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REVIEW PAPER

Anticancer potential of the *Zanthoxylum* genus: A review of phytochemistry and bioactivity

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Abstract. The *Zanthoxylum* genus, belonging to the Rutaceae family, comprises over 250 species and is widely distributed across Asia, Africa, Europe, and the Americas. These species have been appreciated their significance as both spices and medicinal plants with broad therapeutic applications, especially for cancer treatment. *Zanthoxylum* species via *Z. nitidum*, *Z. armatum*, *Z. chalybeum*, *Z. bungeanum*, *Z. piperitum*, *Z. simulans*, *Z. capense*, *Z. schinifolium*, and *Z. zanthoxyloides* were a rich source of cytotoxic components, including crude extracts, essential oils, secondary metabolite compounds, such as alkaloids, flavonoids, lignans, and coumarins that showed potential anticancer agents through many different mechanisms. However, there are some reports on the safety/toxicology of some *Zanthoxylum* species, and advice about using them for a long time must be narrowly supervised, as well as further toxicity investigations to access their safety before *in vivo* trials.

Keywords: *Zanthoxylum*, anticancer, traditional use, extract, essential oil, secondary metabolites.

Classification numbers: 1.2.4, 5.1.2.

1. INTRODUCTION

In the traditional medicines of various countries around the world, *Zanthoxylum* species have been used to treat many diseases from the ancient time, including cancer. In the search for natural anticancer agents, scientists have been very interested in *Zanthoxylum* species because of their potential cytotoxic properties, especially in recent three decades. Many species of *Zanthoxylum* genus contain bioactive compounds, including alkaloids, flavonoids, lignans, and coumarines,

which show cytotoxic effects on cancer cell lines. These compounds induced apoptosis and inhibited cell proliferation, which are essential mechanisms in fighting cancer. Alkaloids like nitidine, chelerythrine, arnottianamide, skimmianine, and magnoflorine are widely present in *Zanthoxylum* species and showed selective cytotoxic effect against cancer cells, often sparing normal cells [1, 2]. Flavonoids derived from *Zanthoxylum*, including quercetin, rutin, and kaempferol, were recognized for their anticancer properties across various cancer models, such as induced apoptosis, inhibited cell proliferation, arrested the cell cycle at G1/S or G2/M phases, and mitigated DNA damage caused by oxidative stress, all of which prevented cancer cell proliferation. *Zanthoxylum* lignans, such as sesamin, have shown promise in inhibiting cancer cell proliferation and metastasis, modulating cancer cell signaling pathways, mainly through the downregulation of NF-κB, which was crucial in tumorigenesis and metastasis [3, 4]. Coumarins such as xanthyletin and psoralen from *Zanthoxylum* species exhibit cytotoxic properties through apoptosis in liver and colon cancer cells by activating the intrinsic pathway of cell death, especially inhibiting tumors of the blood supply needed for growth [5].

2. MATERIAL AND METHODS

The review was carried out using databases of scientific publications, such as PubMed, Google Scholar, Scopus, Science Direct, Web of Science, SciFinder, Wiley, Elsevier, ACS publications, and SpringerLink, using the keywords "*Zanthoxylum",* "anticancer", and "cytotoxic". The related articles were collected from 1911 to 2025. "World of Flora Online" (www.worldfloraonline.org) was used to confirm species names.

3. RESULTS AND DISCUSSION

3.1. Traditional uses of *Zanthoxylum* species

3.1.1. Traditional uses of Zanthoxylum species in Viet Nam

In Viet Nam, there are few taxonomical studies on *Zanthoxylum* species [6-10], including the publication of Guillaumin [6, 10], Pham Hoang Ho [8], and some studies on useful and phytochemistry as Vo Van Chi [7], Do Tat Loi [9]. Recently, the studies of Bui Thu Ha (2010, 2020) were updated, corrected and the taxonomy of *Zanthoxylum* species in Viet Nam was described [11, 12]. The pictures of some *Zanthoxylum* species in Viet Nam are given in Figure S1 of Supporting information.

According to Vo Van Chi, the fruits and seeds of *Z. planispinum* are used to treat fever, stomachache, vomiting, dyspepsia, diarrhea, arthralgia, rashes, and wet cough; the fruits are also used to chew and suck in reducing the toothache; the fruits and seeds of *Z. evodiaefolium* are used in treating cold, stomachache, vomiting, cholera, dysentery, or chewing, the fruits to treat bleeding gum; the fruits of *Z. cuspidatum* (*Z. scandens*) are used to reduce swollen while the leaves are used to treat leprosy; the leaves of *Z. avicennae* are used as a vegetable while the roots or stem barks and root barks are used to treat rashes, ulcer, and scabies; *Z. acanthopodium* is often used to treat stomachache, rheumatism, abdominal trauma causing overwork; *Z. armatum* is used to treat cold, toothache, stomachache, digestive disorder, *Ascaris suum* disease, headache, cough, flu, rheumatism, and poisonous snake bite but the leaves are used externally to treat collarbone, swelling, boil, and skin rashes; the seeds and young leaves of *Z. rhetsa* are used as a spice instead of pepper, often preserved in vinegar and to treat flatulence, diarrhea, and rheumatism, the aromatic gum of leaves is also used to make beer instead of yeast, the seed essential oil is used to

treat cholera, the root barks and barks are used to destroy or force out roundworms and to treat diarrhea, malaria, rheumatism, and stomach disorder; the fruits of *Z. rhetsoides* are used as a spice while the roots and leaves are used to treat cold, rheumatism, collarbone, boils, itch, bleeding wounds, and fire burns; the roots and root barks of *Z. nitidum* are used to treat arthralgia, swollen, backache, rheumatism, collarbone, epigastric pain, toothache, sore throat, snakebite, pyoderma, dermatitis, tetanus; its fruits are used to treat cough, sore throat, rhinorrhea, stomachache, vomiting, diarrhea, malaria, backache, rheumatism, toothache, snakebite and roundworm, and uterine bleeding but the leaves are used as a spice, to make soup or to treat collarbone [7].

According to Pham Hoang Ho, in 11 species of *Zanthoxylum* were identified in Viet Nam, the fruits of *Z. acanthopodium* are used to treat dysentery and stomach pain, while the seeds are fragrant and bitter, cause dryness, and cool down; the fruits and seeds of *Z. armatum* are used as pepper, while the roots are used to treat snake venom; the barks of *Z. avicennae* are used to treat rashes and ulcer; the barks of *Z. rhetsa* are used as a spice, reduce heat, treat rheumatism, bronchitis, asthma, and excessive salivation; the seeds of *Z. myriacanthum* are used as a spice; the seeds of *Z. scandens* are used to reduce heat and benefit menstruation [8].

According to Do Tat Loi, the roots of *Z. avicennae* are processed to treat rashes, ulcer, and watery discharge; the fruits of *Z. nitidum* are used to help digestion, treat worm, toothache, and sometimes mixed with water to make it fragrant [9].

Detailed informations of the traditional uses of *Zanthoxylum* species in Viet Nam are given in Table S1 of Supporting information.

3.1.2. Traditional uses of Zanthoxylum species in the other countries

The *Z. acanthopodium* is used in Indonesia to treat paralysed and skin diseases such as abscess and leprosy [13-15] and also as spices, mainly in processing of fish and meat [16]. In China, many parts of the plant were used as a spice and traditional medicine to treat fever, flu, colic, diarrhea, stomachache, toothache, injury, and insect sting [17].

Z. *ailanthoides* is used in China as a folk medicine for the treatment of heart disease, bone-injury and cold resistance [18, 19].

Z. americanum is used in Canada for the relief of toothache [20].

The *Z. armatum* seeds and barks are used in Pakistan in the treatment of fever, toothache, indigestion/heartburn, stomachic, carminative, cholera and as well as tonic; the branchlets are used as miswak (tooth brush) for cleaning the teeth while the fruit powder is applied in toothache [21, 22]. In India, it is used traditionally as an ethnomedicine for cancer [23], the leaves, stems, barks, fruits, seeds and roots possess medicinal properties, are used in indigenous medicine preparation against various diseases like asthma, bronchitis, indigestion, varicose veins, diarrhea, rheumatism, dyspepsia, cholera and toothache [24]. In Nepal, the leaves, fruits, stems, barks, its seeds are used in several indigenous medicinal practices as carminative, antipyretic, appetizer, stomachic, toothache, dyspepsia [25].

Z. budrunga has a folkloric reputation in India, the aqueous leaf extracts are used to treat dyspepsia and some forms of diarrhea, the bark juice is used in dysentery, cough, headache and vomiting [26].

Z. buesgeniiare roots are used in Sierra Leone as remedy to cure venereal disease, arthritis, and rheumatism; the leaves and barks are used to treat leprosy and relieve pain [27].

Z. bungeanum leaves are used in China as a vegetable [28, 29]; the fruits are widely used as a spice and as a traditional medicine for the treatment of toothache, stomachache, diarrhea and cancer [28]. The Chinese Ministry of Health officially approved *Z. bungeanum* as a dietary medicinal herb to endorse public health since 2002.

