83]. Egg laying capacity of *Bemisia tabaci,* a major tomato pest, can be reduced (85–98%) by using EO of *Z. rhoifolium* and *Z. riedelianum* at 1.0–2.0% concentration [84].

4.10 Nematicidal activity

EO of *Z. armatum* fruit showed more than 90% nematicidal activity 5 mg/mL concentration against *Bursaphelenchus xylophilus*, whereas its components methyl trans cinnamate and ethyl trans cinnamate also exhibited 100% activity at 0.0625–2.0 and 0.25–2.0 mg/mL, respectively [85]. *Z. armatum* leaves AE (100–400 mg/kg body weight concentration) decreased the hatching ability of *Meloidogyne incognita* [13]. The leaves of *Z. armatum* also work as a nematicide on *M. incognita* if added directly in the soil at the concentrations of 8, 10, and 20 g/kg of soil [86].

4.11 Hepatoprotective activity

Glycoprotein isolates of *Z. piperitum* DC fruit inhibited hypoxanthine/xanthine oxidase [87]. It also decreased the level of lactate dehydroenase, thio barbituric acid, while increasing the level of antioxidant enzymes in carbon tetrachloride acute liver damage. The leaf EE of *Z. armatum* significantly decreased all the symptoms of hepatotoxicity in Wistar albino rats by normalizing the elevated levels of hepatic enzymes, which was induced by carbon tetrachloride [24]. It induced hepatoprotective activity at a concentration of 500 mg/kg of body weight in comparison to standard drug silymarin at a dose of 100 mg/kg body weight. This effect was there due to

the radical scavenging activity of the phytochemicals, especially flavonoids present in the plant [24]. In a different study, the EE of bark of *Z. armatum* significantly expressed hepatoprotective activity at concentrations of 100, 200, and 400 mg/kg when administered orally in Wistar albino rats (where liver damage was instigated by paracetamol) by decreasing the levels of hepatic enzymes, bilirubin and at the same time increasing catalase, superoxide dismutase, and glutathione in comparison to silymarin [88]. In a recent study the ME at a dose of 500 mg/kg exhibited successful hepatoprotective activity with 66.87, 64.84, 67.95, 60.76, and 65.85% protection on aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and total protein enzyme levels of the liver, respectively in Wistar rats [89].

4.12 Gastroprotective activity

Z. rhoifolium Lam. stem bark EE prevents the formation of gastric lesions at 125–500 mg/kg dose by increasing enzymes like catalase (reduces oxidative stress) and also mucous secretion, nitric oxide (repair of gastrointestinal tract injury) [36]. It also helps in opening K_{ATP} channel to control H^+ pump and acid secretion. *Z. bungeanum* pericarp extract reduces the level of TNF-α, IL-1β, and IL-12 to reduce the inflammation in J774.1 colon cells [90]. Thus it can be utilized to treat ulcerative colitis.

4.13 Cardiovascular activity

Z. bungeanum EO at the concentration of 5, 10, and 20 mL/kg had a significant effect on deduction of cholesterol, hyperlipidemia, triglyceride, and low-density lipoprotein; it also aided in the induction of high-density lipoprotein [91]. The EO of *Z. bungeanum* also helped in relaxation of contracted aortic muscles by reducing calcium influx via calcium channels [90]. *Z. armatum* fruits hydroethanolic extract (dose administered—200 and 400 mg/kg body weight) succeeded in decreasing the elevated levels of cardiac diagnostic marker enzymes (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase-MB, troponin-T), lipid profile and antioxidants (enzymatic and nonenzymatic), to normal conditions. The results were comparable to a positive control verapamil, expected phytochemicals are yet to be identified [92].

