Chapter

Alkaloids and Their Pharmacology Effects from *Zanthoxylum* Genus

Nguyen Xuan Nhiem, Pham Minh Quan and Nguyen Thi Hong Van

Abstract

Zanthoxylum genus (Rutaceae) comprises about 212 species distributed in warm temperature and subtropical areas in the worldwide. *Zanthoxylum* species have been used in traditional for the treatment of tooth decay, snakebites, blood circulation problems, stomach problems, inflammation, rheumatic, and parasitic diseases. The chemical investigations of *Zanthoxylum* have been studied by many scientists over the world. Several classes of compounds have been isolated from this genus such as alkaloids, coumarins, and monoterpenes. Of these, alkaloids are the main components and play an important role in *Zanthoxylum* species. Alkaloids have been shown the potential promise about biological activities: cytotoxic, antimalarial, leishmanicidal, anti-inflammatory, analgesic, antiviral, and antibacterial activities. This chapter will focus on the structure elucidation and pharmacological activities of alkaloids from *Zanthoxylum* species. In addition, the absolute configuration of some alkaloids from *Zanthoxylum* genus will be also discussed.

Keywords: *Zanthoxylum*, Rutaceae, alkaloids, ^{13}C-NMR, circular dichroism

1. Introduction

Zanthoxylum genus is one of the biggest genera belonging to the Rutaceae family, including 212 species in the world and widely distributed in the warm or tropic temperate zones. Research findings showed that *Zanthoxylum* genus have many interesting biological activities such as antifungal, antibacterial, antiviral, antimalarial, anti-inflammatory, antioxidant, tuberculosis, cardiovascular, and liver protective activities, especially cytotoxic activities. From the *Zanthoxylum* species, many compounds have been isolated, including alkaloids, lignans, coumarins, flavonoids, terpenoids, steroids, etc.; they are the specific classes of compounds in *Zanthoxylum* genus. The main components presented in this genus are alkaloids and coumarins, with significant biological activities, especially anticancer activities. In particular, this genus contains high levels of benzophenanthridine alkaloids that not only shown their potential cytotoxic *in vitro* but also their ability to inhibit tumor *in vivo* through many mechanisms, resistant against many pathogenics including MRSA strain (methicillin-resistant *Staphylococcus aureus*)—a bacterium caused dangerous infections in hospital [1] and also shown anti-inflammatory activity [2] (**Figure 1**).