Z. capense is used in traditional medicine of South African to treat mouth ulcer, toothache, flatulent colic, bronchitis, fever, infertility, HIV; decoction of its roots is used to treat epilepsy [30]. In Mozambique, it is traditionally used to treat tuberculosis, cough, bronchitis, chest complaints, and pneumonia [31].

Z. chalybeum is used in Brazil for the treatment of malaria [32]. In Kenya, many its parts of it are used to treat various ailments, the leaves are commonly utilized for the management of malaria [33, 34]. In Uganda, it is traditionally used for treating various opportunistic infections in HIV, malaria, sickle cell disease, measles, skin infection, jaundice, yellow fever and cough [35].

Z. clava-herculis is used in Canada for the relief of toothache [20].

Z. integrifoliolum barks are utilized in Taiwan traditional medicine as a remedy for snakebite and dyspepsia, and also as an aromatic tonic in fever [36].

Z. leprieurii is used in Cameroon for the treatment of gonococci, urinary infection and dysentery [37, 38]; the roots, leaves, and fruits are used for the treatment of a wide range of disorders, including toothache, urinary and venereal disease, rheumatism and lumbago [39]; the fruits are used for treatment of stomach [40]. In Ghana, the roots, leaves, and fruits let traditional healers use for the treatment of a wide range of disorders, including toothache, urinary and venereal disease, rheumatism and lumbago [39]. In Kenya, the plant is traditionally used in the treatment of HIV/AIDS, malaria, urinary infections, rheumatic pain as well as an antiseptic [41]. In Nigeria, it is used for the treatment of toothache, urinary and venereal disease, rheumatism and lumbago [39]. In Sierra Leone, its roots, leaves, and fruits are used for the treatment of toothache, urinary, rheumatism and lumbago [39]. In Uganda, it is traditionally used in the treatment of HIV/AIDS, malaria, urinary infection, rheumatic pain as well as an antiseptic in Uganda and Tanzania [3].

Z. liebmanniaum stem barks are used in Mexico traditional medicine for the treatment of stomachache, amebiasis, intestinal parasites and as a local anesthetic agent [36].

Z. nitidum is widely used in China to treat toothache, neuralgia, stomachache, sore throat, rheumatoid arthritis, turgescence, and venomous snake bite [42-46].

Z. paracanthum stems and roots are used in Kenya for the management of tumor and other related diseases [47].

Z. piperitum has long been used as an herbal and digestive medicine as well as an anti-inflammatory agent in China and Korea [48, 49]. In Japan, it has traditionally been used as a spice to suppress unpleasant fishy and meaty odour [49, 50].

Z. rhetsa roots are used in Nigeria as chewing stick to clean the mouth [51]. The barks have been reported to be a remedy for stomach and chest pains, to treat snake bite; the fruits and seeds are used to treat toothache, dizzyness and bloating, malaria, urinary diseases and rheumatism; the leaf decoction is used to treat intestinal worm infection as well as insecticide in India [51]. In Bangladesh, the fruits and stem barks are used in the treatment of asthma, bronchitis, heart complaint and rheumatism; the essential oil is used to treat cholera and also as an antiseptic,

disinfectant [52]. In Philippine, it is used as a pain relief and to increase lactation in nursing mothers [51].

Z. rhoifolium roots are used in Brazil as a febrifuge, digestant and tonic while the stem barks are used to treat flatulence, colic, dyspepsia, earache, toothache and snake bite [52, 53].

Z. schinifolium is used in China to invigorate the circulan of blood and regarded as a drug for various pains [48, 54]. In Korea, it has long been used as herbal and digestive medicine as well as an anti-inflammatory agent [48, 49]. In Japan, it is prescribed as herbal medicine in traditional practice to treat several symptoms [48].

Z. simulans is used in Brazil for the treatment of malaria [32]. In China, the plant has been prescribed in traditional medicine for the treatment of stomachache, toothache, intestinal worm, eczema, and pruritus [55].

Z. tetraspermum is used in folklore medicine of Sri Lanka for the treatment of rheumatism and some forms of diarrhea, the barks are used for preventing toothache [36].

Z. usambarense is used as traditional medicine of Kenya for the treatment of malaria, upper respiratory tract infection, cough, rheumatism, tooth decay and sore gums [56].

Z. zanthoxyloides stem, root and fruit essential oils are used in the treatment of gonococci, urinary infection and dysentery in Cameroon [37, 38]. In Ghana, it is used in ethnomedicine against sickle-cell anaemia [38]. In Nigeria, its roots are used as antibacterial toothbrush, the decoctions of leaves and roots are used to wash wounds for healing, the barks are used in the treatment of intestinal worm and edema [57, 58].

In Brazil, people use leaves and roots of *Zanthoxylum* sp. as a kind of tea to relieve toothache [32]. In Nepal, the fruits of *Zanthoxylum* species are useful in dyspepsia, cholera, fever, toothache, carminative and stomachic [59].

Detailed informations of the traditional uses of *Zanthoxylum* species in other countries are given in Table S2 of Supporting information.

3.2. Anticancer potential of *Zanthoxylum* species

3.2.1. Anticancer potential of Zanthoxylum acanthopodium

Some studies demonstrated that the extracts of *Z. acanthopodium* fruits showed potential anticancer. For example, the aqueous extracts reduced tumor volume by 5.13 ± 0.24 mL once compared to the Dalton's Lymphoma Ascites (DLA) group, which induced cancer in Swiss albino mice at a rate of 26.12 ± 0.47 mL, while the ethanol extracts had a fairly active potential as an anti-cancer against the inhibition of MCF-7 cell proliferation with an IC_{50} value of 221.31 μg/mL [16].

Cytotoxic activity for alkaloid fractions at pH 7 and 9 solutions of *Z. acanthopodium* fruits were determined using MTT assays. The results showed a weak cytotoxicity against 4T1, MCF-7, T47D, HeLa, and Raji human B lymphoblastoid cell lines with IC_{50} values of 92.67, 71.87, 159.87, and 103.09 μg/mL for pH 7, and 451.29, 247.18, 318.46, 303.96 and 181.45 μg/mL for pH 9, respectively [14].

The ethyl acetate fraction (EAF) from fruits of the *Z. acanthopodium* displayed a moderate cytotoxicity against T47D cell lines with the IC_{50} value of 48.94 μg/mL, inhibited cell growth at G0/G1 phase (60.48 %) and in control cells (51.69 %) with EAF at 25 μg/mL [13].

The methanol extracts of *Z. acanthopodium* fruits evaluated the changes of cervical tumors using an *in vivo* cytotoxicity test in rats. The results showed that methanol extracts had no significant effect on rat body weight and cervical organs but it impacted haematological parameters in rats with cervical cancer. The extracts significantly decreased the expression of IL1b, TGFb1, and VEGFR1 and it, by contrast, increased the expression of IL-10 thus may be a potential target for molecular cytokine therapy for cervical cancer [60].

In 2023, the essential oil of *Z. acanthopodium* leaves and stems, were evaluated for their cytotoxic activity. Forty-four compounds were identified in the leaf oil (ZACL) with main compounds of dehydroaromadendrane (23.4 %), (*E*)-carpacin (17.6 %), 2-tridecanone (12.2 %), and 9-methyl-2-decanone (11.8 %). The stem oil (ZACS) contained 25 identified constituents, mainly γ-gurjunene (51.1 %) and butyl acetate (11.8 %). ZACL and ZACS showed a moderate cytotoxic activity against all tested cell lines of SK-LU-1, MCF-7 and HepG2 with IC_{50} values of 35.60 and 34.67 μg/mL, 31.09 and 20.11 μg/mL, 26.56 and 16.03 μg/mL, respectively [17].

The chemical structures of some anticancer potential compounds were indicated in Figure S3 of Supporting Information.

3.2.2. Anticancer potential of Zanthoxylum ailanthoides

The chloroform-soluble fraction from the methanol extracts of *Z. ailanthoides* leaves (ZAC) showed cytotoxic activity against two leukemia cell lines, human promyelocytic leukemia (HL-60) and myelomonocytic leukemia (WEHI-3), with IC_{50} values of 73.06 and 42.22 μg/mL, respectively [18].

The 50 % ethanol extracts from *Z. ailanthoides* stems (ZASZ) induced morphological changes and decreased the cell viability through promoting Weel, checkpoint kinase 2 (CHK2), p21 and p53 levels, decreasing cyclin B and cdc25c in connection with G2/M phase arrest, increasing level of glucose-regulated protein 78 (GRP78), reactive oxygen species (ROS) and Ca^{2+} release, decreasing Bcl-2 and increasing Bax levels led to release the cytochrome c and remove the mitochondrial membrane potential (ΔΨm) in human colon adenocarcinoma cells 205 [19].

The crude alkaloid extracts from *Z. ailanthoides* showed remarkable inhibitory activity against three cancer cell lines, SGC-7901, HeLa, HT-29, and the inhibitory rates ranged from 60.71 to 93.63 % at a concentration of 200 μg/mL, in which SGC-7901 cells seemed to be more sensitive to the extracts than the other three cancer cell lines. However, this crude alkaloid extracts were effectiveness on HepG2 cells [61].