4.14 Antiobesity activity

In a study, methyl cinnamate, an important bioactive compound of the *Z. armatum* suppressed the intracellular lipid accumulation [20]. It was possible at a concentration of 25 μM through Ca^{2+}/calmodulin-dependent protein kinase kinase 2 (CaMKK2)-phospho AMP-activated protein kinase (AMPK) signaling pathway, by downregulating the adipogenic transcription factors, sterol regulatory element binding protein-1 (SREBP-1), peroxisome proliferator-activated receptor γ (PPARγ), and CCAAT/enhancer-binding protein α (C/EBPα), as well as inhibiting the activity of PPARγ and glycerol-3-phosphate dehydrogenase (GPDH) in 3 T3-L1 preadipocyte cells [20].

5. *Zanthoxylum* as spice

"Sichuan pepper" with its pungent odor and numbing taste belongs to the genus *Zanthoxylum* [93]. According to Ji et al. [94] five species of Zanthoxylum—*Z. armatum*, *Z. bungeanum*, *Z. shinifolim*, *Z. simulans*, *Z. piperitum,* are commonly considered

as "spice" species of the family. Not only seeds, fruit, leaves, bark, and even root of this genus is used as spice in China, Japan, and Korea [95]. This pepper is used by the people of China to create a special "Mala" flavor, which literally refers to numbness and spiciness. More than hundred volatile compounds have been isolated, which are responsible for the unique spicy note and fragrance of this genus [96]. Some nonvolatile compounds have also been identified like alkylamides (sanshools, capsaicin) and polyphenolic compounds [97]. The genus has found a place in culinary as "five spice powder," in cosmetics, as well as in pharmaceutical too [98]. In cosmetics, the variable fragrance provided by the genus—sweet, spearmint, herbal, floral, fruity, rose, citrus—is of great significance [99]. This diversity is due to the presence of more than hundred volatile compounds like 1,8-cineole, 1-terpineol, 2,-nonenal, 2-tridecanone, α-elemol, α-pinene, β-pinene, geraniol, myrcene, neryl acetate, piperitone, rosefuran etc. [100]. The pungent property of the spice of this genus has been attributed to the presence of α-, β-, γ-δ-sanshool and hydroxyl α and β-sanshool [99]. In pharmacology the presence of polyphenolic compounds like flavonoids and glycosides make Sichuan pepper a good antioxidant and anti-inflammatory agent. Zhu et al. [98] has also reported the presence of antibacterial activity against both gram positive and negative bacteria in EO of *Z. bungeanum* fruit. EO of *Z. shinifolium* and *Z. piperitum* (broad spectrum) has been reported to have antiviral properties [94]. Most significantly, Sichuan pepper and its component sanshool amide have displayed inhibitory action on the formation of hetercyclic amines, which are carcinogenic to humans in beef grilling procedure [11, 101]. Utilization of analytical techniques to compare component analysis is lacking in the literature related to spice knowledge of the genus. Also according to Ji et al. [94] if the effect of heat (while cooking) is elaborated on the spice and its individual compound, it would be more beneficial to the herb and spice world.

6. Conclusion and future perspective

Zanthoxylum genus is a stockpile of medicinal plants brewing with therapeutic properties, as gathered from the above references of the recent decade. The readers can benefit with the traditional and current knowledge on the herbal aspect of several species *Z. acanthopodium, Z. acutifolium, Z. ailanthoides*, *Z. armatum, Z. bungeanum, Z. chalybeum, Z. chiloperone, Z. coreanum, Z. elephantiasis*, *Z. fagara, Z. flavum, Z. heitzii, Z. integrifoliolum*, *Z. leprieurii*, *Z. liebmannianum, Z. limonella*, *Z. martinicense*, *Z. monophyllum, Z. piperitum, Z. planispinum*, *Z. rhoifolium, Z. riedelianum*, *Z. scandens, Z. schinifolium*, *Z. schreberi, Z. tingoassuiba, Z. usambarense, Z. zanthoxyloides* to name a few, of this genus. The information can form the basis of research regarding drug formulations, conservation of medicinal plants, pharmacokinetics, and new drug discoveries, which are plant based in the future.

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