Zanthoxylum nitidum

Zanthoxylum setulosum

Zanthoxylum ovalifolium

Zanthoxylum rhoifolium

Zanthoxylum sprucei

Zanthoxylum monogynum

Zanthoxylum panamense

Zanthoxylum ekmanii

Zanthoxylum zanthoxyloides

Zanthoxylum caribaeum

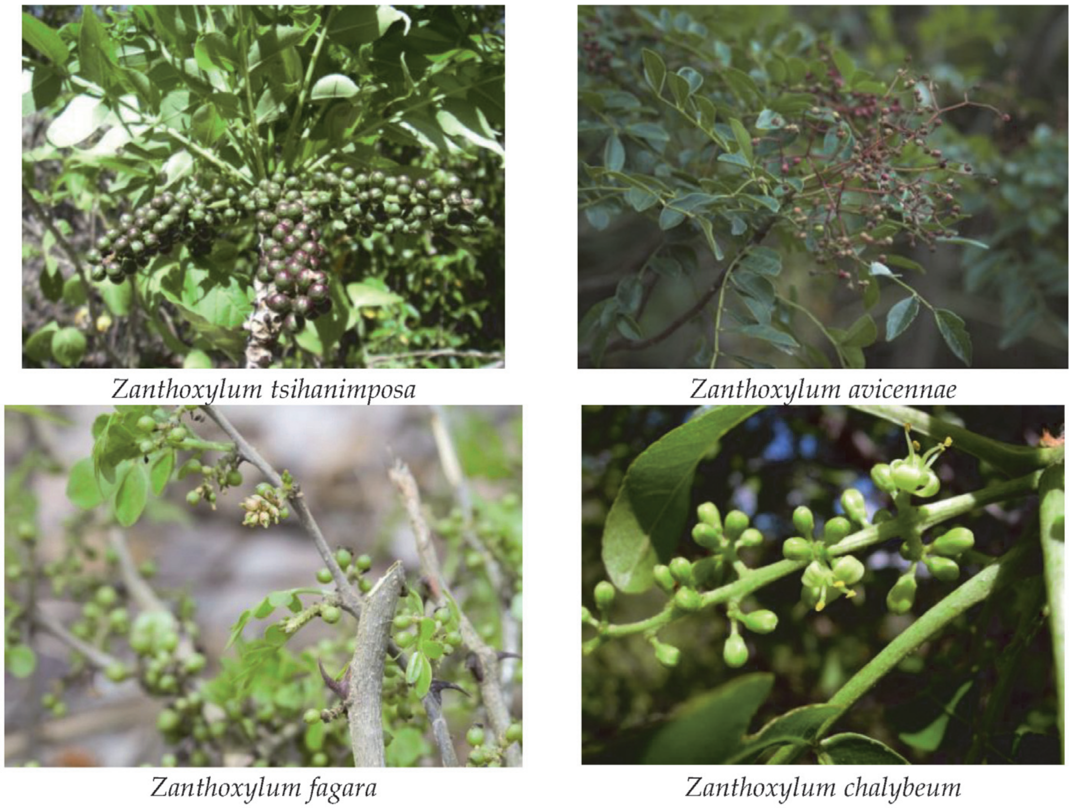

Figure 1.
Photographs of the Zanthoxylum *species. The images were obtained from http://tropical.theferns.info.*

2. Alkaloids constituents from *Zanthoxylum* genus

A total of 35 *Zanthoxylum* species have been studied and showed the presence of alkaloids: *Z. acanthopodium*, *Z. ailanthoides*, *Z. americanum*, *Z. arborescens*, *Z. atchoum*, *Z. austrosinense*, *Z. avicennae*, *Z. bouetense*, *Z. budrunga*, *Z. bungeanum*, *Z. caribaeum*, *Z. chiloperone*, *Z. clava-herculis*, *Z. colantrillo*, *Z. coriaceum*, *Z. culantrillo*, *Z. cuspidatum*, *Z. dimoncillo*, *Z. fagara*, *Z. integrifoliolum*, *Z. lemairei*, *Z. monophyllum*, *Z. myriacanthum*, *Z. nitidum*, *Z. ovalfolium*, *Z. paracanthum*, *Z. procerom*, *Z. rhoifolium*, *Z. riedelianum*, *Z. rubescens*, *Z. schinifolium*, *Z. simulans*, *Z. tingoassuiba*, *Z. usambarense*, and *Z. williamsii*.

2.1 Benzophenanthridine

Benzophenanthridine alkaloids (**1**–**51**) were isolated from *Zanthoxylum* species. Of these, nitidine (**1**), chelerythrine (**2**), and arnottianamide (**48**) were found in almost *Zanthoxylum* species (**Figure 2** and **Table 1**).

2.2 Aporphines and benzylisoquinolines, and furoquinolines

Aporphines and benzylisoquinolines, and furoquinolines (**52**–**75**) were reported from *Zanthoxylum* species. Magnoflorine (**52**), lauriforine (**55**), skimmianine (**69**), γ-fagarine (**70**), and dictamnine (**71**) were found in *Zanthoxylum* species such as *Z. americanum*, *Z. bouetense*, *Z. budrunga*, *Z. caribaeum*, *Z. clava-herculis*, *Z. cuspidatum*, *Z. dimoncillo*, *Z. fagara*, *Z. monophyllum*, *Z. nitidum*, *Z. ovalifolium*, *Z. rubescens*, *Z. schinifolium*, *Z. simulans*, *Z. usambarense*, and *Z. williamsii* (**Figure 3** and **Table 2**).