The compounds pheophorbide-a methyl ester, pheophorbide-b methyl ester, 13^2-hydroxyl (13^2-*S*) pheophorbide-a methyl ester, and 13^2-hydroxyl (13^2-*R*) pheophorbide-b methyl ester were isolated from the chloroform-soluble fraction of methanol extracts of *Z. ailanthoides* leaves. All of these four compounds showed anti-leukemia capability against both leukemia cells HL-60 and WEHI-3 with the IC_{50} ranged from 46.76 to 79.43 nM, due to decreasing cell viability, inducing cell cycle arrest/apoptosis, induced DNA damage in these cells [18].

The neolignan ailanthoidol (AT) - an anticancer active principle from *Z. ailanthoides*, was evaluated for its ability to inhibit the 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced promotion in skin tumors of female CD-1 mice. The five minutes pretreatment with AT with three doses 0.5, 1.0 and 2.5 μM prior to TPA (5 nM) three times weekly for 12 weeks to mice showed 50 %, 50 % and 25 % papilloma formation at the end of 12 weeks, respectively. The average number of papillomas per mouse after 12 weeks in the TPA-treatment alone group was 4.9, while

that of the group pretreated with AT were 1.9, 1.9 and 0.8 papillomas per mouse, respectively [62]. Ailanthoidol suppressed cell viability of hepatoma cells Huh7 (mutant p53: Y220C) with IC_{50} values of 45 and 22 μM at 24h and 48h, respectively. Flow cytometry analysis with Annexin-V/PI staining demonstrated that AT induced G1 arrest, reduced the expression of cyclin D1, CDK2, and mevalonate kinase (MVK), procaspase 3/8 and Bcl-xL/Bcl-2, mutant p53 protein (mutp53), in contrast increased the expression of cleaved PARP and Bax, suppressed the phosphorylation of the signal transducer and activator of transcription 3 (STAT3), and demonstrated ATD's selectivity against mutp53 hepatoma cells involving the downregulation of mutp53 and inactivation of STAT3 [63].

Luvagetin, isolated from the stem barks of *Z. ailanthoides*, inhibited the growth of the human lung cancer A-549 cells with an IC_{50} value of 4.28 μg/mL and suggested to be potential in comparison with 5-fluorouracil [3].

The chemical structures of some anticancer potential compounds were indicated in Figure S4 of Supporting Information.

3.2.3. Anticancer potential of Zanthoxylum armatum

The bark extracts of *Z. armatum* were highly active on the proliferation of human keratinocyte cells (HaCaT) with IC_{50} value of 11 μg/mL, while the root extracts were higher active than the bark extracts on the release of LDH from HaCaT cells after treatment with 0.2 μg/mL extract (129 and 94 μU/mL, respectively) [59]. The leaf extracts of *Z. armatum* induced cytotoxicity in HeLa cell lines through activation of caspase 3, cleavage of poly ADP ribose polymerase (PARP), and activation mitogen-activated protein kinases (MAPK) pathway. Interestingly, this extract can improve sensitize of cancer cells to cisplatin and other chemotherapeutic drugs when pretreatment of cancer cell lines with extracts [24]. The methanol extracts and crude saponins from fruits, barks and leaves of *Z. armatum* have the potential to exert their cytotoxic effects involving apoptosis on MDA-MB-468, MCF-7, and Caco-2 cancer cell lines [21].

Three compounds present in the *Z. armatum*, nevadensin, asarinin, and kaempferol, were selected as hit compounds to examine for their anticancer activity using an array of computational and *in silico* tools on a target protein pyruvate kinase M2 (PKM2). All of three compounds showed a high probability of being antineoplastic through binding affinity with PKM2 ranged from -7.7 to -8.3kcal/mol and binding site in formation a stable complex with PKM2 when simulated under physiological conditions [64].

Tambulin, a flavone extracted from *Z. alatum* (syn. of *Z. armatum*), inhibited some cancer cell lines such as L929 (IC_{50} 33.0 μM), HT-29 (IC_{50} 42.0 μM), and K562 (IC_{50} 45.1 μM) cells. Interestingly, tambulin can ameliorate the tumor mass in solid tumors harbouring animals, increase the life spam in ascites tumor harbouring animals (89.5 %), and decrease of the volume of solid tumors in mice with an administration of 20 mg/kg [62].

Three lignans isolated from *Z. alatum* stem barks, sesamin, kobusin and 4'-O-demethyl magnolin, inhibited the growth of lung carcinoma cell line A549 with IC_{50} values of 37.46±1.097, 34.71±2.331, and 26.47±1.871 μg/mL, and pancreatic carcinoma cell line MIA-PaCa with IC_{50} values of 34.04±1.7621, 32.86±2.0271, and 21.72±1.5071 μg/mL, respectively. These results suggested that *Z. alatum* can be further explored for the development of anticancer drugs [23].

The chemical structures of potential anticancer compounds were indicated in Figure S5 of Supporting Information.

3.2.4. Anticancer potential of Zanthoxylum budrunga

The petroleum ether, chloroform and methanol extracts of the leaves and barks of *Z. budrunga* have been evaluated for their cytotoxic properties. Among them, the most significant cytotoxic activity was found in methanol extracts of the barks (LC_{50} 21.12 ppm), following chloroform extracts of the barks and leaves (LC_{50} 28.42 and 30.92 ppm, respectively), methanol extracts of the leaves (LC_{50} 33.44 ppm), and petroleum ether extracts of the barks and leaves (LC_{50} 68.43 and 56.41 ppm, respectively) [26].

In brine shrimp (*Artemia salina*) lethality bioassay, the ethanol root bark extracts of *Z. budrunga*, with the total phenolic content 647.91 mg GAE/100 g of extracts, exhibited lethality against nauplii in a concentration dependent manner with an LC_{50} of 21.84 μg/mL while that of vincristine sulphate was 0.53 μg/mL [65]. The ethanol leaf extracts of *Z. budrunga* showed cytotoxic activity against brine shrimp nauplii with LC_{50} and LC_{90} values of 72.44 μg/mL and 380.19 μg/mL, respectively [66].

A flavonone, 5-methoxy-7-hydroxy flavonone, isolated from the leaf extracts of *Z. budrunga* showed prominent cytotoxic activity with the LC_{50} and LC_{90} values of 16.24 and 56.56 μg/mL, respectively [67].

In two terpenes tetracyclic isolated from the barks of *Z. budrunga*, lup-20-(29)-1-en-3-one was the most cytotoxic to brine shrimp with LC_{50} value of 11.4 ppm, whereas 11*β*-13-dihydro-1-epireynosin was the least cytotoxic with LC_{50} value of 19.99 ppm [68].

The chemical structures of some anticancer potential compounds were indicated in Figure S6 of Supporting Information.

3.2.5. Anticancer potential of Zanthoxylum bungeanum

Hyperoside, a flavonoid isolated from *Z. bungeanum* leaves, inhibited against human colorectal cancer cell line SW620 with IC_{50} values of 72.35, 36.41 and 19.51 μM, for 24, 48 and 96h, respectively. Furthermore, the percentages of SW620 cell apoptosis were 17.3, 21.2 and 32.9 %, in the 12.5, 25 and 50 μM hyperoside treatment groups, respectively. Hyperoside induced apoptosis of the SW620 cells through the enhancement of p53 (116 %) and p21 (198 %) with IC_{50} value of 25 μM for 48 h. The antitumor potency of hyperoside was attributed its antiproliferative effect on the SW620 human colorectal cancer cells through apoptosis by inducing cell cycle G2/M phase arrest or increasing in the expression of p53 and p21, increased generation of ROS, reduced ΔΨm, and upregulation of B-cell lymphoma 2-associated X protein, cytochrome c, caspase-9, caspase-3, inhibition of the mRNA expression levels of GSH-Px and CAT. These data indicated that hyperoside may be involved in the pro-apoptotic signaling of SW620 human colorectal cancer cells via induction of the caspase-dependent apoptosis and p53 signaling pathways [29].

Bungsteroid A, a steroid isolated from the pericarps of *Z. bungeanum*, showed the antiproliferative effects against HepG2, MCF-7, and HeLa cell lines with the IC_{50} values of 56.3, 64.2, and 74.2 μM, respectively [69].

Hydroxy-*γ*-sanshool (HRS) isolated from *Z. bungeanum* profoundly inhibited growth of HCT-116 cells with an IC_{50} value of 88.01 μM inhibiting cell proliferation but had no cytotoxicity to normal cells (IC_{50} 481.52 μM). Its mechanism had affected to decrease morphological distortion as well as capability of capture the cell cycle at G1 phase (50.31 ± 4.13 % vs. 72.16 ± 8.14 % in control and 130 μM HRS, respectively) through apoptosis. Particularly, the HRS treatment of HCT-116 cells grew the percentage of apoptotic cell of 6.2, 11.9, 19.8, and 30.7 % with the IC_{50} of 0, 50, 90, and 130 μM, respectively. Moreover, in HCT-116 cells, the HRS

significantly decreased cyclin D1, CDK4, PCNA, while increasing P21, P53, Fas, and Caspase 8 [70].

