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Review article

# Pharmacological activities of *Zanthoxylum* L. plants and its exploitation and utilization

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ABSTRACT

The study aims to provide an up-to-date review at the advancements of the investigations on the ethnopharmacology, phytochemistry, pharmacological effect and exploitation and utilizations of *Zanthoxylum* L. Besides, the possible tendency and perspective for future research of this plant are discussed, as well. This article uses "*Zanthoxylum* L." "*Zanthorylum bungeanum*" as the keywords

*Abbreviations:* ZLP, Zanthoxylum L. plants; Z, Zanthoxylum; HD, hydrodistillation; SFE, supercritical fluid CO2 extraction; MAPKs, mitogen-activated protein kinases; AMPK, AMP-activated protein kinase; LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor; PGE2, prostaglandin E2; NO, nitric oxide; ROS, reactive oxygen species; ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NF-κB, nuclear factor-κB; CCL-5, C–C chemokine ligand 5; AP-1, activator protein-1; MyD88, myeloid differentiation factor 88; ZPE-LR, Z. piperitum; MMP-1/2/3/9/13, matrix metalloproteinase-1/2/3/9/13; HPRT1, hypoxanthine adenine phosphoribosyltransferase 1; RPL8, ribosomal protein L8; ZCO, Zanthoxylum coreanum; DNP-BSA, dinitrobenzene bovine serum albumin; DNCB, dinitrochlorobenzene; NC, nitidine chloride; TOP I, topoisomerase I; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; IRF3, interferon regulatory factor 3; CFA, Freund's complete adjuvant; DOX, doxorubicin; Skp2, S-phase kinase-associated protein 2; LC, lung cancer; NPC, nasopharyngeal carcinoma; T2DM, Type 2 diabetes mellitus; ZA, Zanthoxylum alkylamides; GSH, glutathione; SOD, superoxide dismutase; MDA, malondialdehyde; PPARγ, peroxisome proliferator-activated receptor γ; APOE, appolipoprein E; apoE-KO, appolipoprein E knockout; ZBP, polysaccharide in Z. bungeanum; Ve, vitamin E; Vc, vitamin C; MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; HBV, hepatitis B virus; MQEO, Maqian fruits essential oil; ZBE, Zanthoxylum bungeanum pericarp extract; HAS, Hydroxy-α-sanshool; ZBME, Zanthoxylum bungeanum Maxim extract; DTM, Dictamnine; EDN, Eudesmin; HBS, Hydroxyl-β-sanshool; BuOH, n-butanol; ZBBu, Zanthoxylum bungeanum; ALA, Alpha-linolenic acid; DKT, Daikenchuto; PAI-1, plasminogen activator inhibitor; ZSO, Z. bungeanum seed oil; MPO, Myeloperoxidase; ERK1/2, extracellular regulated protein kinases 1/2; Chk2, Checkpoint kinase 2; Bcl-2, B-cell CLL/lymphoma 2; HIF-1α, Hypoxia-inducible factor-1α; EZH2, Enhancer of zeste homolog 2; GSP, Glycosylated serum protein; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ASP, Asprosin; FoxOs, Forkhead box; MAFbx, Atrogin-1; MuRF1, Muscle ring finger 1; IGF-1, Insulin-like growth factor 1; ADP, Adiponectin; GLUT4, Glucose transporter protein 4; ACC, acetyl-CoA-carboxylase; HMGCR, hydroxy methylglutaryl coenzyme A reductase; LDLR, low density lipoprotein receptor; CAT, catalase; GSH-Px, glutathione peroxidase; GABA, Gamma-aminobutyric acid; Glu, Glutamic acid; GAD65, glutamate decarboxylase 65; cAMP, Cyclic adenosine monophosphate; PKA, protein kinase A; CK, Creatine kinase; LDH, lactate dehydrogenase; α-SMA, α-smooth muscle actin; TRPA1, Transient receptor potential ankyrin 1; HDF, human dermal fibroblasts cells; DSS, Dextran sulfate sodium; STZ, Streptozotocin; PTZ, Pentylenetertrazole; ISO, Isoproterenol; MI/R, myocardial ischemia/reperfusion; InMyoFib, Intestinal myofibroblast.

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Pharmacological activity
Exploitation and utilization study

and collects relevant information on *Zanthoxylum* L. plants through electronic searches (Elsevier, PubMed, ACS, Web of Science, Science Direct, CNKI, Google Scholar), relevant books, and classic literature about Chinese herb. The plants of this genus are rich in volatile oils, alkaloids, amides, lignans, coumarins and organic acids, and has a wide range of pharmacological activities, including but not limited to anti-inflammatory, analgesic, anti-tumor, hypoglycemic, hypolipidemic, antioxidant and anti-infectious. This article reviewed both Chinese and international research progress on the active ingredients and pharmacological activities of *Zanthoxylum* L. as well as the applications of this genus in the fields of food, medicinal and daily chemicals, and clarified the material basis of its pharmacological activities. Based on traditional usage, phytochemicals, and pharmacological properties, of *Zanthoxylum* L. species, which indicate that they possess diverse bioactive metabolites with interesting bioactivities. *Zanthoxylum* L. is a potential medicinal and edible plant with diverse pharmacological effects. Due to its various advantages, it may have vast application potential in the food and medicinal industries and daily chemicals. Nonetheless, the currently available data has several gaps in understanding the herbal utilization of *Zanthoxylum* L. Thus, further research into their toxicity, mechanisms of actions of the isolated bioactive metabolites, as well as scientific connotations between the traditional medicinal uses and pharmacological properties is required to unravel their efficacy in therapeutic potential for safe clinical application.

## 1. Introduction

The letter *Zanthoxylum* L. plants (ZLP) pertains to the taxonomic classification of Rutaceae shrubs, encompassing thorn trees and woody vines, with approximately 250 species dispersed globally [1]. ZLP serves as a significant medicinal and edible resource, exhibiting widespread distribution across region in Asia, Africa, Oceania, North America and other regions [2,3]. Both domestic and international research efforts have predominantly concentrated on the exploitation and advancement of ZLP, primarily emphasizing on *Zanthoxylum bungeanum* Manix., *Zanthoxylum schinifolium* Sieb. et Zucc., *Zanthoxylum nitidum* (Roxb.) DC., *Zanthoxylum armatum* DC., *Zanthoxylum echinocarpum* Hemsl., etc. Notably, the 2020 edition of the Chinese Pharmacopoeia incorporates the first three ZLP varieties [4].

According to the 2020 edition of the Chinese Pharmacopoeia, *Z. bungeanum* possesses attributes encompassing the warming of the gastrointestinal tract, alleviating discomfort, insecticidal properties, and itch relief. Its primary applications involve the treatment of conditions such as vomiting, diarrhea, abdominal cold pain, and abdominal discomfort arising from insect bites [4]. Contemporary investigations have confirmed the presence of various chemical components within ZLP, including volatile oils, alkaloids, amides, lignans, coumarins, and organic acids. Research has established that both extracts and individual compounds derived from *Zanthoxylum* L. exhibit a broad spectrum of pharmacological activities, garnering significant attention. These activities encompass anti-inflammatory, analgesic, anti-tumor, hypoglycemic, hypolipidemic, antioxidant, and anti-infectious properties. As a vital economic crop, ZLP possesses comprehensive utilization value, extending beyond food, medicinal and daily chemical applications. In this article, we comprehensively review recent developments concerning the traditional uses, origins, chemical constituents, pharmacological activities, underlying mechanisms and the exploitation and utilization of ZLP to provide a scientific foundation for the further advancement of this valuable resource.

## 2. Traditional uses of *Zanthoxylum* L. Plants (ZLP)

There are about 250 species of *Z.* in Rutaceae in the world. The countries where ZLP are cultivated mainly involve China, Japan, Korea, Nepal and Russia [5,6]. Among them, ZLP have the largest cultivated area and the highest yield in China. In China, this genus is represented by 39 species and 14 varieties [7].

ZLP has played an indispensable role in human health for a long time, as medicinal materials widely used in the medical field. In China, the usages of ZLP are recorded in many well-known medicinal literatures. It has been confirmed by traditional Chinese medicine (TCM) research that ZLP have the effects of promoting blood circulation and removing blood stasis, promoting qi and relieving pain, dispelling wind and dredging collaterals, detoxifying and detumescence, killing insects and relieving itching. It is widely used in the treatment of urinary tract infection, gynecological diseases, vomiting, diarrhea, hernia, stomach pain, toothache, rheumatism arthralgia, abdominal pain and snake bite. According to the 2020 edition of the Chinese Pharmacopoeia, a total of three *Z.* varieties were included, namely *Zanthoxylum bungeanum* Manix., *Zanthoxylum schinifolium* Sieb. et Zucc. and *Zanthoxylum nitidum* (Roxb.) DC. In traditional Chinese medicine compounds, the above three *Z.* plants are ordinarily used for compatibility to treat diseases.

In addition, Chinese people have a special classification system for TCMs, such as flavor, nature and meridians. Based on the conventional theory of the properties and actions in ancient Chinese herbal texts, ZLP possesses the following medical properties: spicy in flavor, warm in nature, and entering the spleen, stomach and kidneys meridians. These medical properties are very important in guiding the clinical application. Besides, it is not only an important TCM but forms a critical part of TCM prescriptions. By combining several drugs guided by the theory of TCM, the effect of drugs can be enhanced or synthesized to improve the original curative effect in clinical settings. Certain representative prescriptions exist, such as *Yu Lin Zhu*, which is composed of Panax ginseng C. A. Meyer, Poria.,

**Table 1**
The Prescriptions and traditional uses of *Zanthoxylum* L. in ancient Chinese Materia Medica.

| Prescriptions | The Title of the Books | Author | Dynasty | Traditional Uses | Efficacy |
|---|---|---|---|---|---|
| *Wu Mei Wan* (乌梅丸) | *Treatise on Febrile Diseases* | Zhang Zhongjing | Han | Visceral cold ascaris syndrome. | Calming intestinal ascaris by warming method |
| *Wu Xiong Ji Zhou* (乌雄鸡粥) | *Peaceful holy benevolent prescriptions* | Wang Huaiyin | Song | Tonifying qi and nourishing blood, stopping collapse and preventing miscarriage. It is suitable for the spleen deficiency and blood deficiency caused by the collapse of the blood or dripping blood or not clean, pale and thin blood color, complexion white or edema, body burnout, limbs not warm, shortness of breath and so on. | – |
| *Yu Lin Zhu* (毓麟珠) | *Jingyue's Complete Works* | Zhang Jingyue | Ming | Women 's qi and blood deficiency, liver and kidney deficiency, irregular menstruation, or after the wrong color light, or less abdominal pain, or continuous leaching, lumbar debility, abdominal cold pain, loss of libido, weak body, long time without conception, etc. | Invigorating vital energy and blood, warming the liver and kidney, strengthening Chong and Ren, regulating menstruation and assisting pregnancy |
| *Shen Xiao Gao* (神效膏) | *Jingyue's Complete Works* | Zhang Jingyue | Ming | Treatment of ecthyma, foot sores. | – |
| *Wan Ling Gao* (万灵膏) | *Wan 's family copied the prescription* | Wan Biao | Ming | Piji, not ulcer swelling toxin, scrofula phlegm nucleus, stumbling flashbacks, and abdominal pain, diarrhea, wind, stick sores. | Stimulating circulation to end stasis, dispersing swelling and relieving pain |
| *Hu Po Gao* (琥珀膏) | *The Golden Mirror of Medicine* | Wu Qian | Qing | Activating blood and detoxifying, resolving putridity. Treatment of hairline sores, germinal hairline edge, shaped like broomcorn millet, itchy pain hard, top white flesh red, and all kinds of sores and ulcers. | – |
| *Hai Tong Pi Tang* (海桐皮汤) | *The Golden Mirror of Medicine* | Wu Qian | Qing | The treatment of fall injury, tendon bone wrong pain more than. | Promoting vital energy and blood, stretching meridians, resolving swelling |
| *Wu Jia Pi Tang* (五加皮汤) | *The Golden Mirror of Medicine* | Wu Qian | Qing | Two frontal bones fall damage broken skin, two eyes and face edema. | Relieving the muscles and stimulating the blood circulation, relieving pain and eliminating blood stasis |
| *Li Zhong An Hui Tang* (理中安蛔汤) | *Classfied Treatments Based on Categorical Identification* | Lin Peiqin | Qing | Inactive yang, abdominal pain of ascaris. | Calming intestinal ascaris by warming method |
| *Lian Mei An Hui Wan* (连梅安蛔丸) | *Popular Treatise on Febrile Diseases* | Yu Genchu | Qing | Ascaris syndrome. | Calming intestinal ascaris by removing liver fire, relieving pain and syncope |
| *Ba Hu Qi Wei San* (巴呼七味散) | *The secret Fang Hai* | Jambala Chidansen Buddha Renlai | 19th century | For Heyi, Badagan Bahu disease (similar to goiter) | – |
| *Wu Wei Ji Li San* (五味蒺藜散) | *Collection of Misty Physicians* | Mirpong Langjatso | Late 19th century | It is used for joint pain and limitation of motion caused by ' Chen Pu ' disease and ' Qi Nai ' disease. | – |

*Z. bungeanum* Maxim., Angelica sinensis and other medicines. The traditional uses of prescriptions containing ZLP are described in Table 1.