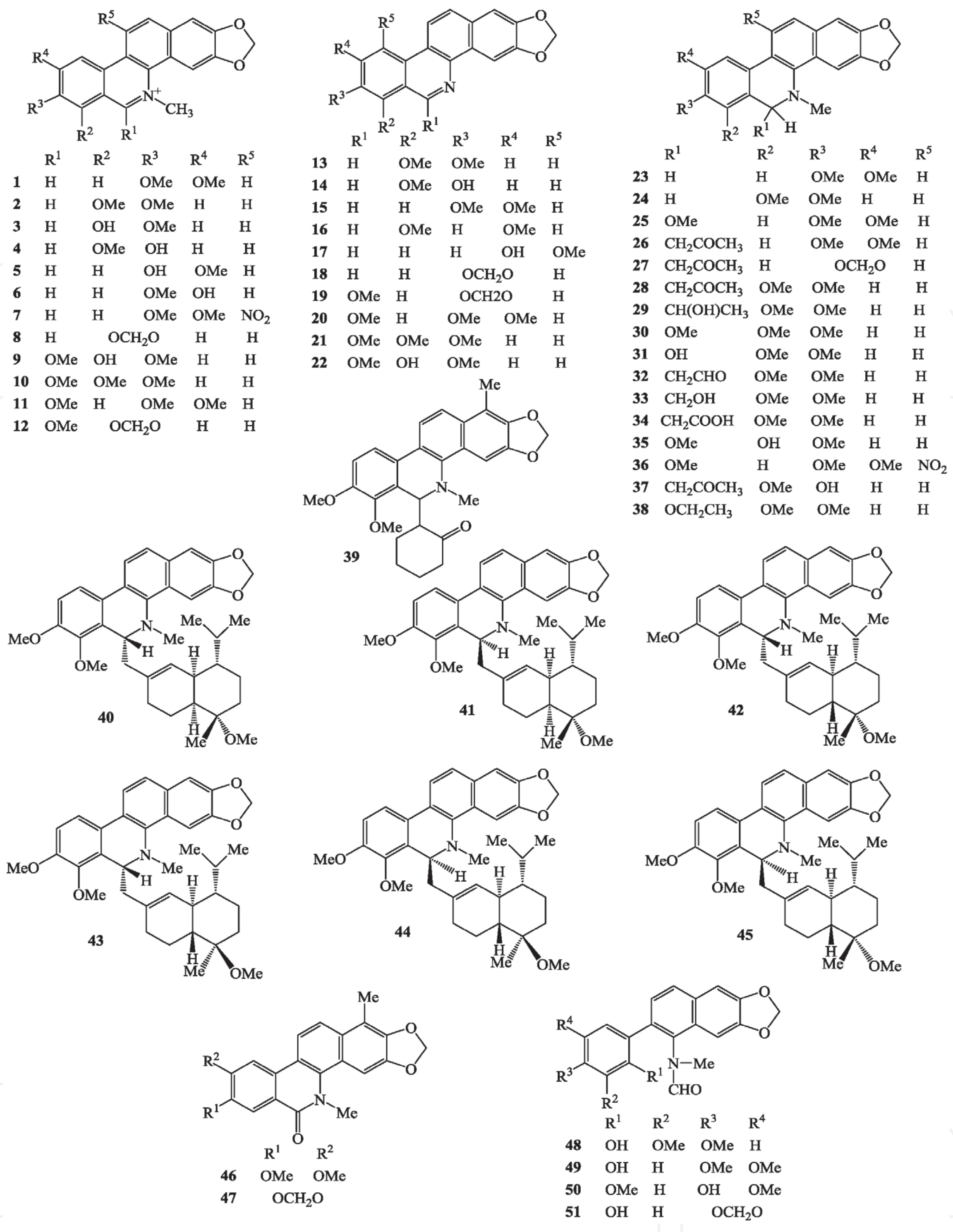

Figure 2.
The structures of alkaloids **1–51**.

2.3 Quinolines, quinolones, and quinazolines

There were 19 quinolines, quinolones, and quinazolines (**79–97**) isolated from *Zanthoxylum* species. They are mainly found in *Z. simulans* and *Z. nitidum* (**Figure 4** and **Table 3**).

2.4 Indolopyridoquinazolines, acridones, and canthinones

There are 10 indolopyridoquinazolines, acridones, and canthinones (**98–107**) isolated from *Zanthoxylum* plants (*Z. atchoum*, *Z. simulans*, and *Z. ovalfolium*).