Behind the secondary metabolites, essential oil from *Z. bungeanum* was also demonstrated a potential anticancer agent. The hydrodistilled *Z. bungeanum* pericarp essential oil (ZBEO) in which the main components were limonene (22.19 %), *β*-myrcene (9.66 %), *trans*-*β*-ocimene (9.58 %), terpinen-4-ol (8.96 %), and *γ*-terpinene (4.45 %) inhibits the proliferation of HaCaT cells, resulting from the induction of cellular apoptosis through inducing S phase arrest, increasing expression of cleaved caspase-8/9/3, PARP, and Bax, decreased Bcl-2 levels. Among constituents of the ZBEO, limonene notably induced HaCaT cell death and had a much lower IC_{50} value (75.78 μg/mL) [71].

The *Z. bungeanum* seed oil (ZBSO) in which the major compounds were conjugated linoleic acid, *γ*-linolenic acid, arachidonoylthio-PC (15:0/20:0), PE (15:0/22:1,13*Z*) and PG (13:0/20:2,11*Z*,14*Z*), absolutely inhibited the proliferation of human melanoma cell line A375 with an IC_{50} value of 0.367 % by G1 phase arrest and induction of apoptosis in comparison with other four tested human cancer cell lines MDA (0.388 %), HeLa (0.408 %), HepG2 (0.450 %) and A549 (0.619 %) [72] and similar to paper of Wang *et al.* (2023), ZBSO had no toxicity in mice while it noticeably reduced A375 cells' tumor volume [73].

The chemical structures of potential anticancer compounds were indicated in Figure S7 of Supporting Information.

3.2.6. Anticancer potential of Zanthoxylum capense

The methanol root extracts of *Z. capense* expressed the cytotoxic activity on SH-SY5Y neuroblastoma cells with LC_{50} 121.3 ± 6.97 μg/mL through the inhibition rotenone-induced activation of caspase-3 [74].

From this extract, three benzophenanthridine alkaloids (decarine, 6-acetonyldihydrochelerythrine, zanthocapensine), a dibenzyl butyrolactone lignan (−)-savinin), and two 2-arylbenzofuranneolignans (zanthocapensol, zanthocapensate) were isolated and evaluated for their cytotoxic activity to HCT116 cells. These compounds reduced cell viability by at least 20 %, induced cell death following 48h exposure at 20 μM concentrations. Specifically, 6-acetonyldihydrochelerythrine was the most cytotoxic compound after 48h of incubation, leading to about 20 % loss of cell viability at 0.5 μM, and to about 95 % at 20 μM, markedly higher than the exposure to 5-FU, a known apoptosis inducer in HCT116 colon cancer cells. Zanthocapensate, decarine and zanthocapensine induced by about 7-, 4- and 4-fold increases while (−)-savinin and zanthocapensol resulted in about 2- and 3-fold increases in apoptosis as compared with DMSO vehicle control, respectively. Zanthocapensate, zanthocapensine, and zanthocapensol induced by about 3-fold increases in apoptosis as compared 5-FU positive control, respectively. 6-Acetonyldihydrochelerythrine and zanthocapensate induced by about 2- and 1.5-fold increases in caspase-3-like activity after incubation compared with the DMSO vehicle control, respectively [75].

In another study, 6-acetonyldihydrochelerythrine, which was isolated from the methanol extracts of *Z. capense* roots, also displayed potent cytotoxic activity in HCT116 and SW620 cells with IC_{50} values of 2.4 and 0.5 μM, respectively, and its activity were better than that of 5-fluorouracil. It significantly increased in LDH release, steady-state expression of p53, and cleavage of poly(ADP-ribose) polymerase, while it reduced the steady-state expression and activation of the pro-survival proteins ERK5 and Akt, as well as expression of XIAP, Bcl-XL, and Bcl-2 in both HCT116 and SW620 cells [76].

Ten compounds (chelerythrine, 6-hydroxydihydrochelerythrine, rutaecarpine, dodecyl-*trans*-*p*-coumarate, sesamin, catechin, lupeol, sitosterol, pheophytin a and lutein), which were isolated from the stem barks and leaves of *Z. capense,* showed an average toxicity on normal kidney (HEK295), but decreased the viability of MCF-7 cells by at least 23 % at concentration 1 μg/mL and Caco-2 cells by at least 15 % at concentration 5 μg/mL. Among all compounds, chelerythrine was the most cytotoxic against both MCF-7 and Caco-2 cells in contrast, dodecyl-*trans*-*p*-coumarate had better selectivity. Peculiarly, chelerythrine and dodecyl-*trans*-*p*-coumarate exhibited good activity against both MCF-7 (IC_{50} 33.2 and 5.0 μg/mL, respectively) and Caco-2 (IC_{50} 53.6 and 60.6 μg/mL, respectively) cells. Chelerythrine and dodecyl-*trans*-*p*-coumarate significantly increased the cell death over 66 % at the concentrations of 1.5 and 25 μg/mL, respectively. The activity of chelerythrine was connected with the conversion of alkanoamine form (a pseudo-base) into lipophilic hydroxide adduct forms, then this compound will establish a new balance inside the tumor cell by creation of the reactive quaternary cation. However, the mechanism of action of dodecyl-*trans*-*p*-coumarate still remains unclear [30].

The chemical structures of some anticancer potential compounds were indicated in Figure S8 of Supporting Information.

3.2.7. Anticancer potential of Zanthoxylum chalybeum

The dichloromethane extracts from the leaves of *Z. chalybeum* exhibited antiproliferative activity against HL-60 cells with an IC_{50} value of 30.16 μg/mL [77]. The ethanol extracts of *Z. chalybeum* were found to be weakly cytotoxic (CC_{50} 231.0 μg/mL) whereas the DMSO extracts were moderately cytotoxic (CC_{50} 39.8 μg/mL) against U87CD4CXCR4 cells [35].

Alkaloids are considered to be the most potent antitumor constituents in the *Zanthoxylum* species, including *Z. chalybeum*. In stem barks, the major alkaloids were in protopine type (59.88 %), together with benzyltetrahydroisoquinoline type (14.42 %), benzophenanthridine type (13.84 %), dihydrobenzophenanthridine type (8.09 %), respectively. The crude alkaloid extracts (ZAs) showed remarkable inhibitory activity against SGC-7901, Hela, HT-29 and HepG2, with the inhibitory rates ranged from 60.71 to 93.63 % at a concentration of 200 μg/mL, however, SGC-7901 cells seemed to be more sensitive to the ZAs than the other three cancer cells [61].

In 2019, one new compound isolated from stem barks of *Z. chalybeum*, named 4-(isoprenyloxy)-3-methoxy-3,4-deoxymethylenedioxyfagaramide, displayed moderate cytotoxicity against two multidrug resistant leukemia cells, drug-sensitive (CCRF-CEM) and multidrug-resistant (CEM/ADR5000), with IC_{50} values of 29.13 ± 2.54 and 31 ± 4.74 μM, respectively. However, it exhibited more active on the normal human peripheral blood mononuclear cells (PBMCs), with IC_{50} value of 8.42±0.001 μM [33].

The chemical structure of potential anticancer compound was indicated in Figure S9 of Supporting Information.

3.2.8. Anticancer potential of Zanthoxylum heitzii

The methanol extracts from the barks of *Z. heitzii* wich had a high cytotoxic activity on THP-1 (IC_{50} 8.4 μg/mL), showed a weak inhibition against HeLa, PC-3, and MCF-7 cancer cell lines with IC_{50} values of 66.0, 76.0 and 42.0 μg/mL, respectively, but no activity on A549 cells. The methanol extracts from the fruits of *Z. heitzii* only presented a weak inhibition against PC-3 cells with IC_{50} value of 56 μg/mL but no activity on the rest [78].

In another study, the aqueous and methanol extracts from the barks, seeds, leaves and roots of *Fagara heitzii* (syn. *Z. heitzii*) were evaluated for their cytotoxic activity in which the methanol

extracts of fruits and barks significantly inhibited HL-60 cells with IC_{50} values of 20 and 12 μg/mL, respectively [3].

3.2.9. Anticancer potential of Zanthoxylum leprieurii

The methanol extracts from the fruits of *Z. leprieuri* exhibited activity against three cancer cell lines, WRL-68, PC-3 and Caco-2, with IC_{50} values of 17.0, 88.0, and 60.0 μg/mL, respectively [39].