The representative plant of *Z.* is *Zanthoxylum bungeanum* Maxim. (or *Zanthoxylum schinifolium* Sieb. et Zucc.). The utilization of *Z. bungeanum* resources in China can be traced back to the Shang Dynasty and can be used as a sacred fragrance. In ancient times, *Z. bungeanum* has been in a wild state; in the Spring and Autumn Period, *Z. bungeanum* has been used as medicine; until the Eastern Han Dynasty, *Z. bungeanum* began to be used as a traditional food condiment and preservative to reflect its application value due to its strong numb and spicy taste, especially the numb taste of the peel [8]. By the end of the Western Jin Dynasty, due to the further development of the practical functions of *Z. bungeanum* and the increase of social demand, China began to cultivate *Z. bungeanum* on a large scale, and gradually formed Hancheng in Shaanxi, Tai 'an in Shandong, Hanyuan in Sichuan, Jiangjin in Chongqing and other famous industrial bases. *Z. bungeanum* has been recorded in Chinese herbal books in past dynasties. It was first seen in the Book of Songs, and was first used as medicine in the Shennong Herbal Classic [9]. According to the 2020 edition of the Chinese Pharmacopoeia, *Z. bungeanum* has the effects of warming the middle and relieving pain, killing insects and relieving itching. It is mainly used to treat abdominal cold pain, vomiting and diarrhea, insect abdominal pain, external treatment of eczema, and Yin itching. In addition, according to the Compendium of Materia Medica, *Z.* bungeanum has the effects of dispelling cold and removing dampness, relieving depression, eliminating food, dredging triple energizer, warming the spleen and stomach, tonifying the right kidney, killing ascaris, and stopping diarrhea [10].

As a folk medicine, *Z.* nitidum has a long history. The ancient herbal medicine records that it mainly uses roots and stems as medicinal parts, and leaves, peels and fruits can also be used as medicine. *Z.* nitidum was first recorded in Shennong Bencao Jing in the name of Manjiao. It has the effects of dispelling wind and dredging collaterals, detumescence and detoxification, and oozing dampness and relieving pain. In ancient times, it was used to treat snake venom bites and toothaches [9]. The anti-inflammatory ingredients contained in *Z.* nitidum can also be used in toothpaste, which can relieve gingival swelling and pain, and improve oral problems. According to the 2020 edition of the Chinese Pharmacopoeia, *Z.* nitidum has the effects of promoting blood circulation and removing blood stasis, promoting qi and relieving pain, removing wind and dredging collaterals, detoxifying and detumescence. Mainly used for fall injury, stomach pain, toothache, rheumatic arthralgia, snakebite; external treatment of burns, scalds, etc.

In addition, *Z.* armatum DC., as one of the important varieties of ZLP, has a wide range of traditional uses. *Z.* armatum DC. is ordinarily made into soup and sauce in Nepal [11]. According to the literature, in Nepal 's local medical system, the decoction, seeds and fruits of *Z.* armatum DC. can play a therapeutic role [12,13]. China, represented by Sichuan and Chongqing, uses *Z.* armatum DC. to assist and beautify the taste of dishes. In addition, fresh *Z.* armatum DC. was directly eaten as pickles in some areas [14,15]. In China, *Z.* armatum DC.can also be used as the main raw material of medicinal wine. Its earliest record is in the Hongya County Chronicle of the Qing Dynasty (1813 A.D.), but it has been widely used as early as the Warring States period [16].

Overall, the above findings indicate outstanding traditional therapeutic applications of ZLP in food, medicine, chemical industry and other fields. However, their herbal uses have been reported to be utilized in only a few countries, primarily in China, Japan, Korea, and Nepal. Besides, folkloric uses of many species of ZLP are yet to be established. Therefore. additional studies should be aimed at assessing more species of this genus in diverse regions of the world to give a robust conclusion on the links between their traditional therapeutic claims and modern pharmacological studies.

## 3. Plant origins and chemical constituents of *Zanthoxylum* L. Plants (ZLP)

The primary active constituents of ZLP predominantly comprise volatile oils, alkaloids, and amides, with research efforts focusing extensively on these three major compounds. Furthermore, the genus is characterized by the presence of a limited quantity of lignans, coumarins, organic acids and flavonoids as additional chemical components. The source information of ZLP is shown in Table 2. Both domestic and international research efforts have predominantly concentrated on its chemical constituents of ZLP, mostly concentrated in 6 species, as shown in Table 3.

### 3.1. Volatile oil

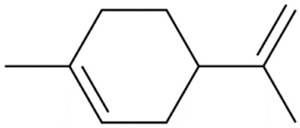
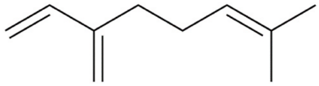
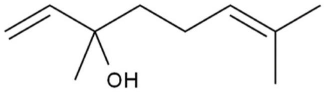
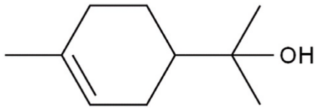
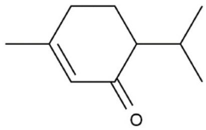
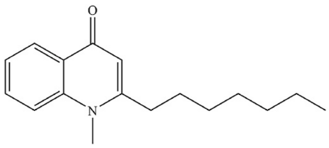
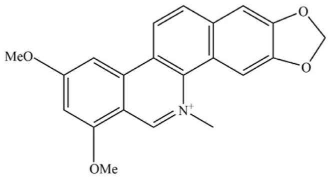
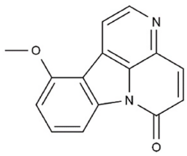
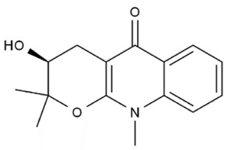
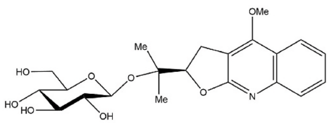
Volatile oil, in plant science, refers to steam-distilled components found in plant tissues, which are typically liquid substances with distinct plant-like odors and often represent the essential aroma of the plant [39]. Volatile oil is typically a complex mixture comprising dozens to hundreds of compounds [40]. Commonly, volatile oils are rich in monoterpenes, sesquiterpenes, and their oxygenated derivatives. However, some volatile oils may contain other important components [41]. Typically, two or three main compounds are present in high concentrations ($> 30\ \%$), while others are found only in trace amounts [42].

Among the various ZLP species, the volatile oil composition of Z. is the most extensively studied. Volatile oil is a critical benchmark for assessing the quality of *Z. bungeanum* and serves as the primary source of its distinct aroma. Its widespread distribution, coupled with variations in climatic conditions, soil composition and storage and extraction techniques, exerts a significant influence on the

**Table 2**
Plant origin from plants of *Zanthoxylum* L.

| No. | Botanical name | No. | Botanical name |
|---|---|---|---|
| 1. | *Zanthoxylum acanthopodium* | 20. | *Z. leprieurii* |
| 2. | *Z. ailanthoides* | 21. | *Z. monophyllum* |
| 3. | *Z. arborescens* | 22. | *Z. myriacanthum* |
| 4. | *Z. armatum* | 23. | *Z. nitidum* |
| 5. | *Z. atchoum* | 24. | *Z. nitidum* var. *tomentosum* |
| 6. | *Z. austrosinense* | 25. | *Z. ovalifolium* |
| 7. | *Z. avicennae* | 26. | *Z. paracanthum* |
| 8. | *Z. beecheyanum* | 27. | *Z. piasezkii* |
| 9. | *Z. buesgenii* | 28. | *Z. piperitum* |
| 10. | *Z. bungeanum* | 29. | *Z. quinduense* |
| 11. | *Z. chiloperone* | 30. | *Z. rhetsa* |
| 12. | *Z. clava-hercuis* | 31. | *Z. scandens* |
| 13. | *Z. dimorphophyllum* | 32. | *Z. schinifolium* |
| 14. | *Z. echinocarpum* | 33. | *Z. simulans* |
| 15. | *Z. esquirolii* | 34. | *Z. syncarpum* |
| 16. | *Z. heitzii* | 35. | *Z. tingoassuiba* |
| 17. | *Z. hyemale* | 36. | *Z. usambarense* |
| 18. | *Z. integrifoliolum* | 37. | *Z. wutaiense* |
| 19. | *Z. kwangsiense* | 38. | *Z. zanthoxyloides* |

**Table 3**
Chemical constituents of plants of *Zanthoxylum* L.

| Classification | Component | Plant origin/site | CAS number | Molecular formula | Structure | References |
|---|---|---|---|---|---|---|
| Volatile oil | Limonene | *Zanthoxylum bungeanum*/- | 138-86-3 | $C_{10}H_{16}$ |  | [17] |
| | Myrcene | *Z. bungeanum*/- | 123-35-3 | $C_{10}H_{16}$ |  | [18] |
| | Linalool | *Z. bungeanum*/- | 78-70-6 | $C_{10}H_{18}O$ |   | [18] |
| | α-Terpineol | *Z. bungeanum*/- | 10482-56-1 | $C_{10}H_{18}O$ |   | [17] |
| | Piperitone | *Z. bungeanum*/- | 89-81-6 | $C_{10}H_{16}O$ |   | [18] |
| Alkaloids | Schinifoline | *Z. schinifolium*/- | 80554-58-1 | $C_{17}H_{23}NO$ |   | [19] |
| | 7-methoxy-8-demethoxynitidine | *Z. nitidum* /Stems, branches | – | $C_{21}H_{18}O_4N^+$ |   | [20] |
| | Amaroridine | *Z. nitidum* /Stems | – | $C_{15}H_{10}N_2O_2$ |   | [21] |
| | Ribalinine | *Z. nitidum* /Roots | 7688-58-6 | $C_{15}H_{17}NO_3$ |   | [22] |
| | Zanthonitiside A | *Z. nitidum* /Stems, branches | – | $C_{21}H_{27}O_8N$ |   | [23] |

(*continued on next page*)

**Table 3** (*continued*)

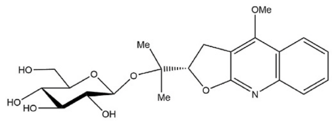
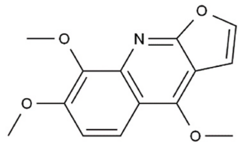
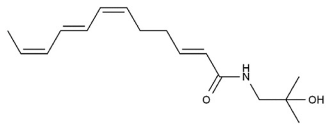
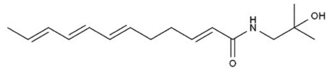
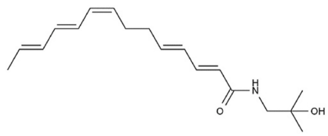
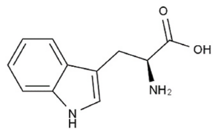
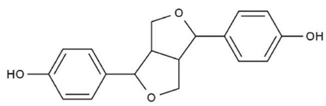
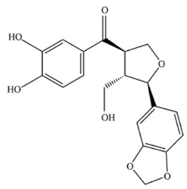
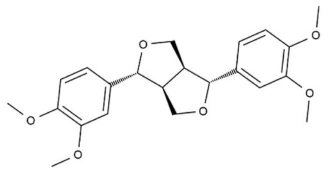
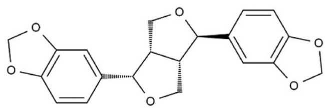
| Classification | Component | Plant origin/site | CAS number | Molecular formula | Structure | References |
|---|---|---|---|---|---|---|
| | Zanthonitiside B | *Z. nitidum* /Stems, branches | – | $C_{21}H_{27}O_8N$ |  | [23] |
| | Skimmianine | *Z. bungeanum*/ Roots, pericarp | 83-95-4 | $C_{14}H_{13}NO_4$ |  | [24] |
| Amides | Hydroxy-α-sanshool (HAS) | *Z. bungeanum*/- | 83883-10-7 | $C_{16}H_{25}NO_2$ |  | [25] |
| | Hydroxy-β-sanshool (HBS) | *Z. bungeanum*/- | 97465-69-5 | $C_{16}H_{25}NO_2$ |  | [25] |
| | Hydroxy-γ-sanshool | *Z. bungeanum*/- | – | $C_{16}H_{25}NO_2$ |  | [25] |
| | Tryptophan | —/— | 73-22-3 | $C_{11}H_{12}N_2O_2$ |  | [26] |
| Lignans | Ligballinol | *Z. nitidum* /Entire plant | – | $C_{18}H_{18}O_4$ |  | [27] |
| | Nitidumlignan A | *Z. nitidum* /Entire plant | – | $C_{19}H_{17}O_7$ |  | [27] |
| | Eudesmin (EDN) | *Z. bungeanum* /Leave | 526-06-7 | $C_{22}H_{26}O_6$ |  | [28] |
| | Asarinin | *Z. bungeanum*/- | 133-04-0 | $C_{20}H_{18}O_6$ |  | [29] |

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**Table 3** (*continued*)