No.	Compound names	Sources	Ref.
1	Nitidine	*Z. myriacanthum*, *Z. williamsii*, *Z. clava-herculis*, *Z. americanum*, *Z. bouetense*, *Z. nitidum*, *Z. usambarense*, *Z. ovalifolium*, *Z. lemairei*, *Z. atchoum*	[3–18]
2	Chelerythrine	*Z. williamsii*, *Z. monophyllum*, *Z. clava-herculis*, *Z. americanum*, *Z. bouetense*, *Z. nitidum*, *Z. usambarense*, *Z. simulans*, *Z. lemairei*, *Z. atchoum*	[4–8, 11, 13, 14, 17]
3	Fagaridine	*Z. nitidum*, *Z. atchoum*	[6, 17]
4	Isofagandine	*Z. nitidum*	[6]
5	Terihanine	*Z. ovalifolium*	[10]
6	Isoterihanine	*Z. ovalifolium*	[10]
7	11-Nitronitidine	*Z. atchoum*	[17]
8	Sanguinarin	*Z. nitidum*	[11, 13]
9	Methoxyfagaridine	*Z. atchoum*	[17]
10	9-Methoxy chelerythrine chloride	*Z. rubescens*	[5]
11	8-Methoxynorchelerythrine	*Z. nitidum*	[9]
12	8-Methoxysanguinarine	*Z. nitidum*	[19]
13	Norchelerythrine	*Z. nitidum*, *Z. simulans*	[17, 20–23]
14	Decarine	*Z. nitidum*, *Z. simulans*	[13, 20–24]
15	*N*-Nortidine	*Z. myriacanthum*	[23, 25]
16	7,9-Dimethoxy-2,3-methylen dioxybenzophenantridine	*Z. myriacanthum*	[25]
17	Zanthoxyline	*Z. rhoifolium*, *Z. nitidum*	[18, 26]
18	Noravicine		[23]
19	Rhoifoline A	*Z. rhoifolium*, *Z. nitidum*	[13, 26, 27]
20	Rhoifoline B	*Z. rhoifolium*	[26]
21	6,7,8-Trimethoxy-2,3-methylen dioxybenzophenantridine	*Z. nitidum*	[11]
22	8-Methoxyisodecarine	*Z. nitidum*	[19]
23	Dihydronitidine	*Z. myriacanthum*, *Z. nitidum*	[3, 12]
24	Dihydrochelerythrine	*Z. coriaceum*, *Z. nitidum*, *Z. simulans*	[9, 11–13, 18, 20, 22, 28]
25	5,6-Dihydro-6-methoxynitidine	*Z. nitidum*	[29]
26	6-Acetonyldihydronitidine	*Z. rhoifolium*, *Z. nitidum*	[12, 26, 30]
27	6-Acetonyldihydroavicine	*Z. rhoifolium*	[26]
28	6-Acetonyldihydrochelerythrine	*Z. rhoifolium*, *Z. nitidum*	[12, 18, 22, 23, 26]
29	(*R*)-8-(1-hydroxyethyl) dihydrochelerythrine	*Z. nitidum*	[9, 23, 31]
30	8-Methoxydihydrochelerythrine	*Z. nitidum*, *Z. bungeanum*	[9, 13, 23]
31	8-Hydroxydihydrochelerythrine	*Z. nitidum*	[9, 13, 23]
32	Dihydrochelerythrinyl-8-acetaldehyde	*Z. nitidum*	[13]

No.	Compound names	Sources	Ref.
33	Bocconoline	*Z. nitidum*	[18]
34	Carboxymethyl dihydrochelerythrine	*Z. nitidum*	[18, 23]
35	6-Methoxy-7-hydroxydihydro chelerythrine	*Z. nitidum*	[23]
36	6-Nitro-8-methoxy-7,8-dihydronitidine	*Z. atchoum*	[17]
37	8-(2′-Cyclohexanone)-7,8-dihydrochelerythrine	*Z. nitidum*	[31]
38	6-Acetonyl-*N*-methyl-dihydrodecarine	*Z. lemairei*, *Z. riedelianum*, *Z. nitidum*	[14, 18]
39	Ethoxychelerythrine	*Z. nitidum*	[32]
40	Zanthomuurolanine	*Z. nitidum*	[33]
41	*epi*-Zanthomuurolanine	*Z. nitidum*	[33]
42	Zanthocadinanine A	*Z. nitidum*	[33]
43	Zanthocadinanine B	*Z. nitidum*	[33]
44	*epi*-Zanthocadinanine B	*Z. nitidum*	[33]
45	*epi*-Zanthocadinanine A	*Z. nitidum*	[22]
46	Oxynitidine	*Z. nitidum*	[17, 22]
47	Oxyavicine	*Z. nitidum*, *Z. ailanthoides*	[9, 11, 13, 22, 23]
48	Arnottianamide	*Z. nitidum*, *Z. simulans*, *Z. bungeanum*, *Z. ailanthoides*, *Z. austrosinense*	[13, 17, 20–23]
49	Isoarnottianamide	*Z. nitidum*, *Z. myriacanthum*	[13]
50	10-*O*-demethyl-17-*O*-methylisoarnottianamide	*Z. lemairei*	[14]
51	Integriamide	*Z. nitidum*	[13]