The brine-shrimp lethality bioassay of the chloroform extracts of *Z. leprieurii* fruits showed modest cytotoxicity with LD_{50} at 13.1 μg/mL. From these extracts, four alkaloids were isolated including 3-hydroxy-1-methoxy-10-methyl-9-acridone, 1-hydroxy-3-methoxy-10-methyl-9-acridone, 1-hydroxy-2,3-dimethoxy-10-methyl-9-acridone, 1,3-dihydroxy-2-methoxy-10-methyl-9-acridone. All of them were active against A549, DLD-1 and WS1 cells with IC_{50} values ranging from 27.0 to 77.0 μM [39]. In 2013, a new acridone alkaloid named 3-hydroxy-1,5,6-trimethoxy-9-acridone was isolated from chloroform extracts of *Z. leprieuri* fruits and had a moderate cytotoxic effect against WRL-68 cells with IC_{50} of 86 μM [79].

The chemical structures of some anticancer potential compounds were indicated in Figure S10 of Supporting Information.

3.2.10. Anticancer potential of Zanthoxylum monophyllum

Berberine was isolated from the barks of *Z. monophyllum* and exhibited cytotoxic activity against four human tumor cell lines, HT-29, MCF-7, Hep-2, and MKN-45 with IC_{50} values of 30.9, 28.7, 19.6, and 40.5 μM, respectively [62].

Lupeol and casearin G were isolated from *Z. monophyllum* and tested cytotoxicity against PC-3 and MCF-7 cell lines. Lupeol (≥ 2 μM) resulted in a reduction of both the phagocytic index and the percentage of phagocytic monocytes and macrophages. Casearin G showed both cytotoxic (IC_{50}, LC_{50}) and cytostatic (GI_{50}) effects against PC-3 (IC_{50} 12.5 μM, GI_{50} 3.3 μM, LC_{50} 51.9 μM) and MCF-7 (IC_{50} 112.8 μM, GI_{50} 11.8 μM, LC_{50} 49.4 μM), as well as a hemolytic effect (≥ 182 μM) [80].

The chemical structures of some anticancer potential compounds were indicated in Figure S11 of Supporting Information.

3.2.11. Anticancer potential of Zanthoxylum myriacanthum

Essential oils extracted by hydrodistillation from fruits (ZMFR), leaves (ZML) and stems (ZMS) of *Z. myriacanthum* presented *p*-cymen-8-ol (24.9 %), *β*-pinene (24.3 %), and *p*-methyl-acetophenone (29.9 %), *α*-terpineol (17.0 %), and *ar*-curcumene (44.6 %), terpinen-4-ol (13.2 %) as the most abundant constituents, respectively. ZMFR and ZML displayed moderate cytotoxicity on SK-LU-1, MCF-7, and HepG2 cancer cell lines with the IC_{50} values ranging from 50.97 to 93.78 μg/mL. ZMS had a cytotoxicity against HepG2 (IC_{50} 69.84 μg/mL) and MCF-7 (IC_{50} 89.28 μg/mL), and showed weak effect on SK-LU-1 (IC_{50} > 100 μg/mL) [81].

The most recently, Phuong *et al.* [82] have studied the effect of nitidine isolated from the bark of *Z. myriacanthum* on NTERA-2 cancer stem cells. The results showed that nitidine suppresses stemness properties, like *in vitro* tumorsphere forming, c-myc, Oct4, and Nanog proteins of NTERA-2 cancer stem cells after 48-hour treatment, in which nitidine selectively induced anti-survival activity by triggering the intrinsic apoptotic process through p53 signaling and lysosome-dependent cell death (LDCD), and molecular docking studies also revealed that

nitidine induces LDCD by effectively inhibiting the MHR1/2 domain of the TRPM2 protein on liposome membrane.

The chemical structures of some anticancer potential compounds were indicated in Figure S12 of Supporting Information.

3.2.12. Anticancer potential of Zanthoxylum nitidum

Liriodenine (L) is an oxoaporphine alkaloid isolated from *Z. nitidum* stems and roots. This compound was proven to have cytotoxic effect on various cancer cell lines, such as on MCF-7, NCI-H460, and SF-268 cell lines with IC_{50} values of 3.19, 2.38, and 2.19 μg/mL, respectively [83], on ECV2, 7111, Tca8113, SPC-A-1, KB, KBV200, MDA-MB-231, SGC-7901, BEL7404, A2780, and HeLa cell lines with IC_{50} ranging from 7.198 ± 0.970 to 48.47 ± 2.113 μg/mL [42], on BEL7404, SMMC-7721, A2780, CNE-1, CNE-2, HT-29, HCT116, 7860, and NIC-460 cell lines with IC_{50} ranged from 3.8 ± 0.3 to 48.5 ± 2.1 μM, respectively [84], on HepG2, MCF-7, SK-OV-3, MGC-803, and NCI-H460 cell lines with IC_{50} ranged from 3.51 ± 0.22 to 11.73 ± 1.65 μM [85]. In particularly, it was reacted with Pt(II) and Ru(II) provided three metal complexes, *cis*-$[PtCl_2(L)]$, *cis*-$[PtCl_2(L)(DMSO)]$, and *cis*-$[RuCl_2(L)(DMSO)_2]\cdot 1.5H_2O$, all of three complexes exhibited the active against of 11 selected tumor cell lines (ECV2, 7111, Tca8113, SPC-A-1, KB, KBV200, MDA-MB-231, SGC-7901, BEL7404, A2780 and HeLa) with IC_{50} ranging from 3.187 ± 1.460 to 13.10 ± 1.497 μM, from 7.569 ± 1.333 to 21.42 ± 2.166 μM, from 11.86 ± 1.255 to 30.58 ± 7.173 μM, respectively; in which two complexes *cis*-$[PtCl_2(L)]$ and *cis*-$[PtCl_2(L)(DMSO)]$ were better than liriodenine. Liriodenine also reacted with Mn(II), Fe(II), Co(II) and Zn(II) to apply four metal complexes, $[MnCl_2(L)_2]$, $[FeCl_2(L)_2]$, $[Co(L)_2(H_2O)_2\cdot Co(L)_2(CH_3CH_2OH)_2](ClO_4)_4$, and $[Zn_2(L)_2(m2\text{-}Cl)_2Cl_2]$, in which $[MnCl_2(L)_2]$, $[Co(L)_2(H_2O)_2\cdot Co(L)_2(CH_3CH_2OH)_2](ClO_4)_4$, and $[Zn_2(L)_2(m2\text{-}Cl)_2Cl_2]$ exhibited more cytotoxicity effect than that of liriodenine on ten typical human tumor cell lines (BEL7404, A2780, HeLa, CNE-1, CNE-2, SMMC-7721, HT-29, HCT116, 7860, and NIC-460) with IC_{50} ranged from 4.7 ± 0.9 to 112.1 ± 18.3 μM, from 8.2 ± 0.4 to 85.1 ± 8.1 μM, from 1.7 ± 0.3 to 40.7 ± 9.3 μM, from 5.8 ± 1.2 to 26.2 ± 8.2 μM, respectively [84]. In another study (2011), liriodenine reacted with $HAuCl_4$ and $NaAuCl_4$ to provide $[LH][AuCl_4]$ and $[AuCl_3L]$, and these two complexes exhibited their cytotoxic activity against five typical human tumor cell lines HepG2, MCF-7, SK-OV-3, MGC-803, and NCI-H460 with IC_{50} ranged from 3.71 ± 0.27 to 15.24 ± 0.71 μM, from 2.48 ± 0.06 to 10.88 ± 0.81 μM, respectively. The results showed that $[AuCl_3L]$ exhibited remarkably promoted cytotoxicity towards MCF-7 and MGC-803 with IC_{50} values of 4.58 and 2.48 μM, separately, and more effective than $[LH][AuCl_4]$ and liriodenine [85].

From stem barks of *Z. nitidum*, skimmianine and (–)-xanthoxylol-3,3-dimethylallyl ether were isolated and tested for their cytotoxic activity. The obtained results showed that these two compounds exhibited significant cytotoxicity against MCF-7 cancer cell line with IC_{50} values of 8.03 ± 0.49 and 18.65 ± 1.91 μg/mL, respectively [83].

Nitidine, a natural benzophenanthridine alkaloid derived from *Z. nitidum* and known for its anticancer potential. In details, nitidine significantly suppressed the growth of gastric tumor xenografts (the inhibition rate of 65 % at dosage of 7 mg/kg/d) with an IC_{50} value at about 20 μmol/L and also dramatically reduced neovascularization [86]. It was also proven as a promising chemotherapeutic candidate against HSC3 and HSC4 cells through its capacity of decreasing cell viability and induced apoptosis via dephosphorylating STAT3 in a concentration- and time-dependent manner without liver or kidney toxicity [87]. Nitidine exhibited its tumor xenograft capacity according to differentially expressed genes in several cancer-associated pathways such as transforming growth factor-β and phosphatidylinositol 4,5-bisphosphate 3-kinase/RAC-α

serine/threonine-protein kinase signaling [88]. Furthermore, nitidine was also potently suppressed the growth of 786-O and A498 cells with cell viability and flow cytometric apoptosis assays *in vitro* and significantly decreased phosphorylation of ERK and Akt, accompanied by up-regulation of P53, Bax, cleavage caspase-3 and cleavage PARP, downregulation of Bcl-2, caspase-3 and PARP on the xenograft model performed in nude mice *in vivo* [89]. In the other hand, a complex NC@CB[7] of nitidine and cucurbit[7]uril - a potential drug carrier formed by acid-catalyzed condensation of glycoluril and formaldehyde, showed significantly lower toxicity (IC_{50} 6.87 ± 0.80 μM) on LO2 cells, and higher cytotoxicity (IC_{50} 2.94 ± 0.15 μM) on MCF-7 cells when compared with the free drug cucurbit [7]uril on these two cell lines (IC_{50} of 3.48 ± 0.49 μM and 7.28 ± 0.36 μM, respectively) [90].