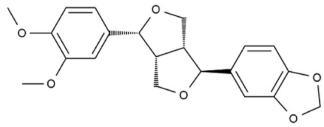
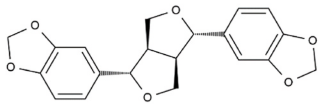
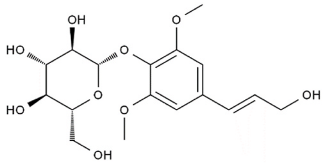
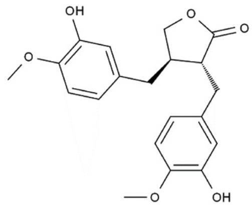
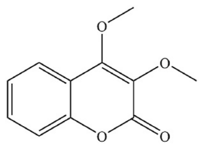
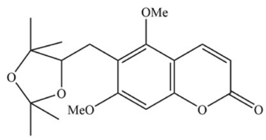
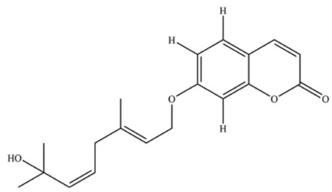
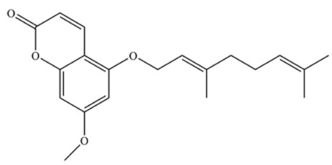
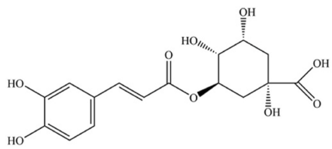
| Classification | Component | Plant origin/site | CAS number | Molecular formula | Structure | References |
|---|---|---|---|---|---|---|
| | Fargesin | *Z. bungeanum/-* | 31008-19-2 | $C_{21}H_{22}O_6$ |  | [30] |
| | Sesamin | *Z. bungeanum/* Entire plant | 607-80-7 | $C_{20}H_{18}O_6$ |  | [27] |
| | Syringin | *Z. nitidum* /Entire plant | 118-34-3 | $C_{17}H_{24}O_9$ |  | [27] |
| | Prestegane B | *Z. nitidum/-* | 93376-04-6 | $C_{20}H_{22}O_6$ |  | [25] |
| Coumarins | Dimethoxycoumarin | *Z. nitidum/-* | 6850-95-9 | $C_{11}H_{10}O_4$ |  | [31] |
| | Isopranferin | *Z. nitidum* /Roots | – | $C_{19}H_{24}O_6$ |  | [31] |
| | 7-[(E)-7′-Hydroxy-3′, 7′-Dimethylocta-2′, 5′-Dienyloxy]-Coumarin | *Z. tingoassuiba/-* | – | $C_{19}H_{22}O_4$ |  | [32] |
| | 5-Geranyloxy-7-methoxycoumarin | *Z. nitidum/-* | 7380-39-4 | $C_{20}H_{24}O_4$ |  | [33] |
| Organic acid | Chlorogenic acid | *Z. bungeanum/-* | 327-97-9 | $C_{16}H_{18}O_9$ |  | [34] |

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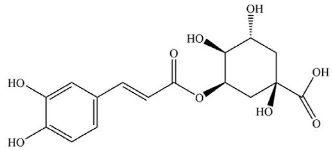
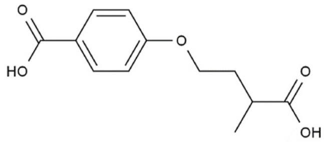
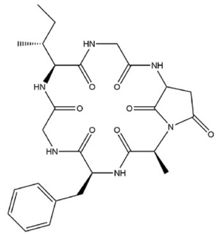
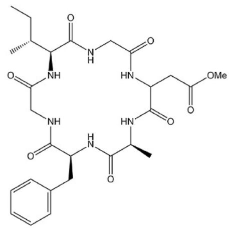
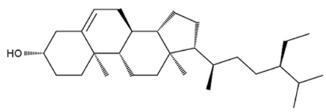
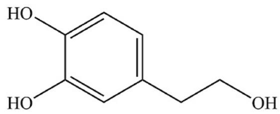
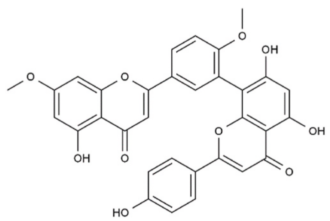
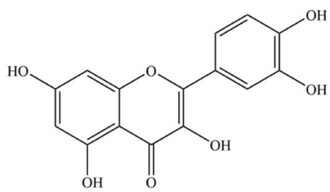
**Table 3** (*continued*)

| Classification | Component | Plant origin/site | CAS number | Molecular formula | Structure | References |
|---|---|---|---|---|---|---|
| | Neochlorogenic acid | *Z. bungeanum*/- | 906-33-2 | $C_{16}H_{18}O_9$ |  | [34] |
| Others | Sporovexin A | *Z. nitidum* /Entire plant | – | $C_{12}H_{14}O_5$ |  | [35] |
| | Nitidumpeptin A | *Z. nitidum* /Entire plant | – | $C_{26}H_{34}N_6O_7$ |  | [36] |
| | Nitidumpeptin B | *Z. nitidum* /Entire plant | – | $C_{27}H_{38}N_6O_8$ |  | [36] |
| | β-Sitosterol | *Z. bungeanum*/ Pericarp | 5779-62-4 | $C_{29}H_{50}O$ |  | [37] |
| | Hydroxytyrosol | *Z. bungeanum*/- | 10597-60-1 | $C_8H_{10}O_3$ |  | [26] |
| | Ginkgetin | *Z. nitidum* /Entire plant | 481-46-9 | $C_{32}H_{22}O_{10}$ |  | [35] |
| | Quercetin | *Z. bungeanum*/- | 117-39-5 | $C_{15}H_{10}O_7$ |  | [38] |

volatile oil's chemical constituents and content [43–46]. The constituents of the volatile oil in *Z. bungeanum* can be categorized into olefins, alcohols, ketones, aldehydes, esters and epoxy compounds. Currently, methods for extracting and distilling volatile oil from *Z. bungeanum* primarily include steam distillation, organic solvent extraction and supercritical carbon dioxide extraction, among others. Key components found in the volatile oil of *Z. bungeanum* comprise limonene, linalool, linalyl acetate and γ-terpineol.

Zhang et al. [17] used both the method of hydrodistillation (HD) and supercritical fluid $CO_2$ extraction (SFE) to extract volatile oil from *Z. bungeanum*, and in the HD extract, the primary components they identified were linalool (25.99 %), limonene (19.34 %), linalyl anthranilate (12.22 %), 4-terpineol (10.49 %), eucalyptus oil (6.53 %) and α-terpineol (5.02 %). On the other hand, the SFE extracts were predominantly composed of nonanoic acid (21.43 %), γ-terpinene (14.51 %), eucalyptus oil (13.45 %), α-terpineol (5.83 %) and caryophyllene oxide (5.48 %). These different extraction methods resulted in notable variations in the volatile oil components of *Z. bungeanum*. Zhang et al. [18] also conducted a comparative analysis of volatile oil components in fresh and dried *Z. bungeanum* using the GC-MS method and revealed that the content of the five main components, namely linalool, D-limonene, eucalyptus oil, 3-nonanone and β-myrcene, was similar in both fresh and dried *Z. bungeanum*. In a separate study, Bian et al. [47] utilized the GC-MS method to assess the volatile oil components in *Z. bungeanum* before and after stir-frying and reported that the compounds with higher content in the stir-fried *Z. bungeanum* were identified as linalyl acetate, linalool and limonene and that the volatile oil content in stir-fried products was lower than in raw products.

### 3.2. Alkaloids

Alkaloids are a class of compounds commonly present in ZLP, particularly in the roots and stem bark, where they are distinctive components [48]. These alkaloids in ZLP are characterized by complex nitrogen heterocyclic structures and can be categorized into four structural types based on their parent nucleus: quinoline derivatives (I), isoquinoline derivatives (II), benzophenanthridine derivatives (III) and quinolone derivatives (IV), mainly isoquinoline derivatives [49,50]. They may exist either in a free form or as quaternary ammonium salts. To date, over 200 alkaloids have been identified in ZLP. Notably, schinifoline is the first 4-quinolinone alkaloid discovered in this genus [51]; Additionally, Wu et al. [52] were the first to isolate and identify simulanoquinoline, a dimeric alkaloid formed by a carbon-carbon bond between dihydrobenzo[c] phenanthridine and 2-quinolone, which exhibit a diverse range of unique and significant physiological effects in ZLP.

### 3.3. Amides

Based on existing literature, approximately 26 species of ZLP have been identified as containing amides, with *Z. bungeanum* being the species richest in amides [53]. Amide compounds are distributed in various parts of ZLP, including the roots, stems, leaves, peels, fruits, seeds and other plant components [53]. Moreover, it has been established that amides are characteristic constituents within the genus. Amide compounds found in ZLP can be broadly categorized into aliphatic and aromatic amide components, with aliphatic amides comprising the majority of these compounds (about 66.7 % of the total) [54]. Presently, there exist several methods for extracting amides from ZLP, including steam distillation, organic solvent extraction, supercritical $CO_2$ extraction, and others.

The amide compounds found in ZLP are also referred to as *Zanthoxylum numb-taste*. Numerous studies have indicated that they serve as a notable source of nitrogen and belong to a series of chain-like unsaturated fatty acid amides, sharing similar structural characteristics. Some of these amides exhibit strong irritation properties, while others possess aromatic ring structures [55]. These numbing or pungent-tasting substances are primarily concentrated in the peel, with lower levels found in the flowers and leaves of ZLP. It is worth noting that the content and composition of these numbing-tasting substances vary depending on factors such as harvest time and the plant's origin [56,57]. Despite the wealth of research, the relationship between the molecular structure of amide components and the pungent flavor characteristics of *Z. bungeanum* has not been thoroughly explored, and there is a lack of systematic reports on the correlation between molecular structure and pungency intensity. The discovery of the first amide compound, α-sanshool, by researcher CROMBIE L [58]. from the bark of *Zanthoxylum clava-herculis* dates back to 1954. Based on the research conducted by scholars, the polyene amides in *Z. bungeanum* are predominantly represented by "sanshool," encompassing α-sanshool, β-sanshool, γ-sanshoo, δ-sanshool and their homologs, which contain one hydroxyl group in the amino group (hydroxyl-α-sanshool, hydroxyl-β-sanshool, hydroxyl-γ-sanshool, hydroxyl-δ-sanshool) [59–64].

### 3.4. Lignans

Lignans constitute a distinctive class of natural compounds resulting from the oxidative polymerization of phenylpropanoid derivatives (i.e., C6–C3 monomers). They are widely distributed in nature and are known for their diverse pharmacological activities, primarily as dimers, though some exist as trimers or tetramers [65]. Lignan molecules contain multiple asymmetric carbon atoms that make them susceptible to isomerization when exposed to acids or alkalis. The pharmacological activity of lignans is closely related to their specific molecular configurations. In the context of ZLP, the lignans present are predominantly diepoxy lignans, specifically diphenyl bis-tetrahydrofuran derivatives, with most belonging to type I (L-isomer), and sometimes the bis-tetrahydrofuran ring may undergo cleavage [66]. Most lignans in this genus are found in their free form, although a few exist as glycosides. Notable examples of ZLP lignans include eucalyptol, sesamin, asarinin, and Fargesin [29].

### 3.5. Coumarins

Coumarins, also known as 1,2-benzopyranone or *o*-naphthone, represent a broad class of natural compounds characterized by a benzo-α-pyranone nucleus. Their distinctive blue fluorescence is a result of their capacity to absorb ultraviolet light [67]. The simplest coumarin, known as basic coumarin, was first isolated from Dipteryx odorata [68]. Subsequently, it has been determined that coumarin is present in both monocotyledonous and dicotyledonous plants, with significant concentrations found in the roots, stems, and leaves of Umbelliferae, Rutaceae, and Asteraceae. Moreover, small quantities of coumarin are also found in animals and microorganisms. In plants, coumarin generally exists in the form of either a free compound, which typically possesses an aromatic scent or glycosides, which lack fragrance once glycosylated [67]. To date, over 70 distinct coumarin compounds have been isolated from ZLP. These coumarins can be categorized into three main groups based on their structural substituents and positions: simple coumarins, furan coumarins, and pyran coumarins. Notably, pyran coumarins are thought to form through the cyclization of isopentenyl and o-hydroxyl groups on the benzene ring of coumarins, in addition to furan coumarins [69,70]. In ZLP, the predominant type of coumarins present is simple coumarins.

### 3.6. Organic acids

Organic acids are a class of acidic compounds found in both natural and synthetic forms, which are distributed widely in various plant parts, particularly in leaves, roots and fruits [71]. The most prevalent type of organic acid is carboxylic acid (R–COOH), characterized by the carboxyl (-COOH) functional group. Carboxyl-containing organic acids are commonly found in various Chinese herbal medicines. In the context of ZLP, more than 10 distinct organic acids have been successfully isolated and identified, which include 10 common fatty acids and 4 aromatic acids. The principal fatty acid components are palmitic acid, palmitoleic acid, oleic acid, linoleic acid and linolenic acid [72]. Of significance, α-linolenic acid was isolated and identified by Yang et al. [73] from *Z. bungeanum*.

### 3.7. Other components

ZLP also contains various other components, including terpenoids, sterols, hydrocarbons and flavonoid glycosides [74,75]. The flavonoids are predominantly found in the flowers, leaves and fruits of ZLP, typically in the form of glycosides [69,34].

## 4. Pharmacological activity and mechanism of *Zanthoxylum* L. Plants (ZLP)

### 4.1. Anti-inflammatory

Inflammation represents a defensive response of vascularized living tissues to various injurious stimuli, which can manifest in any part or tissue of the body [76]. Extracts and individual compounds derived from ZLP, including volatile oils, phenylpropanoids, alkaloids, amides and flavonoids, exhibit anti-inflammatory properties, which in ZLP can mitigate the inflammatory response through various mechanisms, both *in vitro* and *in vivo*. These mechanisms include inhibiting the activation of mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) signaling pathways, reducing the release of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, tumor necrosis factor (TNF)-α, prostaglandin E2 (PGE2), LTC4S, nitric oxide (NO) and reactive oxygen species (ROS), as well as down-regulating the protein expression of adhesion molecules like intercellular cell adhesion molecule-1 (ICAM-1), E-selectin and vascular cell adhesion molecule-1 (VCAM-1). Furthermore, they decrease superoxide anion production and elastase release while increasing the release of the anti-inflammatory cytokine IL-10. These findings offer valuable insights into the underlying mechanisms of inflammation and provide novel avenues for inflammation treatment. The mechanism of action is shown in Fig. 1.