Table 1.
Benzophenanthridines from Zanthoxylum *species.*

Until now, only a small number of this class of compounds have been published (**Figure 5** and **Table 4**).

2.5 Other alkaloids

Amines were mainly found in *Z. coriaceum*. But tryptamines were only found in *Z. nitidum*. 16 amines and 6 tryptamines have been reported (**Figure 6** and **Table 5**).

3. Biological activities of alkaloids

The abundance and diversity as well as the valuable properties in terms of chemical compositions and biological activities of the *Zanthoxylum* genus have attracted the attention of many research scientists. The studies have shown that the extracts and alkaloids from *Zanthoxylum* species have many valuable biological

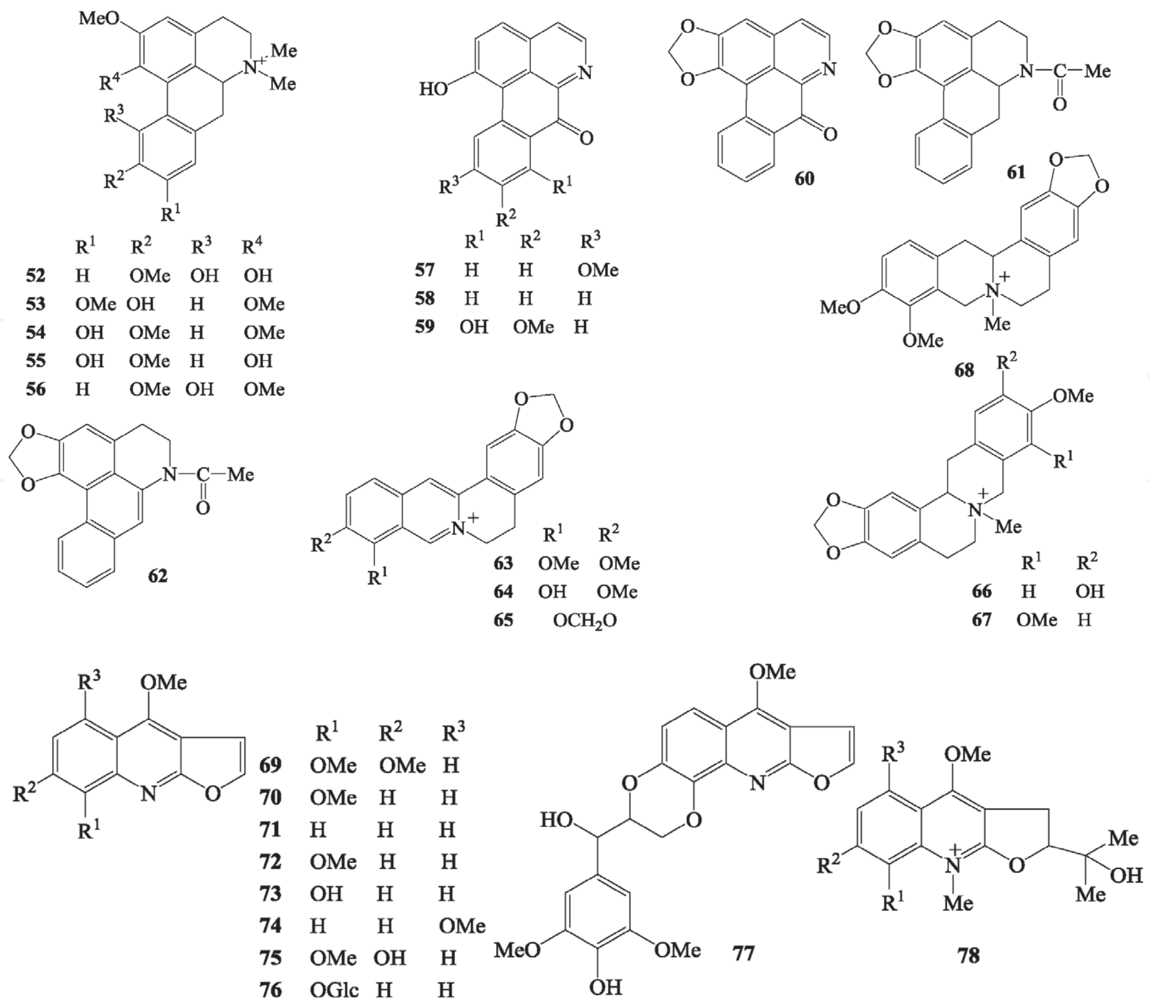

Figure 3.
The structures of alkaloids 52–78.

activities: anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, and antioxidant activities. Many trials of biological properties of these species have been studied and evaluated promising applications in medicine. However, the most prominent compounds with cytotoxic activity in the genus *Zanthoxylum* are amides and alkaloids.

3.1 Cytotoxic activities

In folk medicine, many species of *Zanthoxylum* are used as drugs to treat cancer, such as: the people in Kakamega, Kenya use the leaves and roots of *Z. gilletii* to treat breast and skin cancers [48]; fruits of *Zanthoxylum* species are used in Indians and South Korea for chemopreventive effects [49, 50], while Cameron people use them to treat anemia disease sickle erythrocytes [51] and Japanese people use as one of the main components in the traditional medicine daikenchuto to treat gastrointestinal and chronic diseases [52]. The chloroform-soluble fraction of *Z. ailanthoides* showed cytotoxic activity against HL-60 and WEHI-3 cell lines with IC_{50} values of 73.06 and 42.22 μg/ml, respectively [53].