Three mannopyranosides of indole alkaloids, methyl 7-(*β*-D-mannopyranosyloxy)-1H-indole-2-carboxylate, methyl 7-[(3-O-acetyl-*β*-D-mannopyranosyl)oxy]-1H-indole-2-carboxylate, and 2-methyl-1H-indol-7-yl-*β*-D-mannopyranoside isolated from ethanol extracts of *Z. nitidum* roots and exhibited their cytotoxic activity against eight tumor cell lines (A-549, BGC-823, HCT15, HeLa, HepG2, MCF-7, SGC-7901, and SK-MEL-2), in which, 2-methyl-1H-indol-7-yl *β*-D-mannopyranoside presented a higher cytotoxic activity (IC_{50} 9.21-12.75 μM) than methyl 7-(*β*-D-mannopyranosyloxy)-1H-indole-2-carboxylate and methyl-7-[(3-O-acetyl-*β*-D-mannopyranosyl)oxy]-1H-indole-2-carboxylate (IC_{50} 23.47-28.12 μM) [43].

Angoline (8-methoxy-dihydrochelerythrine) was isolated from roots of *Z. nitidum* and showed significant inhibitory effect on the STAT3 signaling pathway (IC_{50} 11.56 μM), potent inhibitory effect on cell proliferation of three human cancer cells (MDA-MB-231, H4, and HepG2) with IC_{50} ranging from 3.14 to 4.72 μM [91].

In thirteen benzophenanthridine alkaloids isolated from the roots of *Z. nitidum* var. *fastuosum*, 6-methoxy-7-hydroxydihydrochelerythrine exhibited the best potency against A549, HeLa, SMMC-7721 and EJ cancer cell lines with IC_{50} values of 27.50, 37.50, 16.95 and 60.42 μM, respectively. 6-Methoxydihydrochelerythrine and 8-(10-hydroxyethyl)-7,8-dihydrochelerythrine also showed strong cytotoxicity against four human cancer cell lines A549 (IC_{50} of 42.30 and 34.03 μM, respectively), HeLa (IC_{50} of 37.61 and 72.43 μM, respectively), SMMC-7721 (IC_{50} of 17.93 and 47.56 μM, respectively) and EJ (IC_{50} of 70.81 and 64.65 μM, respectively) while only *N*-nornitidine and noravicine displayed cytotoxicity in inhibiting BALL-1 proliferation (IC_{50} of 67.37 and 74.08 μM, respectively) [46].

Sesquilignans PD, a natural phenylpropanoid compound isolated from *Z. nitidum* var. *tomentosum*, markedly inhibited the proliferation and migration of two liver cancer cells (SK-Hep-1 and HepG2) through inducing apoptosis, autophagy, reactive oxygen species (ROS) production, and also increased the protein levels of p-p38 MAPK and p-ERK1/2 in liver cancer cells [92].

In 2024, chrysosplenol-D was discovered for the first time from *Z. nitidum*, *Zanthoxylum* genus and Rutaceae family and evaluated for cytotoxic activity on five human cancer cell lines (A549, MCF-7, HepG2, T24 and HeLa) by CCK-8 assay. The obtained results exhibited that chrysosplenol-D significant cytotoxicity toward HepG2 and T24, with IC_{50} values of 2.49 and 7.0 μM, respectively [93].

The chemical structures of potential anticancer compounds were indicated in Figure S13 of Supporting Information.

3.2.13. Anticancer potential of Zanthoxylum paracanthum

An alkaloid canthin-6-one and a lignan sesamin were isolated from the MeOH/CH_2Cl_2 (1:1) extracts of the stem barks of *Z. parachanthum*. The canthin-6-one showed moderate cytotoxicity against two drug sensitive CCRF-CEM, multidrug-resistant CEM/ADR5000 and PBMCs cell lines with IC_{50} values of 15.82, 10.52 and 20.12 μM, respectively. Similar to sesamin, it presented cytotoxicity against CCRF-CEM, CEM/ADR5000 and PBMCs cell lines with IC_{50} values of 40.78, 30.70 μM and 82.69 μM, respectively. Furthermore, the canthin-6-one was more active than doxorubicin (IC_{50} 26.78 μM). Both canthin-6-one and sesamin showed good selectivity on leukemia cells than normal cells [33].

Besides, stigmasterol, sesamin, 8-acetonyldihydrochelerythrine, 10-methoxycanthin-6-one, canthin-6-one and 8-oxochelerythrine were isolated from the MeOH/CH_2Cl_2 (1:1) extracts of the root barks of *Z. parachanthum* and had antiproliferative activity against the human breast cancer (HCC 1395) and human prostate cancer (DU 145) cell lines, with IC_{50} values of 0.42, 3.39, 9.99, 14.7, 8.12 and 14.09 μg/mL; 140.49, 115.06, 66.82, 1.58, 9.43 and 63.41 μg/mL, respectively. However, these compounds were less cytotoxic on normal (Vero E6) cell lines with IC_{50} values of 123.88, 135.31, 47.83, 53.95, 41.81 and 135.32 μg/mL, respectively [47].

Three alkaloids dihydrochelerythrine, 6-hydroxymethyldihydronitidine and *bis*-[6-(5,6-dihydrochelerythrinyl)] ether were isolated from the root of *Z. parachanthum* and showed cytotoxicity against CCRF-CEM (IC_{50} 2.00, 2.31, and 0.11 μM, respectively) compared with doxorubicin (IC_{50} 0.01 μM), especially, *bis*-[6-(5,6-dihydrochelerythrinyl)] ether displayed stronger cytotoxicity against CEM/ADR5000 (IC_{50} 2.34 μM) than the doxorubicin (IC_{50} 26.78 μM) [94].

The chemical structures of some anticancer potential compounds were indicated in Figure S14 of Supporting Information.

3.2.14. Anticancer potential of Zanthoxylum piperitum

The anticancer potential components of *Z. piperitum* were proven as aqueous extracts and fatty acid amides isolated from the fruits. The aqueous extracts of *Z. piperitum* fruits (ZFE) were evaluated its effect on DLD-1, HepG2, Caco-2, A549, MCF-7 and WiDr cancer cell lines and the results showed that, after 72 hours of treatment with ZFE, the viability and number of DLD-1 cells decreased by about 45 % and 25 %, respectively, compared to the control group, but there was no inhibition on A549, MCF-7 and WiDr cells. Previously, the proliferation of DLD-1, HepG2 and Caco-2 cells was significantly inhibited after 48-hour treatment with ZFE. On the other hand, the reduction in proliferation following treatment with ZFE was significantly attenuated by ATG5 because of decreased LC3-II levels and suppressed autophagic vacuolization in ZFE-treated DLD-1 cells. Besides, JNK inhibitor treatment had resulted in proliferation following treatment with ZFE noticeably. Interestingly, the normal intestinal cells (IEC-6) were not affected by the ZFE [95]. In addition, the ethanol extracts of *Z. piperitum* (ZPE) decreased cell proliferation and induced apoptosis by inhibiting Akt and MDM2 expression of human gastric carcinoma AGS cells (with IC_{50} ranged from 10 to 85 μg/mL) but that did not happen on gastric fibroblast Hs746T cells. Particularly, ZPE decreased the expression of anti-apoptotic proteins (p-Akt, p-MDM2, Bcl-2), while increased pro-apoptotic proteins (cleaved PARP, p53, pro-Caspase 3, Bax) in AGS cells [49]. Therefore, the *Z. piperitum* is one of the constituents of Kampo preparation Daikenchuto (DKT), a Japanese herbal therapy (Kampo medicine) wields an antitumor effect against various cancer cells via KYSE790, MKN45, MCF7, DLD cell lines, and

diminished the number of peritoneal dissemination of gastric cancer in nude mice without showing apparent adverse reactions, such as diarrhea, in nude mice [96].

Three fatty acid amides, hydroxy-*α*-sanshool, hydroxy-*β*-sanshool, and hydroxy-*ε*-sanshool isolated from the seeds of *Z. piperitum* showed a low cytotoxic activity in the A-549 cell line with LC_{50} values of 56, 16, and 55 μg/mL, respectively [62].

The chemical structures of some anticancer potential compounds were indicated in Figure S15 of Supporting Information.