Zhang et al. [77] demonstrated the robust anti-inflammatory activity of petroleum ether and ethyl acetate extracts (Decarine), known as Decarine, derived from *Zanthoxylum myriacanthum* var. pubescens. This activity was evident in the reduction of lipopolysaccharide (LPS)-induced production of NO, TNF-α and IL-1β in both RAW264.7 and THP-1 cells. Santhanam et al. [78] investigated the anti-inflammatory potential of hesperidin, a flavonoid compound isolated from *Z. rhetsa*, on UVB-induced (290–320 nm) HDF cells. The experimental findings revealed that hesperidin significantly inhibited the production of inflammatory cytokines such as IL-6, IL-1β and TNF-α in these cells. Furthermore, hesperidin down-regulated the expression of NF-κB, matrix metalloproteinase-1 (MMP-1), MMP3 and MMP9. In addition, the ethanol extract from the leaves and twigs of *Z. piperitum* (ZPE-LR) effectively reduced ear edema induced by 12-oxo-tetradecanol-13-acetate (TPA) in mice, reducing both the thickness and weight of the edema. This extract also dose-dependently down-regulated the mRNA expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), as well as the protein expression of COX-2. Furthermore, *in vitro* studies revealed that ZPE-LR significantly down-regulated the expression of iNOS and COX-2 proteins in LPS-induced RAW 264.7 cells and inhibited the production of ROS and hypoxanthine adenine phosphoribosyltransferase 1 (HPRT1) while increasing the production of ribosomal protein L8 (RPL8) [79].

The volatile oil derived from ZLP exhibits potent anti-inflammatory effects by reducing the levels of inflammatory mediators. Specifically, the volatile oil from *Zanthoxylum coreanum* (ZCO) significantly inhibits the release of IL-4 in RBL-2H3 cells induced by 2,4-dinitrobenzene bovine serum albumin (DNP-BSA) and PMA/A23187. It also diminishes the release of TNF-α, IL-6 secretion and NO production in LPS-stimulated RAW 264.7 macrophages while concurrently reducing the expression of iNOS and COX-2 proteins. Furthermore, ZCO lowers the transcription of NF-κB and the expression of NF-κB p65 protein, inhibits the phosphorylation of JNK, ERK and p38 proteins, and elevates the level of IkB-α. *In vivo* studies have demonstrated that ZCO can mitigate ear edema induced by DNCB

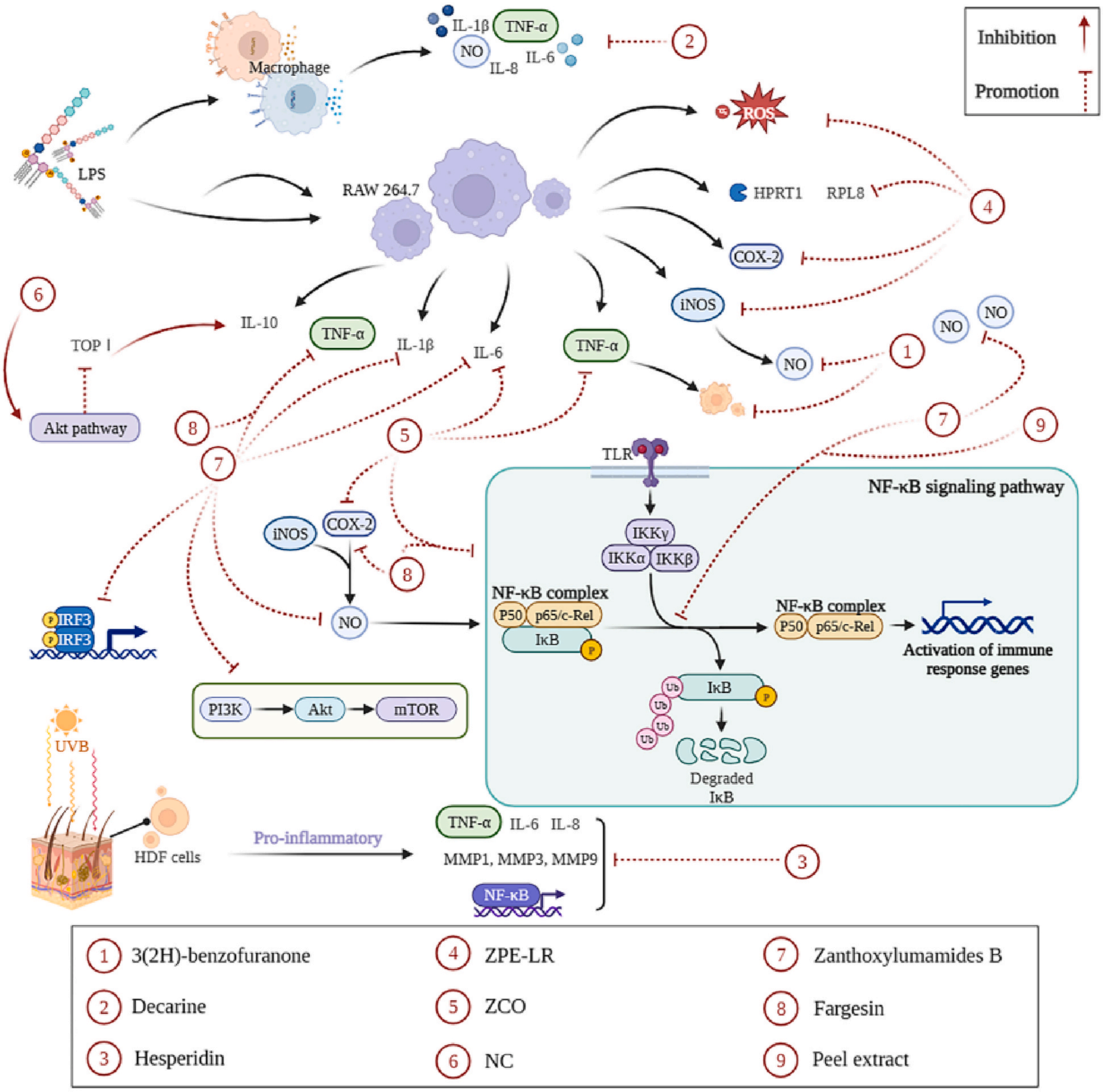



**Fig. 1.** The mechanism of anti-inflammatory effect of *Zanthoxylum* L. plants (ZLP).

in mice, ameliorate skin damage and significantly reduce epidermal and dermal thickness, along with reducing inflammatory cell infiltration [80].

Qin et al. [27] evaluated the *in vitro* anti-neuroinflammatory activity of 20 phenylpropanoids isolated from various *Z. nitidum* using LPS-induced BV-2 microglial cells. The results revealed that four compounds exhibited significant inhibitory effects on LPS-induced NO production. Notably, sesaminone was found to primarily reduce neuroinflammation by targeting the LPS-induced NLRP3/caspase-1 signaling pathway in BV-2 microglia. The phenanthridine alkaloid nitidine in *Z. nitidum*, also known as nitidine chloride (NC), which is naturally present in chloride form, was investigated by Yang et al. [81]. Their findings demonstrated that NC (2 μM) significantly increased the production of IL-10 and its mRNA levels in LPS-stimulated RAW 264.7 macrophages. Further mechanistic studies revealed that NC increased IL-10 production by enhancing the protein kinase B (Akt) signaling pathway while inhibiting DNA topoisomerase I (TOP I). Zanthoxylumamides B displayed effective inhibition of mRNA and protein expression of iNOS, COX-2, IL-1β, TNF-α and IFN-β. Additionally, they down-regulated the activation of phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and MAPKs (ERK, p38, and JNK), as well as interferon regulatory factor 3 (IRF3). These compounds also reduced the nuclear translocation of NF-κB subunits and prevented the over-expression of IKKα/β and IkB-α phosphorylation. Their mechanism of action may be associated with the inhibition of NF-κB activation, myeloid differentiation factor 88 (MyD88), and IRF3 signaling pathways in LPS-stimulated macrophages [82].

Furthermore, Pham et al. [83] discovered that Fargesin could inhibit PKC-dependent AP-1 and NF-κB signaling pathways, thereby demonstrating anti-inflammatory properties in monocyte-macrophage (THP-1) cells. Existing literature indicates that Fargesin can reduce inflammation by promoting pathways related to RCT, CEBPα$^{S21}$/LXRα and TLR4/NF-κB, ultimately inhibiting atherosclerosis [84]. Additionally, it may inhibit NF-κB signal transduction to exert anti-inflammatory effects in chemical-induced inflammatory bowel disease [85]. Guan et al. [86] reported that pyrrolezanthine (33 μmol/L) can inhibit the expression of TNF-α protein through the MAPK p38 and NF-κB signaling pathways. This inhibition is coupled with the stimulation of IL-1β and IL-6 release, resulting in anti-inflammatory effects on LPS-induced RAW-264.7 cells. Su et al. [87] identified Isofraxidin as a compound capable of mitigating inflammation in human nucleus pulposus cells induced by IL-1β. This anti-inflammatory effect is achieved through the inhibition of inflammatory mediators and cytokines.

### *4.2. Analgesic*

ZLP and its active ingredients can exert analgesic effects through various signal transduction mechanisms. In a study conducted by Qin et al. [88], a mouse model of Freund's complete adjuvant (CFA)-induced analgesia was established, and *Z. nitidum* extract (100 mg/kg) was administered as an intervention. The results indicated that compared to the model group, the administration group exhibited a significant reduction in foot swelling volume, alleviation of inflammatory foot injury, and a notable decrease in the number of neutrophils. Additionally, the mechanical threshold and thermal hyperalgesia induced by CFA were significantly increased following 3–7 days of drug treatment. Furthermore, the mRNA expression levels of TNF-α, IL-1β, IL-6 and NF-κB p65 were down-regulated. The *Z. nitidum* extract also effectively inhibited the overexpression of ERK1/2 and NF-κB p65 phosphorylation. Taken together, these findings suggest that the potential analgesic mechanism of *Z. nitidum* extract involves the reduction of CFA-induced inflammatory pain by inhibiting the ERK1/2 and NF-κB signaling pathways to mitigate inflammatory responses and alleviate inflammatory injury.

Wu et al. [37] employed network pharmacology to investigate and elucidate the mechanism underlying the analgesic effect of *Z. bungeanum* and reported that its analgesic effect is mediated through three key signaling pathways: mitogen-activated protein kinase, phosphoinositide 3-kinase-protein kinase B-mammalian target of rapamycin, and IκB kinase-nuclear factor κB-cyclooxygenase 2, which collectively contribute to the analgesic effects.

Amide compounds serve as the foundational components responsible for the treatment of inflammatory pain by ZLP. Pereira et al. [89] demonstrated that *Z.* significantly alleviates pain induced by formalin and capsaicin. Tsunozaki et al. [90] also revealed that hydroxy-α-sanshool (HAS), a compound found in ZLP, exerts analgesic effects by inhibiting the excitation of voltage-gated $Na^+$ channels on Aδ mechanical pain receptors. Additionally, studies have suggested that the active ingredient skimmianine within ZLP may also play a central role as the primary material basis for its analgesic properties [91].

### *4.3. Anti-tumor*

In recent years, researchers have conducted extensive investigations into the anti-tumor properties of various parts of the natural ZLP plant, including its roots, stems, leaves and fruits, revealing that extracts from ZLP and its individual components possess a wide-ranging spectrum of anti-tumor effects and may effectively inhibit the growth and proliferation of various tumor cell lines, showcasing significant potential for further exploration in oncology research. The mechanism of action is shown in Fig. 2.

Pang et al. [92] discovered that *Z. bungeanum* seed oil effectively inhibits the invasion and proliferation of melanoma cell line A375 by inducing apoptosis and arresting cells in the G1 phase. This inhibitory effect is selective, primarily targeting A375 cells. Meng et al. [93] isolated a new compound, bungsteroid A, from the ethyl acetate fraction of *Z. bungeanum*. This compound exhibits inhibitory activity against human hepatoma cell Hep G2, human breast cancer cell MCF-7 and human cervical cancer cell HeLa, with half inhibitory concentration ($IC_{50}$) values of (56.3 ± 1.1), (64.2 ± 0.9), and (74.2 ± 1.3) μmol/L, respectively.

The structural diversity of ZLP's main chemical components underpins its wide array of pharmacological activities, with particularly notable anti-tumor potential. Tian et al. [94] observed inhibitory effects against four tumor cell lines (i.e., gastric tumor cell SGC7901, cervical tumor cell HeLa, colon tumor cell HT29 and liver tumor cell Hep G2) when using total alkaloid extracts from *Z. ailanthoides*, *Z. simulans* and *Z. chalybeum*. At a concentration of 200 μg/mL, the inhibition rate was 60.71 %–93.63 %. Component analysis results further indicated that the anti-tumor activity of these three plants likely originates from benzophenanthridine alkaloids. In related investigations, it was found that NC could exert anti-ovarian cancer effects through various pathways, including the ERK signaling pathway, Fas signaling pathway and Akt pathway, among others. The mechanisms involved are as follows: (1) Suppression of MMP-2/9 expression via the ERK signaling pathway, consequently inhibiting the migration and invasion of ovarian cancer cells [95]; (2) Inhibition of ovarian cancer cell proliferation and induction of apoptosis by activating the Fas signaling pathway [96]; (3) Induction of apoptosis and inhibition of cell proliferation through the Akt pathway, with a synergistic inhibitory effect when combined with doxorubicin (DOX) in ovarian cancer cells [97]; (4) Reduction of S-phase kinase-associated protein 2 (Skp2) expression in ovarian cancer cells, thereby exerting its anti-tumor activity [98].