The methanol, hexane, and chloroform extracts from *Z. usambarense* were evaluated for cytotoxicity against two breast cancer cell lines, MDA-MB-231 and MCF-7 and one brain tumor cell line, U251 using MTT assay [54]. The crude extract of *Z. setulosum* collected in Monteverde, Costa Rica showed potent cytotoxic activity (100% cells killed at 100 μg/ml) on three cancer cell lines, MCF-7, MDA-MB-231,

No.	Compound names	Sources	Ref.
	Aporphines		
52	Magnoflorine	*Z. fagara*, *Z. williamsii*, *Z. monophyllum*, *Z. clava-herculis*, *Z. americanum*, *Z. usambarense*, *Z. nitidum*	[4, 7, 8, 34]
53	Cocsarmine	*Z. tingoassuiba*	[4]
54	Xanthoplanine	*Z. tingoassuiba*	[4]
55	Lauriforine	*Z. fagara*, *Z. williamsii*, *Z. clava-herculis*, *Z. americanum*	[4, 34]
56	*N*-methyl isocorydine	*Z. caribaeum*, *Z. coriaceum*	[28, 34]
57	Zanthoxoaporphine A	*Z. paracanthum*	[35]
58	Zanthoxoaporphine B	*Z. paracanthum*	[35]
59	Zanthoxaporphine C	*Z. paracanthum*	[35]
60	Liriodenine	*Z. nitidum*	[11, 13, 20, 22, 32, 36]
61	(−)-*N*-acetylanonanine	*Z. simulans*, *Z. nitidum*	[21, 22]
62	*N*-acetyldehydroanonaine	*Z. simulans*, *Z. nitidum*	[21, 22]
	Benzylisoquinolines		
63	Berberine	*Z. caribaeum*, *Z. monophyllum*, *Z. clava-herculis*	[34, 4]
64	Berberubine	*Z. nitidum*	[11, 13]
65	Coptisine	*Z. nitidum*	[11, 13]
66	(−)-Usambarine	*Z. usambarense*	[7]
67	(−)-cis-*N*-methylcanadine	*Z. usambarense*, *Z. nitidum*	[7, 8]
68	*N*-methylcanadine	*Z. coriaceum*	[28]
	Furoquinolines		
69	Skimmianine	*Z. dimoncillo*, *Z. caribaeum*, *Z. fagara*, *Z. williamsii*, *Z. americanum*, *Z. rubescens*, *Z. bouetense*, *Z. simulans*, *Z. nitidum*, *Z. atchoum*	[4, 5, 17, 21, 22, 29, 34, 37]
70	γ-Fagarine	*Z. americanum*, *Z. simulans*, *Z. nitidum*, *Z. cuspidatum*	[4, 21, 22, 24, 29, 37]
71	Dictamnine	*Z. budrunga*, *Z. ovalifolium*, *Z. nitidum*, *Z. schinifolium*, *Z. avicennae*, *Z. acanthopodium*	[10, 13, 29, 37, 38]
72	8-Methoxy dictamnine	*Z. rubescens*	[5]
73	Robustine	*Z. simulans*, *Z. nitidum*	[21, 24]
74	5-Methoxydictamine	*Z. ovalifolium*, *Z. nitidum*	[10, 29]
75	Haplopine	*Z. nitidum*	[37]
76	4-Methoxyfuro[2,3-b] quinoline-8-*O*-β-D-glucopyranoside	*Z. nitidum*	[24]
77	Zanthonitidine A	*Z. nitidum*	[24]
78	(+)-*N*-methylplatydesmine	*Z. usambarense*	[7]