3.2.15. Anticancer potential of Zanthoxylum rhesta

An alkaloid 8-methoxy-*N*-methylflindersine was isolated from the light petroleum extracts of *Z. rhesta* stem barks, and showed a moderate activity on brine shrimps nauplii (LC_{50} 53.96 μg/mL). The petroleum extracts also exhibited its effect on brine shrimps nauplii (LC_{50} 179.09 μg/mL) [97].

From the root barks of *Z. rhetsa*, five compounds, specifically, chelerybulgarine, simulanoquinoline, 2'-episimulanoquinoline, 2,11-didemethoxyvepridimerine B, and rhetsidimerine were isolated and tested for cytotoxicity. All isolated compounds showed the weak cytotoxic activity against six human stomach-cancer cell lines, SCL, SCL-6, SCL-3706, SCL-9, Kato-3 and NUGC-4 with ED_{50} ranged from 37.47 to 94.28 μM [52].

The methanol leaf extracts showed concentration-dependent cytotoxicity against Jurkat T cells via apoptotic mechanism through arresting cells at G0/G1 and S phases of cell cycle, increasing in the expression of pro-apoptotic markers (p53, Bax, cytochrome C, caspase 3, and MMP) but decreasing of anti-apoptotic marker (Bcl2); and DNA fragmentation [98].

An alkaloid (±)-8-acetonyldihydronitidine was isolated from the twigs of *Z. rhetsa* and showed moderate cytotoxicity toward the SW1353 cancer cell line (IC_{50} 18.90 μg/mL), weak cytotoxic activity against MDA-MB-231, A549 and HCT116 cell lines (IC_{50} 49.86-71.32 μg/mL) [99].

Six alkaloid compounds containing 6-butanoyldihydrochelerythrine, 6-acetonyldihydronitidine, 6-acetonyldihydrochelerythrine, isocorydine, (*O*)-methyltembamide, and *N*-(4-methoxyphenethyl)benzamide from the stem barks of *Z. rhetsa* in which 6-butanoyldihydrochelerythrine, 6-acetonyldihydronitidine, (*O*)-methyltembamide, and *N*-(4-methoxyphenethyl)benzamide exhibited weak activity against MCF7 and A549 cell lines with IC_{50} values ranging from 125.03 to 248.97 μM. Additionally, the isocorydine showed angiotensin II converting enzyme inhibitory activity *in vitro* with IC_{50} value of 65.58 μM and *in silico* with a docking score of −11.52 kcal/mol [100].

The chemical structures of some anticancer potential compounds were indicated in Figure S16 of Supporting Information.

3.2.16. Anticancer potential of Zanthoxylum rhoifolium

The ethanol extracts of *Z. rhoifolium* leaves showed the inhibition against two cancer cell lines HepG2 and HL-60 with GI values of 15.53 ± 5.03 % and 14.00 ± 4.00 %, respectively [53]. and toxicity to brine shrimp (LC_{50} 363 μg/mL) [101].

The leaf essential oils of *Z. rhoifolium* which contained main compounds of germacrene D (14.6 %), limonene (12.5 %), *trans*-2-hexenal (11.3 %), *β*-elemene (9.2 %), 2-undecanone (9.2 %), myrcene (7.9 %), bicyclogermacrene (7.5 %), and germacrene A (5.2 %), were active in the

brine shrimp lethality test (LC_{50} 18.5 μg/mL) [37]. These essential oils showed cytotoxic effects against A-549, HeLa, HT-29 cells with CD_{50} values of 82.3, 90.7 and 113.6 μg/mL, respectively, whereas did not have activity against Vero monkey kidney cell line and mice macrophages [102].

3.2.17. Anticancer potential of Zanthoxylum schinifolium

The young sprout of *Z. schinifolium* contains a large amount of phenolics (142.5 mg/kg) and showed the high anticancer activity against Calu-6 cells with $IC_{50} < 25.0$ μg/mL, but low inhibition on SNU-601 cells with IC_{50} value of 345.1 μg/mL [103].

Evaluating the anti-proliferative potential against human bladder cancer T24 cells, the ethanol extracts of *Z. schinifolium* leaves showed no effect on the cell viability at concentration of <50 μg/mL, whereas significantly reduced the cell viability at concentration of >100 μg/mL, induces apoptosis but no necrosis at concentration of 300 μg/mL [48].

Moreover, the methanol extracts from the fruits of *Z. schinifolium* significantly inhibited tumor development of HuH-7 human hepatoma cells while the essential oil significantly reduced the cell viability due to extensive cell death, induced apoptosis due to the oil-promoted massive formation of ROS by a caspase-3 independent manner in HepG2 cells [62].

In 2011, a new coumarin named 7-[(*E*)-3',7'-dimethyl-6'-oxo-2',7'-octadienyl]oxy coumarin together three known compounds schinilenol, schinindiol and 7-[(*E*)-7'-hydroxy-3',7'-dimethylocta-2',5'-dienyloxy]-coumarin were isolated from the methylene chloride fraction of *Z. schinifolium* leaves. Among them, the 7-[(*E*)-3',7'-dimethyl-6'-oxo-2',7'-octadienyl]oxy coumarin showed potent cytotoxicity (IC_{50} 8.1 μM) against Jurkat T cells while schinilenol and 7-[(*E*)-7'-hydroxy-3',7'-dimethylocta-2',5'-dienyloxy]-coumarin exhibited cytotoxicity weakly (IC_{50} values of 71.68 and 60.94 μM, respectively) [104].

A secondary metabolite auraptene extracted from the fruits of *Z. schinifolium*, has strong cytotoxic activity against Jurkat T cell clone E6.1 with IC_{50} value of 16.5 μg/mL [105].

Three coumarins collinin, 8-methoxyanisocoumarin H, and acetoxyschinifolin which were isolated from a methanol extracts of the stems of *Z. schinifolium* significantly reduced the proliferation of HL-60 cells (IC_{50} 4.62, 5.02 and 5.12 μM, respectively), PC-3 cells (IC_{50} 4.39, 12.22 and 33.81 μM, respectively) and SNUC5 cells (IC_{50} 6.26, 33.5 and 35.11 μM, respectively) [54].

A 4-quinolinone derivative, schinifoline, was found in pericarps of *Z. schinifolium* and had a cytotoxicity on a A549 cells with IC_{50} values of 33.7 ± 2.4, 21.9 ± 1.9 and 16.8 ± 2.2 μg/mL after 6, 12, and 24h treatments, respectively [106].

In another study, the volatile extracts from dried pericarps of *Z. schinifolium* decreased the cell viability and induced apoptotic death in HepG2 cells in a concentration and time-related manner, increased the production of reactive oxygen species in a dose-dependent manner. However, caspase- 3 activity was not changed in the extract-treated cells, suggesting that the extract-induced apoptosis of HepG2 cells is caspase-3 independent. Besides, in nude mice inoculated with HuH-7 cells, the extracts significantly inhibited tumor development [107].

The chemical structures of some anticancer potential compounds were indicated in Figure S17 of Supporting Information.

3.2.18. Anticancer potential of Zanthoxylum setulosum

The crude bark extracts of *Z. setulosum* were notably cytotoxic (100 % kill at 100 μg/mL) to MCF-7, MDA-MB-231, and MDA-MB-468 cell lines *in vitro*. Phytochemical studies of this extracts revealed the triterpenoid lupeol, the lignan sesamin, the sesquiterpene sesquichamaenol, and lichexanthone, in which lupeol proved to be the only cytotoxic component against MCF-7, MDA-MB-231, and MDA-MB-468 cells with IC_{100} of 100 μg/mL[108].

The leaf essential oil of *Z. setulosum*, with main components including *β*-phellandrene (37.5 %), *β*-caryophyllene (13.7 %), *α*-pinene (11.9 %), germacrene D (10.9 %), was active in the brine shrimp lethality test with LC_{50} value of 3.9 μg/mL [37].

The chemical structures of some anticancer potential compounds were indicated in Figure S18 of Supporting Information.

3.2.19. Anticancer potential of Zanthoxylum simulans

Two new pyranoquinoline alkaloids, zanthosimuline and huajiaosimuline, were isolated from the root barks of *Z. simulans* (syn. *Z. coreanum*). The zanthosimuline showed a moderate cytotoxicity against many human cancer cell lines such as BC-1, ZR-75-1, HT-1080, Lul, Mel, Co12, KB, KB-V1, A431, LNCaP, U373, and P-388 with an ED_{50} values ranging from 5.2 to 30.4 μM. Huajiaosimuline exhibited cytotoxic activity on Mel, KB and KB-V1, P-388, and ZR-75-1 cells with an ED_{50} values ranging from 4.0 to 46.4 μM. Additionally, the activity against KB-V1 of zanthosimuline increased three times (ED_{50} 6.5 μM) while that of huajiaosimuline was up to six times in the presence of vinblastine (ED_{50} 4.0 μM). Although both zanthosimuline and huajiaosimuline have showed greatest activity with ZR-75-1 and P-388 cells, they were weak cytotoxic activity in comparison with the positive control compound, 1*α*,25-dihydroxyvitamin D_3 [109].