Furthermore, Qin et al. [36] discovered that Nitidumpeptins B from *Z. nitidum*, in combination with gefitinib, exhibited a synergistic anti-proliferative effect in acquired gefitinib-resistant non-small cell lung cancer cells (HCC827-gef). The potential mechanism underlying this synergy may be linked to the inhibition of YAP expression in these cells. Jiang et al. [28] also reported that EDN, with an $IC_{50}$ of 18.3 μmol/L, effectively inhibited the growth of lung cancer (LC) A549 cells, which is likely associated with the induction of

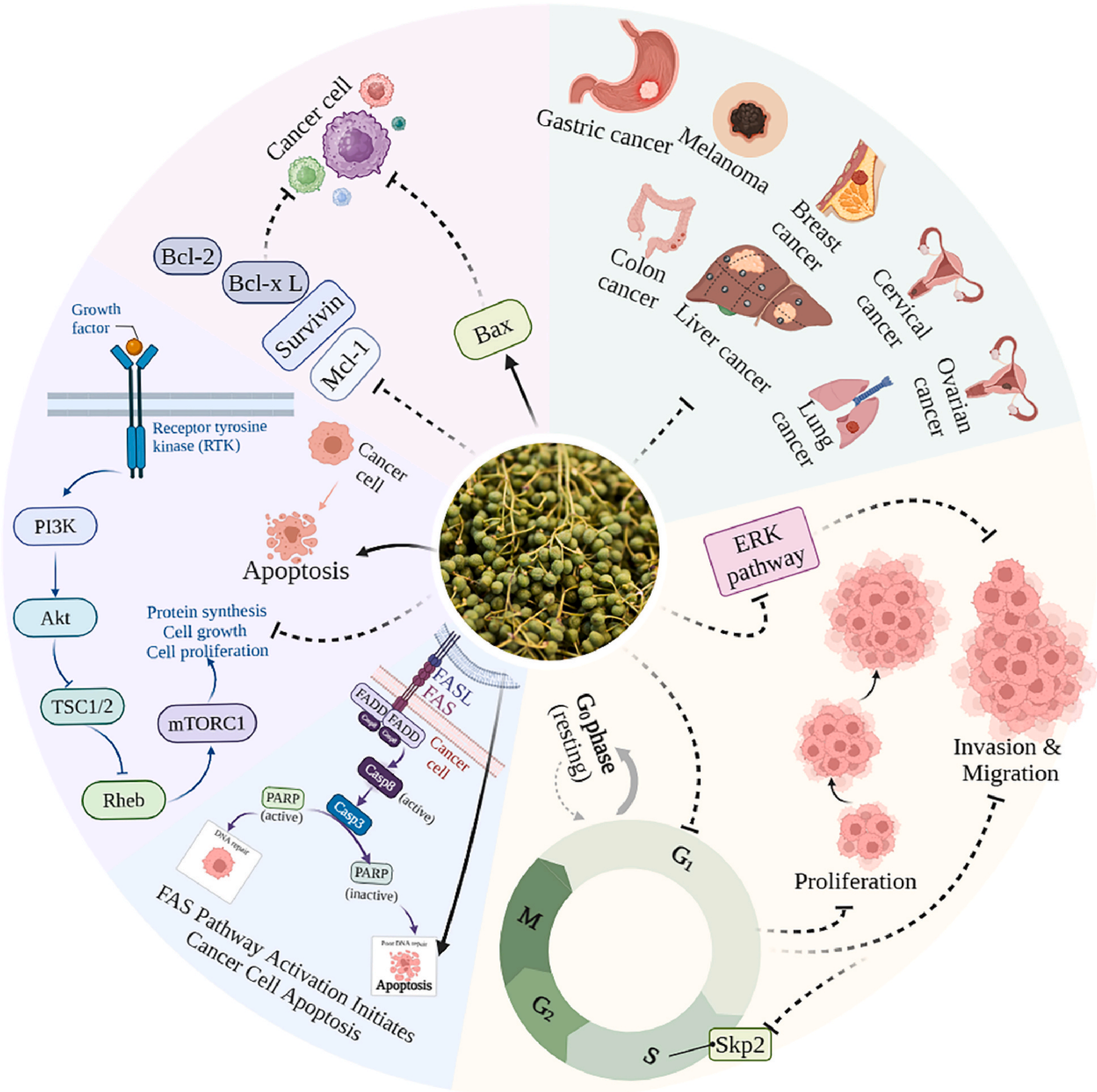



**Fig. 2.** The mechanism of anti-tumour effect of *Zanthoxylum* L. plants (ZLP).

mitochondrial-mediated apoptosis. Additionally, EDN, at concentrations of 10, 20 and 30 μmol/L, down-regulated the expression of EZH2 by inhibiting the Akt signaling pathway, leading to the inhibition of viability and induction of apoptosis in nasopharyngeal carcinoma (NPC) cells [99].

## 4.4. Hypoglycemic

ZLP and their active ingredients could exert hypoglycemic effects by regulating glucose and lipid metabolism and inhibiting α-glucosidase.

### 4.4.1. Regulation of glycolipid metabolism

Research has demonstrated the tightly coordinated relationship between glucose and lipid metabolism pathways. Insulin signaling plays a pivotal role in this synergy by influencing the expression of enzymes like fatty acid synthase and acetyl-CoA carboxylase through the regulation of the PI3K pathway, subsequently impacting fatty acid synthesis and lipid metabolism. Conversely, disruptions in lipid metabolism, such as lipid inflammation and ectopic lipid accumulation, can result in insulin resistance, which is characterized by impaired glucose metabolism, reduced glucose uptake and elevated blood glucose levels, ultimately leading to type 2 diabetes. Furthermore, it can also impair the function of β-cells in insulin-target organs, further reducing insulin sensitivity [100]. Glucose and lipid metabolism are inherently interconnected processes that collaborate to supply the body with the energy it requires for vital functions, underscoring how disorders in both glucose and lipid metabolism are primary contributors to the development and progression of various chronic diseases.

In modern medicine, the assessment of the physiological benefits of *Z. alkylamides* (ZA), a distinctive pharmacological active compound found in *Z. bungeanum*, has emerged as a prominent research focus. Wei et al. [101] conducted experiments using a rat model of Type 2 diabetes mellitus (T2DM) to explore the potential of ZA in ameliorating T2DM through the regulation of protein metabolic imbalances and found that ZA could effectively alleviate T2D by enhancing protein metabolism. It has been observed that *Z.* amide (mainly HAS, hydroxy-β-sanshool and hydroxy-γ-sanshool) exhibits substantial hypoglycemic effects by modulating glucose and lipid metabolism disorders in animal models with diabetes [102].

#### 4.4.2. Inhibition of α-glucosidase activity

α-glucosidase, an exoglycosidase, catalyzes the release of α-D-glucose from the non-reducing ends of oligosaccharides and disaccharides, and plays a pivotal role in the digestion and absorption of dietary carbohydrates, participating in the metabolic pathways of starch and glycogen, which ultimately release glucose, potentially leading to elevated blood sugar levels or hyperglycemia. Consequently, the physiological function of α-glucosidase is closely linked to the increase in postprandial blood glucose. Some researchers have proposed that α-glucosidase inhibitors represent a primary approach to diabetes treatment. These inhibitors function by slowing down carbohydrate digestion and glucose absorption, effectively inhibiting glucosidase activity and, as a result, reducing postprandial blood glucose levels [103].

Song et al. [104] conducted an *in vitro* study to assess the inhibitory potential of alkaloids extracted from *Z. bungeanum* on α-glucosidase (yeast-derived, mouse small intestine-derived) and its underlying mechanism. The results revealed that both lipid-soluble and water-soluble alkaloids exhibited a certain degree of inhibition against α-glucosidase. The $IC_{50}$ values for lipid-soluble alkaloids and water-soluble alkaloids against yeast-derived α-glucosidase were (0.73 ± 0.17) mg/mL and (2.74 ± 0.28) mg/mL, respectively. Furthermore, the $IC_{50}$ value for lipid-soluble alkaloids against α-glucosidase from the small intestine of mice was (1.94 ± 0.13) mg/mL.

Li et al. [105] discovered that both HAS and hydroxy-β-sanshool found in *Z. bungeanum* exhibited potent inhibitory effects on α-glucosidase, demonstrating $IC_{50}$ values of 9.5 μg/mL and 18.6 μg/mL, respectively. Notably, when compared to positive control drugs, these two sanshool compounds displayed lower $IC_{50}$ values, signifying their superior enzyme inhibitory capabilities and significant potential as α-glucosidase inhibitors. Additionally, Zhang et al. [106] determined that HAS inhibited α-glucosidase through non-competitive inhibition, as indicated by enzyme inhibition kinetics.

### 4.5. Hypolipidemic

Elevated blood lipid levels often result in lipid metabolism disorders, leading to the development of hyperlipidemia. Recent studies have investigated the impact of numb-taste substances on lipid metabolism in ZLP. These studies have demonstrated that *Z.*, *Z.* volatile oil and *Z.* ephedrine can significantly reduce serum and liver cholesterol and triglyceride levels in rats. They also increase bile acid and neutral sterol content in feces while down-regulating the expression of CYP7A1 and HMG-CoA reductase mRNA in the liver. Among these, *Z.* ephedrine showed the most pronounced effect [107,108]. Ren et al. [60] established a rat model of type 1 diabetes induced by STZ and found that *Z. bungeanum* could significantly reduce lipid and cholesterol levels in diabetic rats. Additionally, it increased the expression levels of AMPK and *p*-AMPK proteins, indicating that *Z. bungeanum* improves glucose and lipid metabolism in type 1 diabetic rats through the AMPK pathway. Intracellular MDA, a product of lipid peroxidation, increases significantly under oxidative stress and is considered a biomarker of oxidative stress that can cause cell membrane damage [109]. Wang et al. [110] established a rat model of hyperlipidemia and found that HAS increased the levels of reduced glutathione (GSH) and the activity of superoxide dismutase (SOD) in the liver while reducing malondialdehyde (MDA) levels. Furthermore, it up-regulated the expression of peroxisome proliferator-activated receptor γ (PPARγ) and appolipoprein E (APOE) in the liver, thereby reducing liver oxidative stress, improving lipid metabolism, and contributing to weight loss and lipid reduction.

Furthermore, Wu et al. [111] conducted studies using sitosterol-induced Hep G2 cells as an *in vitro* model and male apolipoprotein E knockout (apoE-KO) mice to establish an *in vivo* model with a high-fat diet to investigate the lipid-lowering activity of the n-butanol fraction from *Z. bungeanum* extract. Their research confirmed that the n-butanol fraction of *Z. bungeanum* extract exhibited the following effects: it reversed lipid accumulation, reduced apoB levels, and enhanced apoA1 secretion. Moreover, it increased the content of LDLR protein, leading to a significant inhibition of the target molecules SREBP-1 and SREBP-2, which are involved in the regulation of RCT. The n-butanol fraction of *Z. bungeanum* extract promoted the expression of RCT-related genes, including CYP27A1, LXR-a, and ABCG1. Additionally, it decreased the levels of TC and TG in the serum of apoE-KO mice, highlighting that the n-butanol fraction of *Z. bungeanum* extract induces the expression of RCT-related genes by increasing the number of LDLR proteins, offering the potential for regulating lipid metabolism.

### 4.6. Antioxidant

Recent studies have demonstrated that various components of ZLP, including crude extract [112], volatile oil [113], flavonoids [111], polysaccharides [112] and amides [114], possess antioxidant properties. ROS are free radicals derived from oxygen and its products, and their excessive levels can lead to oxidative stress in cells, resulting in cell damage or death. For instance, $H_2O_2$, which is an important member of the ROS family, has high cell membrane permeability and can easily traverse the cell membrane to generate hydroxyl radicals, causing severe cellular damage, attacking biomolecules, and ultimately leading to oxidative stress with potentially serious consequences [115]. Additionally, organisms have various enzymes that can scavenge ROS, including SOD, CAT and GSH-Px [116,117].

Li et al. [112] conducted a comprehensive assessment of the antioxidant potential of *Z. bungeanum* extract through various assays, including $Fe^{3+}$ reduction, 1,1-diphenyl-2-trinitrophenylhydrazine radical scavenging, $Fe^{2+}$ chelation ability, and hydroxyl radical scavenging experiments. Their findings revealed that the polysaccharide component in the *Z. bungeanum* (ZBP) extract displayed significant antioxidant activity, with $IC_{50}$ values of 0.011, 0.021, 0.056 and 0.008 mg/mL in each of the four methods, respectively. In a separate study, Yamazaki et al. [116] isolated an antioxidant activity factor from *Z. bungeanum* peel, identifying the methanol extract as the primary active constituent, which exhibited antioxidant activity on par with vitamin E (Ve) and maintained stability under thermal conditions. Zhao et al. [118] and Meng et al. [119] isolated 12 polyphenol glycoside compounds from *Z. bungeanum*, and their evaluation of antioxidant activity using the ABTS + free radical scavenging assay identified four *Z. bungeanum* compounds with strong antioxidant properties. Notably, arbutin demonstrated antioxidant activity comparable to the positive control, vitamin C (Vc), with an $IC_{50}$ value of 4.5 μmol/L.