Table 2.
Aporphines and benzylisoquinolines, and furoquinolines from Zanthoxylum *species.*

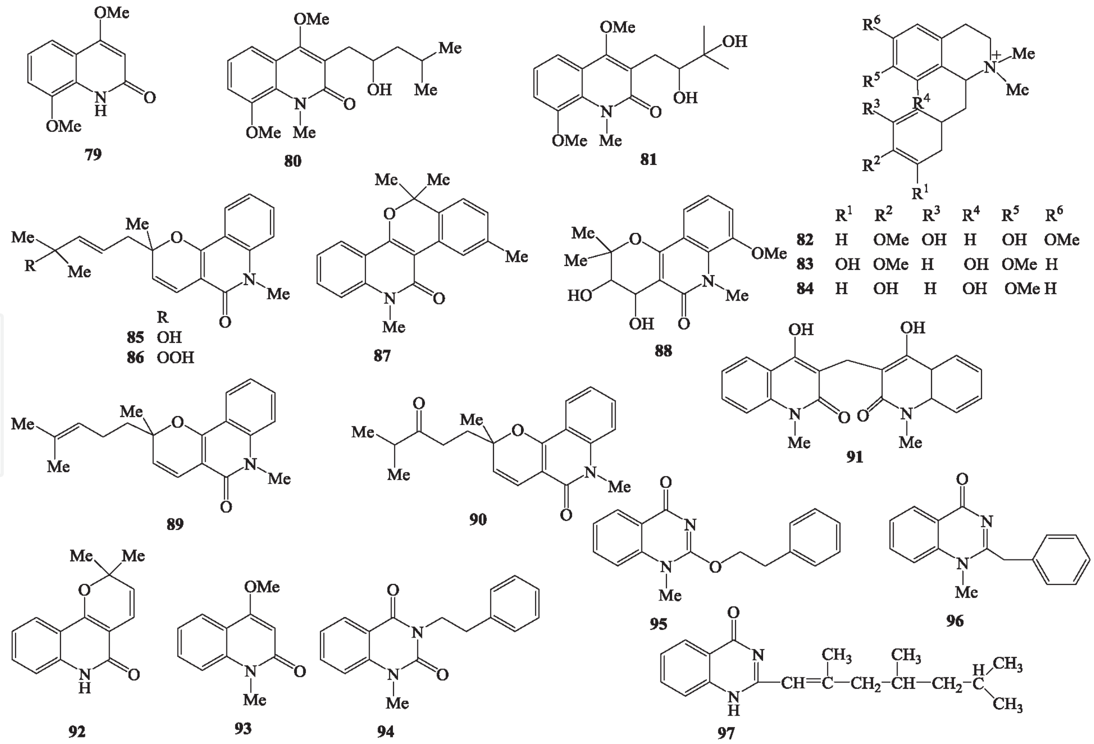

Figure 4.
The structures of alkaloids 79–97.

and MDA-MB-468 [55]. The methanol extract of *Z. avicennae* inhibited the highly metastatic HA22T liver cancer cell migration and invasion effects through PP2A activation [56]. Most recently, the methanol extract of *Z. alatum* showed the apoptotic activity on Ehrlich ascites tumor in Swiss albino mice [57].