In another report, five acridone alkaloids named normelicopidine, normelicopine, melicopine, melicopidine, and melicopicine, which were isolated from the root barks of *Z. simulans*, exhibited cytotoxicity against PC-3M and LNCaP at a range values of IC_{50} from 12.5±1.9 to 64.2±4.7 μg/mL. Among them, normelicopidine was the most active against PC-3M and LNCaP cells with IC_{50} values of 12.5 and 21.1 μg/mL, respectively. However, all five compounds were no cytotoxicity to HEK293 cells [55].

The essential oil from *Z. coreanum* (syn. *Z. simulans*) demonstrated the cytotoxic activity on A549 and Detroit 551 cancer cell lines with IC_{50} values of 0.03877 and 0.1736 % (v/v), respectively. In the essential oil-treated Detroit 551 and A549 cell lines, the expression level of caspase-3 gene, an apoptosis marker gene, was increased in high concentrations of *Z. simulans*. After treatment with the *Z. coreanum*, the gene expression of cyclin A, a cell-cycle regulation marker, decreased concentration-dependent manner in A549 and Detroit 551 cells. After treatment with essential oil, the expression of cyclin B in A549 decreased but no change in Detroit 551 cells. The cyclin D expression decreased in A549 cells, increased in Detroit 551 cells. However, there was no tendency for change in A549 and Detroit 551 cell cyclin E expression after treatment with this oil [110].

The chemical structures of some anticancer potential compounds were indicated in Figure S19 of Supporting Information.

3.2.20. Anticancer potential of Zanthoxylum zanthoxyloides

The methanol extracts of *Z. zanthoxyloides* fruits exhibited anticancer activity against WRL-68, Caco-2, PC-3, and MCF-7 cell lines with IC_{50} values of 17, 66, 59, and 55 µg/mL, respectively [40].

The alkaloidal extracts of *Z. zanthoxyloides* leaves (100 and 200 mg/kg) decreased tumor incidence, improved serum GGT, hepatohistological distortions induced by CCl4/olive oil and liver/body weight ratio in HCC cells through reduction of tumor incidence [111].

Two new acridone alkaloids, namely 3-hydroxy-1,5,6-trimethoxy-9-acridone and 4-methoxyzanthacridone, isolated from the fruits of *Z. zanthoxyloides*. Among them, 3-hydroxy-1,5,6-trimethoxy-9-acridone had a low cytotoxic effect on WRL-68, MCF-7 and PC-3 cell lines with IC_{50} values of 86, 229, and 272 µM, respectively; while 4-methoxyzanthacridone showed activity against only MCF-7 cell lines with IC_{50} value of 205 µM [79].

In 2013, from the hexane extracts of *Z. zanthoxyloides* fruits, a new monoterpenoid named zantholic acid was isolated and possessed a selective cytotoxic activity towards MCF-7 cell lines with an IC_{50} of 0.42 µg/mL but no action against WRL-68, Caco-2, and PC-3 cell lines (IC_{50} >100 µg/mL) [38].

From the root barks of *Z. zanthoxyloides,* three compounds involving dihydrochelerythrine, sesamin and hesperidin were isolated and evaluated for their cytotoxic activity. Of all, dihydrochelerythrine inhibited proliferation of HCC, BT549 cancer cells with IC_{50} values of 8.9 and 21.2 µM, respectively; sesamin exhibited moderately selective inhibitory activity against BT549 cancer cells (IC_{50} 47.6 µM) while hesperidin showed low inhibitory activity against A549 and HEP_2 (Larynx) cell lines with IC_{50} values of 64.7 and 67.6 µM, respectively, but it was significantly toxic to normal immortalized LO2 and BEAS cell lines with IC_{50} values of 30.6 and 7.1 µM, respectively. Besides, five compounds strongly bind to cyclin-dependent kinases (CDK2 and CDK6) and weakly bind to caspases 3 and 8 suggesting that they inhibit cancer cells by inducing cell cycle arrest and apoptosis *in silico* [112].

The chemical structures of some anticancer potential compounds were indicated in Figure S20 of Supporting Information.

4. SAFETY/TOXICOLOGICAL ASPECTS OF *ZANTHOXYLUM* SPECIES

Although many *Zanthoxylum* species have been used as traditional medicine agents in various countries to treat many diseases for long time but there are only a few reports on their safety/toxicology. There is a need to develop products with good efficacy and safety profile. However, most studies are small-scale and not systematic of total phytochemical and/or biological activities.

Accordingly, the acetone extracts of *Z. capense* leaves were low cytotoxic against Vero (African green Monkey) kidney cell line (IC_{50} > 1000 µg/mL) [122]. The crude extracts of *Z. gilletii* leaves and stem barks did not exhibit any sign of cytotoxicity on monkey kidney cells even at 500 µg/mL [123]. The ether extracts from *Z. fagara* aerial parts displayed low toxicity to Vero cells with LC_{50} 396.2 µg/mL [124].

However, the ethanol extracts of *Z. zanthoxyloides* stem barks showed cytotoxicity and genotoxicity against human leukocytes lead to DNA damage at the highest concentration tested of 150 µg/mL. Therefore, it should be carefully regarding the dosage and the frequency of use of

Z. zanthoxyloides extracts [58]. The stem bark aqueous extracts of *Z. heitzii* were evaluated acute toxicity on the rats of two sexes, 3 months old and weighing 250 ± 10 g with a single dose (3-18 g/kg body weight) by oral way during 14 days. As a result, the maximum tolerated dose was 6 g/kg and the lethal doses LD_{50} and LD_{100} were 11.7 and 18 g/kg, respectively. The biochemical analysis of plasma revealed that the aqueous extracts of *Z. heitzii* caused, dose-dependent, a significant reduction of ASAT and ALAT, specifically, two sex rats that were treated with the doses 12-15 g/kg increased their rectal temperatures after 6h then decreased 24h later. This results suggested that although the medicinal values of *Z. heitzii*, it can damage on liver with high doses in rats so that the human exposure to this plant for a long time must be narrowly supervised [125].

Z. armatum is an herbal medicine with various active ingredients and pharmacological effects. However, modern studies found that *Z. armatum* is hepatotoxic. The liver injury induced by methanol and ethyl acetate extracts of fruits involved many different lipid metabolites and lipid metabolic pathways when these extracts were administered to mice by gavage [126, 127]. Additionally, its methanol extracts to rats via gavage at a dose of 1.038 g/kg resulted in various neurotoxicity symptoms, such as drooling, decreased appetite and movement, and increased respiratory rate [128]. The neurotoxic components of fruits may be organic acids and compounds containing amino groups. In contrast, its ethyl acetate extracts can induce the mitochondrial apoptotic pathway by accumulating ROS in cells, leading to apoptosis [129]. In another study, Xiang *et al.* (2024) indicated that hydroxy-*α*-sanshool, an amide compound in the fruits, has hepatotoxic effects, which can induce fatty acid synthesis and mitochondrial function damage by inhibiting the AMPK signaling pathway, resulting in aberrant lipid increases [130]. Essential oil of fruits with linalool (56.10 %) and methyl cinnamate (19.73 %) as major components, was found to have negligible mammalian toxicity as its LD_{50} value of 6124 µL/kg body weight through oral administration on mice [131].

A benzophenanthridine alkaloid decarine and an *N*-isobutylamide, *N*-isobutyl-(2*E*,4*E*)-2,4-tetradecadienamide, which were isolated from the methanol extracts of the roots of *Z. capense,* showed a low macrophage cytotoxicity (IC_{50} 460 µg/mL), indicating considerable selective activity. However, 6-acetonyldihydronitidine revealed cytotoxicity on human THP-1 macrophages (IC_{50} 1.7 µg/mL) [132].

Hesperidin isolated from the root barks of *Z. zanthoxyloides* was significantly toxic to LO2 and BEAS cell lines with IC_{50} values of 30.6 and 7.1 µM, respectively. Due to high toxicity of hesperidin against normal lung and liver cells, it deserves further toxicity investigations to access its safety before *in vivo* trials [112].

5. CONCLUSION

The *Zanthoxylum* species represents a promising source of cytotoxic bioactive compounds with significant potential for anticancer drug discovery and development. Numerous phytochemical investigations have revealed a variety of secondary metabolites such as alkaloids, lignans, flavonoids, coumarins, and essential oils that exhibit strong cytotoxic and antiproliferative effects against various cancer cell lines. Several significant compounds found in the genus *Zanthoxylum*, such as alkaloids, flavonoids, lignans, and coumarins, have been shown to inhibit cancer cell growth by inhibiting cell division, promoting apoptosis, and inhibiting angiogenesis, which are necessary for tumor growth. In addition, compounds from *Zanthoxylum* also have cytotoxic effects, meaning they can selectively kill cancer cells without causing much harm to normal cells, making the genus *Zanthoxylum* a potential research subject in developing

anticancer drugs. However, more preclinical and clinical studies are needed to confirm the efficacy and safety of constituents from the genus *Zanthoxylum* when applied in cancer treatment. Therefore, *Zanthoxylum* species possess considerable potential as valuable natural sources for developing novel plant-based anticancer agents.

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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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