In addition, *Z. bungeanum* also has antioxidant effects. It can enhance SOD enzyme activity in Hep G2 cells and reduce MDA levels when administered at an appropriate dose, showing robust free radical scavenging capabilitie [120]. You et al. [121] highlight that *Z. bungeanum*'s numbing compounds possess antioxidant capabilities and can induce apoptosis in Hep G2 cells via the mitochondrial pathway, underscoring *Z. bungeanum*'s antioxidant potential.

### 4.7. Anti-infectious

Infectious diseases are caused by various harmful microorganisms and parasites such as bacteria, fungi, viruses and parasites. ZLP contains a range of pharmacological active compounds, some of which, or their monomer components, can combat infections due to their antibacterial, antiviral, and insecticidal properties.

#### 4.7.1. Antibacterial

The extracts and monomer components of ZLP have broad-spectrum antibacterial activity. These substances have shown effectiveness against Staphylococcus aureus, including methicillin-resistant Staphylococcus aureus (MRSA), which can lead to various health issues, ranging from skin infections to severe, life-threatening diseases.

Zuo et al. [33] discovered that four coumarins (5,7-dimethoxy-8-prenyloxycoumarin, 5-geranyloxy-7-methoxycoumarin, isopimpinellin and phellopterin) obtained from the methanol extract of *Z. nitidum*'s root could enhance the effectiveness of antibacterial drugs and reverse drug resistance. These coumarins demonstrated significant antibacterial activity against both MSSA and MRSA strains, with vancomycin as a positive control, and their minimum inhibitory concentration (MIC) ranged from 8 to 64 mg/L. Zhao et al. [122] isolated (±)-zanthonitidine A from *Z. nitidum*'s root. When tested against Enterococcus faecalis and Staphylococcus aureus, (±)-zanthonitidine and (−)-zanthonitidine exhibited moderate inhibitory activity with MIC values of 21.97, 21.97 and 12.54, 25.09 mg/L, respectively. Additionally, Costa et al. [123] isolated a compound called N-methylhydroberberine from the root bark of *Z. tingoassuiba* and found that it had a stronger inhibitory effect on Staphylococcus aureus compared to chloramphenicol. Yang et al. [124] also observed that eucalyptol had an inhibitory effect on H. pylori growth in comparison to the reference strain.

#### 4.7.2. Antiviral

ZLP also exhibits inhibitory effects on viruses. *Zanthoxylone* alkaloids and collinin, isolated by Chang et al. [125] from *Z. schinifolium*, have demonstrated inhibitory effects on hepatitis B virus (HBV) DNA synthesis, with $ED_{50}$ of 68.3 μg/mL, $ID_{50}$ of 17.1 μg/mL and SI of 3.99. Cheng et al. [126] revealed that *Z. ailanthoides* Sieb.et.Zucc., *Z. integrifoliolum* Merr. and *Z. japonica* possess significant anti-HIV activity and successfully isolated the active anti-HIV ingredients from these compounds. Furthermore, Yang et al. [19] discovered that the essential oil derived from *Z. bungeanum* seeds exhibited inhibitory activity against feline calicivirus and murine norovirus. Notably, it had a more pronounced inhibitory effect on feline calicivirus, effectively preventing the virus from attacking host cells.

#### 4.7.3. Insecticidal

The insecticidal properties of ZLP are mainly demonstrated in parasitic killing, particularly targeting malaria parasites, acting as a mosquito repellent, and preventing and controlling storage pests [32]. Kou et al. [127] conducted research using the pericarp of *Z. bungeanum* as their focus and Tribolium castaneum as the test insect. They assessed the effects of different pericarp extracts of *Z. bungeanum* on Tribolium castaneum through various methods, including contact, stomach toxicity, fumigation and avoidance tests. The results indicated that the n-butanol extract displayed the highest contact activity against Tribolium castaneum, with an $LC_{50}$ value of 1.086 g/mL. On the other hand, the petroleum ether extract exhibited the most repellent activity against Tribolium castaneum, achieving a repellent rate of 93.617 %. This study highlighted that extracts from different polar parts of *Z. bungeanum* peel possess

**Table 4**
Pharmacological activity mechanism of plants of *Zanthoxylum* L. (↑increase, ↓decrease).

| Research compounds | Pharmacological activity | Mechanisms | Dose/system | References |
|---|---|---|---|---|
| Decarine | Anti-inflammatory | ↓NO;<br>↓TNF-α, IL-1β;<br>↓IL-6, IL-8 | 48.43 μM<br>Lipopolysaccharide (LPS)-induced RAW264.7 cells;<br>LPS-stimulated THP-1 cells;<br>TNF-α + IL-1β-induced Caco-2 cells | [77] |
| The ethyl acetate fraction/ EtOAc fraction; Hesperidin | Anti-inflammatory | ↓IL-6, IL-1β, TNF-α, NF-κB, MMP 1, MMP 3, MMP 9 | EtOAc fraction (250 and 125 μg/ml); hesperidin (250 and 125 μg/ml)<br>UVB-induced human dermal fibroblasts cells (HDF) | [78] |
| ZPE-LR (90 % EtOH extract of *Zanthoxylum piperitum*) | Anti-inflammatory | ↓Mouse ear thickness and biopsy punch weight, iNOS, COX-2, acetic acid, heat and formalin-induced pain;<br>↓p65, ROS, HPRT1<br>↑RPL8 | 50 and 100 mg/kg<br>Mouse model of inflammation induced by TPA (12-*O*-tetradecanoylphorbol-13-acetate);<br>LPS-induced RAW264.7 cells | [79] |
| The essential oil from fruits of *Zanthoxylum coreanum Nakai (ZCO)* | Anti-inflammatory | ↓β-hexosaminidase release, IL-4;<br>↓TNF-α, IL-6, NO;<br>↓iNOS, COX-2;<br>↓NF-κB, NF-κB p65 translocation;<br>↓Phosphorylation of MAPK (JNK, ERK, p38); ↑IkB-α<br>↓Ear swelling and AD-like skin lesions | 0.0025, 0.005, and 0.01 % (*In vitro*)<br>IgE-antigen complex or PMA/A23187-induced RBL-2H3 mast cells;<br>LPS-induced RAW264.7 cells;<br>PMA-activated 293T cells;<br>1, and 2 % (*In vivo*)<br>DNCB-induced atopic dermatitis model in BALB/c mice | [80] |
| Sesaminone | Anti-inflammatory | ↓NO, TNF-α, IL-6, IL-1β | 20, 30 and 40 μM<br>LPS-induced BV-2 microglial cells | [27] |
| Nitidine chloride (NC) | Anti-inflammatory | ↓TOP I<br>↑Akt, IL-10 | 2 μM<br>LPS-stimulated myeloid cells;<br>LPS-stimulated RAW264.7 cells | [81] |
| Zanthoxylumamides B | Anti-inflammatory | ↓NO, NF-κB, MyD88, IRF3 | 10, 20, and 40 μM<br>LPS-induced RAW264.7 macrophage cells | [82] |
| Fargesin | Anti-inflammatory | ↓iNOS, COX-2, IL-1β, TNF-α, CCL-5, NF-κB, AP-1 | 5, 10, and 20 μM<br>PMA-stimulated THP-1 human monocytes | [83] |
| Isofraxidin | Anti-inflammatory | ↓NO, iNOS, COX-2, PGE2, TNF-α, IL-6, MMP-3, MMP-13, NF-κB | 10, 20, and 40 μM<br>IL-1β-induced human NPCs | [87] |
| Xanthoxyletin, alloxanthoxyletin, 8-formylalloxanthoxyletin | Anti-inflammatory | ↓ROS, superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide and granule proteases (elastase, cathepsin G) | –<br>fMLP/CB-induced human neutrophils | [139] |
| The Maqian fruits essential oil (MQEO) | Anti-inflammatory | ↓Diarrhea, rectal bleeding, body weight loss, colon length shortening, histopathological damage;<br>↓MPO, MMP-9, IL-1β, IL-6, IL-12p35, NF-κB p65;<br>↓TNF-α, IL-1β, phosphorylation of IKK and IκB, TLR4 | 35 and 70 mg/kg (*In vivo*)<br>Dextran sulfate sodium (DSS)-induced intestinal inflammation in mice<br>0.01 ‰–0.05 ‰(v/v) (*In vitro*)<br>LPS-stimulated THP-1 cell line | [140] |
| Zanthoxylum bungeanum pericarp extract (ZBE) | Anti-inflammatory | ↓Body weight loss, colon length shortening, colonic pathological damage;<br>↓TNF-α, IL-1β, IL-12 | 0.5, 1, and 2 g/kg b.wt. (*In vivo*)<br>DSS-induced experimental colitis in mice;<br>100, 200, and 400 μg/ml (*In vitro*)<br>LPS-triggered inflammation in J774.1 cells | [141] |
| The extract of Zanthoxylum nitidum (Roxb.) DC. | Analgesic | ↓The paw edema volume, the paw tissues inflammatory damage, and the numbers of neutrophils;<br>↓TNF-α, IL-6, IL-1β, NF-κBp65, ERK1/2, NF-κB | 100 mg/kg<br>CFA-induced chronic inflammatory pain in C57BL/6J mice | [88] |
| Hydroxy-α-sanshool (HAS) | Analgesic | ↓Aδ mechanonociceptors, the activity of multiple voltage-gated sodium channel subtypes ($Na_v1.7$), AP firing | Aδ nociceptors | [90] |
| Zanthoxylum bungeanum Maxim extract (ZBME) | Anti-tumor | ↓Mcl-1,Survivin, Bcl-x L<br>↑Bax | 8 μg/ml<br>HepG2 cells | [142] |
| NC from the roots of Zanthoxylum nitidum | Anti-tumor | ↑γH2AX (Ser139), Chk2 (Thr68), p53, Bim, Cytochrome *c* release, c-caspase 3, c-PARP | 0.5, 1, 5, and 10 μM<br>Human cervical cancer cell lines (HEp-2 and KB cells) | [143] |
| NC | Anti-tumor | ↓MMP-2, MMP-9, *p*-ERK | 0, 1, 2.5, 5 and 10 μM<br>A2780 ovarian cancer cells | [95] |
| NC | Anti-tumor | ↑Fas, FADD, caspase-8, caspase-3 | 0, 0.3125, 0.625, 1.25, 2.5, 5 and 10 μg/ml<br>SKOV3 ovarian carcinoma cells | [96] |

(*continued on next page*)

**Table 4** (*continued*)

| Research compounds | Pharmacological activity | Mechanisms | Dose/system | References |
|---|---|---|---|---|
| NC | Anti-tumor | ↓Bcl-2, *p*-Akt,<br>↑Bcl-2-associated X protein, p53, caspase-3, caspase-9, | 0, 2.5, 5, 10, 20 and 50 μM<br>A2780 human ovarian cancer cell line | [97] |
| NC | Anti-tumor | ↓Skp2 | 0, 2.5, 5.0, 7.5, and 10 μM<br>SKOV3 and OVCAR3 ovarian cancer cells | [98] |
| Dictamnine (DTM) | Anti-tumor | ↓Hypoxia-inducible factor-1α (HIF-1α), Slug | 0, 50, and 100 μM<br>HCT116 cells | [144] |
| Eudesmin (EDN) | Anti-tumor | ↓Bcl-2, Akt<br>↑Bax, caspase-3, caspase-9, p53, JNK | 10, 20 and 40 μM (*In vitro*)<br>LC A549 cells<br>10, 20 and 40 mg/kg (*In vivo*)<br>Xenograft athymic nude mouse | [28] |
| EDN | Anti-tumor | ↓Enhancer of zeste homolog 2 (EZH2), Akt, *p*-Akt | 10, 20, and 30 μM<br>NPC cell lines CNE-1 and HONE-1 | [99] |
| Zanthoxylum alkylamides (ZA) | Hypoglycemic | ↓Glycosylated serum protein (GSP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), FT3, FT4, Asprosin (ASP), Forkhead box O (FoxOs), Atrogin-1 (MAFbx), Muscle ring finger 1 (MuRF1)<br>↑Insulin-like growth factor 1 (IGF-1), IGF-1R, Adiponectin (ADP), AMPK, Glucose transporter protein 4 (GLUT4), PPARγ, PI3K/Akt | 2, 4, and 8 mg/kg bw ZA daily<br>T2DM rats | [101] |
| Alkaloids (fat-soluble and dissoluble alkaloids) | Hypoglycemic | ↓α-glucosidase (non-competition inhibition) | 0.25–5.0 mg/mL<br>α-glucosidase from murine small intestine | [104] |
| HAS; Hydroxyl-β-sanshool (HBS) | Hypoglycemic | ↓α-glucosidase (non-competition inhibition) | HAS (44.27–115.28 mg/g DW);<br>HBS (0.36–1.22 mg/g DW) | [105] |
| HAS | Hypoglycemic | ↓α-glucosidase (non-competition inhibition) | 8.33–50 μg extract/mL | [106] |
| ZA | Hypolipidemic | ↓Fasting blood glucose, fructosamine content, organ enlargement, serum, liver triglyceride, malondialdehyde, free fatty-acid contents, total cholesterol<br>↑AMPK, *p*-AMPK (Thr172), silencing information regulator 1, acetyl-CoA-carboxylase (ACC), protein *p*-ACC (Ser79), GLUT4 | 2, 4, and 8 mg/kg bw<br>Streptozotocin (STZ)-induced diabetes | [60] |
| HAS | Hypolipidemic | ↓Body weight gain, food efficiency ratio, abdominal adipose tissues, liver adipocytes, T-CHO, TG, LDL-C, MDA<br>↑Glutathione (GSH), SOD, HDL-C, PPARγ, APOE | 18 and 36 mg/kg<br>Hyperlipidemic rats | [110] |
| the n-butanol (BuOH) fraction isolated from Zanthoxylum bungeanum (ZBBu) | Hypolipidemic | ↓Lipid accumulation, apoB, HMGCR (hydroxy methylglutaryl coenzyme A reductase), TC, TG<br>↑ApoA1 secretion, low density lipoprotein receptor (LDLR), CYP27A1, LXR-α, ABCG1 | 0.05, 0.1, and 0.2 mg/ml (*In vitro*)<br>Cholesterol overloading HepG2 cells induced by sterols;<br>50, and 200 mg/kg/d (*In vivo*)<br>Male apolipoprotein E knockout (apoE-KO) mice with high fat diet | [111] |
| Zanthoxylum bungeanum polysaccharide (ZBP) | Antioxidant | ↑Reducing $Fe^{3+}$ power, scavenging DDPH activity, chelating $Fe^{2+}$ ability and scavenging hydroxyl radical activity | – | [112] |
| Sanshool | Antioxidant | ↑SOD, the scavenging activity on DPPH and hydroxyl radicals (·OH)<br>↓MDA | 100 μg/mL<br>HepG2 cells | [120] |
| Alpha-linolenic acid (ALA) | Anti-platelet aggregation | ↓The thrombosis on A-V bypass and platelet aggregation, PI3K, Akt, P-selectin secretion and GP *IIb/IIIa*<br>↑The hemorrhage and coagulation time | 50, 100, and 250 mg/kg<br>Mice, rats | [73] |
| HAS | Neuroprotection | ↓ROS, MMP, MDA, caspase-3, Bax<br>↑SOD, catalase (CAT), glutathione peroxidase (GSH-Px), p-PI3K, Akt, *p*-Akt, Bcl-2 | 15, 30, and 60 μM<br>$H_2O_2$-stimulated PC12 cells | [134] |
| EDN | Neuroprotection | ↓Gamma-aminobutyric acid (GABA), caspase-3<br>↑Glutamic acid (Glu), glutamate decarboxylase 65 (GAD65), GABAA, Bcl-2 | 5, 10, and 20 mg/kg<br>Pentylenetertrazole (PTZ)-induced seizures in male mice | [145] |
| Fargesin | Cardioprotection | ↓Cyclic adenosine monophosphate (cAMP), protein kinase A (PKA); | 0.1–20 μM (*In vitro*)<br>Isoproterenol- (ISO-) induced cells injury | [30] |

(*continued on next page*)

**Table 4** (*continued*)

| Research compounds | Pharmacological activity | Mechanisms | Dose/system | References |
|---|---|---|---|---|
| | | ↓Creatine kinase (CK), lactate dehydrogenase (LDH), infarct size, MDA, ROS, caspase-3<br>↑Histopathological changes of ischemic myocardium, COX, SOD, CAT, GSH-Px | in the high expression β1 adrenergic receptor/Chinese hamster ovary-S (β1AR/CHO–S) cells<br>15 μM/kg (*In vivo*)<br>Occluding the left coronary artery- (LAD-) induced myocardial ischemia/reperfusion (MI/R) injury in rats | |
| Sanshool | Skin protection | ↓MMP-1, MMP-3, JAK2/STAT3 | 0, 10, 20, and 40 μM (*In vitro*)<br>UVB-irradiated HDFs<br>20 mg/kg (*In vivo*)<br>UVB-irradiated nude mouse | [137] |
| Daikenchuto (DKT) (HAS [6],-shogaol) | Digestive system protection | ↓Type I collagen, α-smooth muscle actin (α-SMA), *p*-Smad-2, p-p38-MAPK, myocardin<br>↑Transient receptor potential ankyrin 1 (TRPA1) | 0.001 %, 0.01 %, and 0.1 % EtOH extract (HAS (1 μmol/L [6],-shogaol (10 μmol/L)) (*In vitro*)<br>Intestinal myofibroblast (InMyoFib) cells<br>5 mg/kg/d (*In vivo*)<br>2,4,6-trinitrobenzenesulfonic acid (TNBS) chronic colitis model of wild-type and TRPA1-knockout (TRPA1-KO) mice | [135] |

insecticidal activity. In a separate study, Pavela et al. [128] identified gemacrene D-4-ol and α-cadinol in *Z. monophyllum*, both of which demonstrated insecticidal activity against Anopheles subpictus, A. albopictus, and Culex tritaeniorhynchus. Additionally, de Paula Carlis et al. [129] conducted *in vitro* experiments on platycladi's anthelmintic activity and found that it could completely inhibit the development of ovine gastrointestinal nematode eggs and larvae at mass concentrations ranging from 75 to 1250 μg/mL. The $EC_{50}$ values for ovicidal and larval migration were 68.38 and 0.34 μg/mL, respectively.

Amide compounds have demonstrated significant insecticidal activity against various pests, including Plutella xylostella, Spodoptera exigua, Spodoptera litura, and more. KUMAR et al. [130] reported that N-(3′-bromo-4′-methoxyphenethyl) cinnamamide in *Z. armatum* exhibited potent insecticidal activity against P. xylostella larvae. Moreover, Jullian et al. [131] extracted seven alkaloids, including nitidine, from the traditional French plant *Z. rhoifolium*, which have shown anti-malarial effects. Alkaloids and amides isolated from the stems of *Z. rubescens* by Penali et al. [132] also exhibit anti-malarial properties.

### 4.8. Others

In addition to the seven major pharmacological activities mentioned earlier, ZLP also possesses other pharmacological activities such as anti-platelet aggregation [73,133], neuroprotection [134], cardioprotection [30,115], digestive system protection [135,136], and skin protection [137,138]. The pharmacological activity mechanism of plants of *Zanthoxylum* L. is shown in Table 4.

## 5. Study on the development and utilization of *Zanthoxylum* L. Plants (ZLP)

ZLP, as an important economic crop, has various valuable uses. For instance, its roots have medicinal properties and hold great potential for further development. The woody sprouts of ZLP are highly prized for their nutritional value and distinctive flavor, making them popular among consumers. The leaves can be used as a food seasoning, pickling, or making tea. ZLP peels are renowned as one of the 'eight condiments' in Chinese cuisine. Additionally, the kernel of ZLP contains valuable volatile oil that can be extracted and used as an excellent biodiesel. Currently, the primary focus of research on ZLP revolves around the study of its volatile oil, amides and alkaloids. The list of commercially available products of plants of *Zanthoxylum* L. is shown in Table 5.

### 5.1. Research on the application value of food

China has the largest planting area and a wide variety of ZLP. Over the centuries, the use of *Z. bungeanum* has evolved from a simple spice to a versatile condiment. In recent years, the consumption of ZLP products in China has expanded beyond its traditional uses. There is a growing interest in developing various processed products and derivatives, such as Majiao essential oil [146], *Z.* seasoning oil [147], Tengjiao hot pot seasoning [148,149], pepper leaf salt, pepper cookies [150], vine pepper sauce [151], pepper seed protein antimicrobial peptides [152], pepper oleoresin [153], and microcapsule preparations [154]. These developments reflect the adaptability and versatility of ZLP in culinary and industrial applications, making it a hot topic in the food and chemical industries.

*Z. bungeanum* is renowned as one of the eight essential condiments. Its distinctive peel carries a robust and numbing flavor that can effectively eliminate unwanted fishy odors in dishes. The seeds of *Z. bungeanum*, constituting approximately 60 % of its total mass, are the primary by-products of this spice. Research has demonstrated that pharmacological active compounds, such as HAS and HBS, can be extracted from ZLP to create edible food flavors [146], which are responsible for the characteristic numbing sensation associated with ZLP, with HAS exhibiting the most pronounced numbing effect. Additionally, compounds like alpha-sanshool and gamma-sanshool contribute to the tingling or burning sensation, while beta-sanshool, HBS and gamma-sanshool are primarily

**Table 5**
List of commercially available products of plants of *Zanthoxylum* L.

| Application type | Product name | Main components | Production enterprise | Function | URL |
|---|---|---|---|---|---|
| Food | Walnut flower fermented food with auxiliary blood sugar and blood fat reducing effect and preparation method thereof | Walnut flower, ginger, star anise, *Z. bungeanum*, etc. | [Yunnan] Southwest Forestry University | Reducing blood sugar and blood fat | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN114947119B) Accessed May 30, 2022. |
| | Rattan pepper flavored hotpot seasoning sauce and preparation method thereof | Sesame paste, *Z.* oil extract, *Z.* water extract, alpha-cyclodextrin, neutral protease, etc. | [Hebei] Bazhou Jinkai Foods Co. | Flavouring | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN112674321B) Accessed February 2, 2021. |
| | Strong satiety vine pepper flavor flour paste and preparation method and application thereof | Rapeseed oil, vine pepper, yeast extract, medium chain fatty acid, resistant starch, fructo-oligosaccharide, etc. | [Hunan] South Central Cereals, Oils and Foodstuffs Scientific Research Institute Co. | Reducing the feeding amount, delaying the rising speed of blood sugar | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN112167637B) Accessed October 29, 2020. |
| | Degradable antioxidant packaging film prepared from food processing byproducts and preparation method thereof | Oil tea cake pulppricklyash peel cake, potato starch, glycerin, etc. | [Sichuan] Sichuan Agricultural University | Preservation of lipid foods | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN114479504B) Accessed March 2, 2022. |
| | Fruit and vegetable preservative film and preparation method and application thereof | Pricklyash peel essential oil, polyvinyl alcohol, cyclodextrin | [Sichuan] Chengdu University | Prolong the preservative period of food | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN114059234B) Accessed November 26, 2021. |
| | Mushroom fresh-keeping packaging paper | Wood pulp fiber, silica powder, polyethylene, alkaloid, etc. | [Henan] Luoyang Siongtian Agricultural Development Co. | Prolong the shelf life of the mushrooms | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115613386B) Accessed October 27, 2022. |
| Medicinal | Pseudo-ginseng pain-relieving paste with stable active ingredients and preparation method | Cinnamon, rheum officinale, *Z.*, radix zanthoxyli, pseudo ginseng prepared frankincense, etc. | [Beijing] Sailing Pharmaceutical Technology Group Co. | Promoting blood circulation to remove blood stasis, dispelling wind and removing dampness, warming channels and dredging collaterals | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115944677B) Accessed March 15, 2023. |
| | Traditional Chinese medicine for treating sore throat and preparation method thereof | Chinese olive, platycodon grandiflorum, peppermint, radix zanthoxyli, etc. | [Guangdong] The Third Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine | Treating sore throat | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN114699481B) Accessed April 7, 2022. |
| | Composition for treating oral ulcer, preparation method | Patchouli, rhizoma atractylodis, schizonepeta, *Z. bungeanum*, mint, etc. | [Yunnan] Yunnan Baiyao Group Co. | Treating dental ulcer | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/ |

(*continued on next page*)

**Table 5** (*continued*)

| Application type | Product name | Main components | Production enterprise | Function | URL |
|---|---|---|---|---|---|
| | and pharmaceutical application thereof | | | | default.html (CN114832044B) Accessed April 29, 2022. |
| | Botanical biocontrol bacterium preparation for preventing and treating rubber anthrax | EM bacterium fermentation liquor, radix zanthoxyli aqueous extract, citrus peel ethanol extract | [Hainan] Hainan University | Prevent and treat the rubber anthracnose | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN113598201B) Accessed August 2, 2021. |
| | Oyster peptide powder with liver protection function and preparation method thereof | Oyster peptide, sea buckthorn extract, nitidine chloride, etc. | [Guangdong] Guangzhou Tianqi Biotechnology Co. | Liver protection | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN112675283B) Accessed December 3, 2020. |
| | Traditional Chinese medicine composition for treating chronic skin pruritus and preparation method and application thereof | Shrubalthea bark, amur corktree bark, Chinese prickly ash, camphor and borneol, etc. | [Jiangsu] Xuzhou Hospital of Traditional Chinese Medicine | Relieve itching and skin damage symptoms of patients with chronic skin itch | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115414427B) Accessed October 9, 2022. |
| | Composition for treating eczema or urticaria, preparation method and pharmaceutical application thereof | Patchouli, rhizoma atractylodis, cinnamon, schizonepeta, elsholtzia, folium artemisiae argyi, clove, pepper and mint | [Yunnan] Yunnan Baiyao Group Co. | Relieve itching and pain, diminish inflammation, reduce swelling and prevent infection | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN114617919B) Accessed April 29, 2022. |
| | Use of pentapapriine for treating endometrial cancer | Zanthobungeanine | [Shandong] Shandong Mulan Biomedical Co. | Treating endometrial cancer | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN111803496B) Accessed August 17, 2020. |
| | Composition for promoting wound healing and intelligent coating material | Boric acid modified sanshool, indole coating | [Sichuan] West China Hospital of Sichuan University | Promoting wound healing | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115444845B) Accessed August 5, 2022. |
| | Vascular embolism agent and preparation method and application thereof | Alkaloid, lipoic acid, tannic acid, gallic acid, etc. | [Guangdong] The Fifth Affiliated Hospital of Sun Yat-sen University | Treating arterial embolism of benign and malignant tumors | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115463246B) Accessed August 24, 2022. |
| Daily chemicals | Production equipment and process of skin care product stock solution with natural anti-corrosion function | *Z. bungeanum*, fructus forsythiae, wormwood and perilla | [Guangdong] Guangdong Shengmei Biotechnology Co. | Natural anti-corrosion function | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN116200245B) Accessed July 14, 2023. |

(*continued on next page*)

**Table 5** (*continued*)

| Application type | Product name | Main components | Production enterprise | Function | URL |
| --- | --- | --- | --- | --- | --- |
| | Bath foam with antibacterial and antipruritic functions and preparation method thereof | *Z. bungeanum*, keratin trehalose | [Guangdong] Guangzhou Goody Group Co. | Antibacterial and antipruritic | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN113797135B) Accessed October 25, 2021. |
| | Preparation method of pure natural plant acaricide | *Z. bungeanum*, nux vomica | [Beijing] Beijing Zhongnong Lu'an Organic Agriculture Technology Co. | Acaricide | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN113498795B) Accessed August 17, 2021. |
| | Chinese herbal medicine health care pillow | Safflower, frankincense, angelica dahurica, angelica, *Z. bungeanum*, etc. | [Hunan] Yuan Jinhai | Sleep-helping | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN113662402B) Accessed August 3, 2021. |
| | Preparation method and application of amino acid-mediated sanshool all-natural functional gel | p-aldehyde benzoic acid, 4-Dimethylaminopyridine, arginine, HAS, etc. | [Sichuan] Sichuan Shengjia Technology Co. | Degradability, biological activity and antioxidant activity | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115154650B) Accessed July 8, 2022. |
| | Application of hydroxy-alpha-sanshool in preparation of insecticide and/or antifeedant | HAS, lignin, diatomite, etc. | [Sichuan] Southwest Jiaotong University | Pest control | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN114375952B) Accessed December 29, 2021. |
| | Electrothermal mosquito-repellent incense liquid and preparation method thereof | Linalool, lavender acetate, Insecticidal pyrethroid, etc. | [Guangdong] Foshan Nanhai Aodi Fine Chemical Co. | Mosquito eradication | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115517270B) Accessed October 25, 2022. |
| | Moisturizing and whitening composition and application thereof in radio frequency beauty and medical skin care | Glycerin, arbutin, dihydroavenanthramide, etc. | [Guangdong] Guangzhou Aizhuo Bio-technology Co. | Moisturizing and whitening | https://ras.cdutcm.lib4s.com:7080/s/com/innojoy/www/G.http/searchresult/default.html (CN115444772B) Accessed October 26, 2022. |

responsible for the bitter taste. ZLP is also rich in essential oils, a class of plant secondary metabolites known for their antioxidant and antibacterial properties [155]. The application of *Z. bungeanum* essential oil in hot pot dishes not only preserves the pepper's aroma and numbing effect but also offers benefits in terms of storage and transportation cost reduction. Ma et al. [156] have shown that combining *Z. bungeanum* with its essential oil can significantly enhance the aroma and numbing taste in hot pot dishes.

ZLP has a variety of pharmacological activities, making it a valuable ingredient in the food industry. Its seeds are particularly noteworthy as a potential oil resource. They are rich in unsaturated fatty acids, including alpha-linolenic acid, and can be directly processed into a healthy edible oil, which has beneficial effects such as softening blood vessels, reducing blood lipid levels, promoting blood circulation, and clearing blocked blood vessels. Innovative food products have been developed using various parts of the *Z. bungeanum* plant [157]. For example, Zhang et al. [150] utilized *Z. bungeanum* leaves, a by-product of Hanyuan *Z. bungeanum*, to create *Z. bungeanum* leaf salt and pepper cookies through process optimization. These cookies offer a unique and natural pepper and numbing flavor, and they benefit from the antibacterial and antioxidant properties of *Z. bungeanum* leaf components, resulting in improved shelf life. Luo et al. [158] developed a natural compound antioxidant for Chinese sausages that includes *Z. bungeanum* leaf extract, aroma extract, and Vc. This antioxidant blend, when used in the right proportions, exhibits a significant synergistic effect. It effectively delays the oxidation of Chinese sausages during storage, enhancing their color, aroma, texture and overall acceptability. As a result, the shelf life of the sausages can be extended by at least 45 days. Furthermore, Qu et al. [159] investigated the interaction between konjac glucomannan and glutenin from *Z. bungeanum* seeds using various spectroscopic techniques. This interaction not only improves food quality but also extends the shelf life of food products, providing economic benefits through the full utilization of *Z. bungeanum* seeds. Jiang et al. [160] employed pepsin to produce antimicrobial peptides from *Z. bungeanum* seeds, which can be utilized in alkaline beverages, high-temperature drinks, bread, dairy products, and other foods. These peptides also serve as O/W (oil in water) emulsifiers.

The development of various *Z. bungeanum* products has made this plant more market-oriented. These products are not only visually appealing with vibrant colors but are also convenient to consume, making them easily promotable. Additionally, they excel in preserving and utilizing the flavorful compounds found in the genus. Furthermore, many oil processing companies have recognized the value of *Z. bungeanum* seeds and are increasingly focusing on the research and processing of *Z. bungeanum* seed oil and *Z. bungeanum* seed protein. There is also growing interest in studying the nutrient content of *Z. bungeanum* seeds.

Overall, existing studies demonstrate that ZLP plays a significant role in food preservation by inhibiting mold and microbial growth, ultimately extending the shelf life of food products and playing a unique role in the field of natural food.

### *5.2. Research on the application value of medicinals*

*Z. bungeanum* has a rich history of medicinal use dating back to ancient times, as documented in the 'Shennong's Herbal Classic': 'The main wind evil, warm, except cold Bi, firm teeth hair, bright eyes. The main evil qi cough, warm, by the bone joint skin dead muscle, cold dampness arthralgia, lower qi' [161]. Modern studies have shown that the medicinal value of ZLP is infinitely extensive, which is embodied in: (1) Anesthesia and analgesic effects: In the clinic, *Z. bungeanum* extracts and volatile oils are employed in dentistry for anti-inflammatory and analgesic purposes, offering an alternative to clove oil [162]. These agents induce local anesthesia and may contain scorpionine as an active analgesic component [24]. Furthermore, *Z. bungeanum* extracts can temporarily impede nerve impulse transmission, reducing nerve excitation [163]; (2) Gastrointestinal health: *Z. bungeanum* has the effect of warming the middle and dispersing cold. For example, its peel could treat spleen and stomach deficiency and cold syndrome, especially vomiting and diarrhea caused by internal invasion of cold evil and trapped yang qi, warm qi, abdominal cold pain, poor appetite, etc. In addition, it could also treat liver injury, gastric ulcer, inflammatory and gastrointestinal dysfunctions, and abdominal pain [164]; (3) Inhibition of thrombosis: *Z. bungeanum* has a significant inhibitory effect on thrombosis [165]. *Z. bungeanum* extract has plasminogen activator inhibitor (PAI-1) inhibitory activity, which can be used to treat thrombosis and liver fibrosis [166]. Early studies have shown that *Z. bungeanum* volatile oil could play a role in the formation of experimental atherosclerosis in guinea pigs, and the mechanism may be related to its reduction of serum lipid peroxide level and anti-lipid peroxidation damage [167]; (4) Other functions: Hazarika et al. [168] synthesized a nanocomposite using water extract from *Z. armatum* fruit and metal precursors like graphene oxide, tetrachloroauric acid, and silver nitrate. This nanocomposite displays anti-cancer and anti-diabetic pharmacological activities. Furthermore, Mirza et al. [169] created copper oxide nanomaterials from water extract of *Z. armatum* leaves and copper acetate, possessing antibacterial and antioxidant properties, making them valuable in biology, biomedicine, and environmental applications.

### *5.3. Research on the value of daily chemical products application*

ZLP has significant potential for development in various industries, including the chemical industry, clean energy sector, and as a source of raw materials for biological pesticides.

The oil-rich components of ZLP can be harnessed as a valuable oil resource, with potential applications to extract aromatic oils and flavors. Moreover, the active ingredients found in *Z. bungeanum* seed oil can serve as natural additives in cosmetics, including components such as 4-terpineol, 1,8-cineole and menthol, known for their skin-enhancing properties [170]. Additionally, *Z. bungeanum* seed oil-based water-soluble alkyd resin offers advantages such as cost-effectiveness, environmental friendliness, and degradability, as well as exceptional chemical resistance, physical attributes, and thermal stability [171]. Being a semi-dry oil, *Z. bungeanum* seed oil's capacity for oxidative polymerization film formation is similar to Tongzi oil, making it a high-quality raw material suitable for coatings production [172].

Lei et al. [173] prepared an activated carbon from the branches and leaves of *Z. bungeanum*, which has an efficient removal effect on toluene vapor in the air. The unique microporous and mesoporous structure of activated carbon makes it have a large adsorption capacity for toluene. On the one hand, the overlapping adsorption force of adjacent microporous walls has a strong adsorption force on toluene molecules, while on the other hand, the rich mesopores promote the mass transfer and adsorption of toluene. In addition, Qu et al. [174] used the glutelin hydrolysate of *Z. bungeanum* seed kernel as an emulsifier, which provided a theoretical basis for the industrial utilization of the natural emulsifier of *Z. bungeanum* seed kernel.

In the industrial sector, *Z. bungeanum* seed oil (ZSO) holds potential for biodiesel production, offering a more environmentally friendly alternative energy source with reduced pollution. Zhang et al. [175] used ZSO and ethanol as feedstocks to produce ethyl ester biodiesel through transesterification. Moreover, the essential oil extracted from *Z. bungeanum* peel can serve as a primary ingredient in insecticides and disinfectants. Notably, β-phellandrene, a component of the volatile oil, exhibits significant efficacy in eliminating Tribolium castaneum adults and effectively repelling Aedes aegypti. Additionally, *Z. bungeanum* seeds can also be used as raw materials in various daily chemical products, including soap, moisturizing shower gel, paint, and more.

## 6. Discussion and future perspectives

Both Chinese and international researchers have conducted extensive studies on the traditional uses, chemical compositions, pharmacological activities, and mechanisms of action of ZLP, which have confirmed its practical utility across various domains. Recent reports have identified six major groups of chemical constituents within ZLP, including volatile oils, alkaloids, amides, lignans, coumarins, and organic acids. Among these, volatile oils, alkaloids and amides were identified as the primary active components of this genus. Furthermore, ZLP contains additional compounds such as terpenoids, sterols, hydrocarbons and flavonoid glycosides.

Existing studies have shown that ZLP exhibits a diverse array of pharmacological activities, including significant anti-inflammatory, analgesic, anti-tumor, hypoglycemic, hypolipidemic, antioxidant, and anti-infective properties. The specific focus of individual researchers may vary, with some examining single compounds, others exploring crude extracts, and still others studying the genus as a whole. Despite these differences in research subjects, the collective findings consistently highlight the multifaceted pharmacological activities of ZLP. Therefore, we could put forward the hypothesis: What are the key components responsible for, individually or collectively, mediating the anti-inflammatory, analgesic, antioxidant, hypoglycemic, hypolipidemic, and other activities of ZLP. This question underscores the potential importance of identifying and understanding the specific components or synergistic combinations of substances that contribute to the genus's diverse pharmacological effects. Further research in this direction holds promise for unveiling the mechanisms behind these activities. In addition, in future studies, we also need to further study the toxicity of ZLP, the mechanisms of actions of the isolated bioactive metabolites, and the scientific connotations between the traditional medicinal uses and pharmacological properties, in order to reveal the effectiveness of its therapeutic potential and thus safely applied to clinical practice.

Although ZLP is rich in several types of resources, scholars have mostly performed research on the development and utilization of the peels of the plants, while most of the by-products of ZLP, such as its roots, branches, leaves, seeds, etc., have been discarded and not fully utilized, which has resulted in a certain degree of waste of resources and environmental pollution problems. Promoting comprehensive and high-value utilization of these by-products is essential for sustainable development in the field of functional materials. With the advancement of modern science and technology, the comprehensive and effective utilization of this plant genus's resources is an inevitable trend to maximize the value and functional benefits of ZLP. To unlock the full pharmacological activities and potential of ZLP, several core issues merit in-depth exploration: (1) Enhancing the extraction and purification processes for ZLP's pharmacological active components and their derivatives, thus providing a theoretical foundation for advanced product development; (2) Pioneering innovative applications of ZLP by-products in composite materials, transcending their conventional role as food flavorings to create functional products for food, medicine, daily chemicals, pharmacological agents and related fields, to expand their applicability; (3) Leveraging modern technology and integrating various high-tech approaches into research and development processes to improve product conversion rates; (4) Exploring the cultural significance of ZLP and introducing a series of culturally relevant products to enhance their market competitiveness. Taken together, these strategies could help harness the full potential of ZLP and contribute to sustainable and functional material development.

## 7. Conclusion

The ZLP of the family Rutaceae is rich in resources and is known far and wide, with a long history of dual use in medicine and food. This genus includes volatile oils, alkaloids, amides, lignans, coumarins and organic acids, which have significant anti-inflammatory, analgesic, anti-tumor, hypoglycemic, hypolipidemic, antioxidant and anti-infectious, and are widely used in the fields of food, medicinal and daily chemicals. This article presented a systematic and comprehensive review of the above research results, with a view to providing scientific references for the in-depth study of ZLP and the sustainable use of its resources.

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## Data availability statement

No data was used for the research described in the article.

## CRediT authorship contribution statement

**Jiayu Wen:** Writing – original draft, Conceptualization. **Qiwen Xiang:** Writing – original draft, Data curation. **Jiafu Guo:** Data curation. **Jian Zhang:** Data curation. **Nannan Yang:** Data curation. **Yan Huang:** Writing – review & editing. **Yan Chen:** Writing – review & editing. **Tingting Hu:** Writing – review & editing. **Chaolong Rao:** Supervision, Project administration, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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