A screening study of cytotoxic activity of the extracts from 11 species used as salad in Korea showed that the methanol extract of *Z. schinifolium* had the strongest cytotoxic against Calu-6 cell line with the IC_{50} values < 25.0 μg/ml, meanwhile the methanol extract of *Z. piperitum* exhibited antioxidant effects through ability to arrest radical DPPH. Through the results of this study, the authors suggested that these salad vegetables can be used as functional foods to support cancer treatment [58]. The linear fatty acid amides of the sandshool class are the major ingredient found in seeds of *Z. piperitum* exhibited cytotoxicity in the A-549 cell line [59]. Glycoprotein from the seeds of *Z. piperitum* prevented damage to liver tissue caused by *N*-nitrosodiethylamine in the experimental mouse model [49].

Thirteen benzophenanthridines were isolated from *Z. nitidum* by Wang et al. [23]. The research indicated that 6-methoxy-7-hydroxydihydrochelerythrine exhibited the moderate cytotoxic activity against A549, Hela, SMMC-7721 and EJ, with the IC_{50} values of 27.50, 37.50, 16.95 and 60.42 μM, respectively. 6-Methoxydihydrochelerythrin and 8-(10-hydroxyethyl)-7,8-dihydrochelerythrine also showed strong cytotoxicity when tested against the four human cancer cell lines (A549, Hela, SMMC-7721 and EJ). These results suggested that benzophenanthridines may become a valid alternative of potential basis for new anti-proliferative agents [23]. Methyl 7-(β-D-mannopyranosyloxy)-1*H*-indole-2-carboxylate (**126**), methyl 7-[(3-*O*-acetyl-β-D-mannopyranosyl)oxy]-1*H*-indole-2-carboxylate (**127**), and 2-methyl-1*H*-indol-7-yl β-D-mannopyranoside (**128**) were isolated from the ethanol extract of *Z. nitidum* roots. Biological evaluation revealed that these alkaloids possess significant cytotoxicities against all the tested tumor cell lines with the IC_{50} values of less than 30 μM [46]. Liriodenine (**60**) was the active compound against the MCF-7, NCI-H460, and SF-268 cell lines with IC_{50} values of 2.19, 2.38, and 3.19 μg/ml, respectively [22]. In addition, normelicopidine (**101**)

No.	Compound names	Sources	Ref.
	Quinolines		
79	Edulitine	*Z. simulans*, *Z. nitidum*	[21, 24, 37]
80	Lunacridine	*Z. budrunga*	[39]
81	Edulinine	*Z. williamsii*, *Z. nitidum*	[4, 37]
82	Tembetarine	*Z. fagara*, *Z. usambarense*, *Z. nitidum*	[4, 7, 8]
83	(*R*)-(+)-isotembetarine	*Z. nitidum*	[8]
84	(−)-Oblongine	*Z. usambarense*	[7]
85	Simulenoline	*Z. simulans*	[21]
86	Peroxysimulenolin	*Z. simulans*	[21]
87	Benzosimulin	*Z. simulans*	[21]
88	Zanthodioline	*Z. simulans*, *Z. nitidum*	[21, 24, 37]
89	Zanthosimuline	*Z. simulans*	[21]
90	Huajiaosimuline	*Z. simulans*	[21]
91	Zanthobisquinolone	*Z. simulans*	[21]
	Quinolones		
92	Flindersine	*Z. nitidum*	[22]
93	4-Methoxy-1-methyl-2-quinolone	*Z. nitidum*	[22, 24]
	Quinazolines		
94	1-Methyl-3-(2′-phenylethyl)-lH,3Hquinazoline-2,4-dione	*Z. arborescens*	[34]
95	1-Methyl-3-[2′-(4″-methoxyphenyl) ethyl]-lH,3H quinazoline-2,4-dione	*Z. arborescens*	[34]
96	Arborine	*Z. budrunga*	[38]
97	2-(2′,4′,6′-Trimethyl-heptenyl)-4-quinozolone	*Z. budrunga*	[38]

Table 3.
Quinolines, quinolones, and quinazolines from Zanthoxylum *species.*

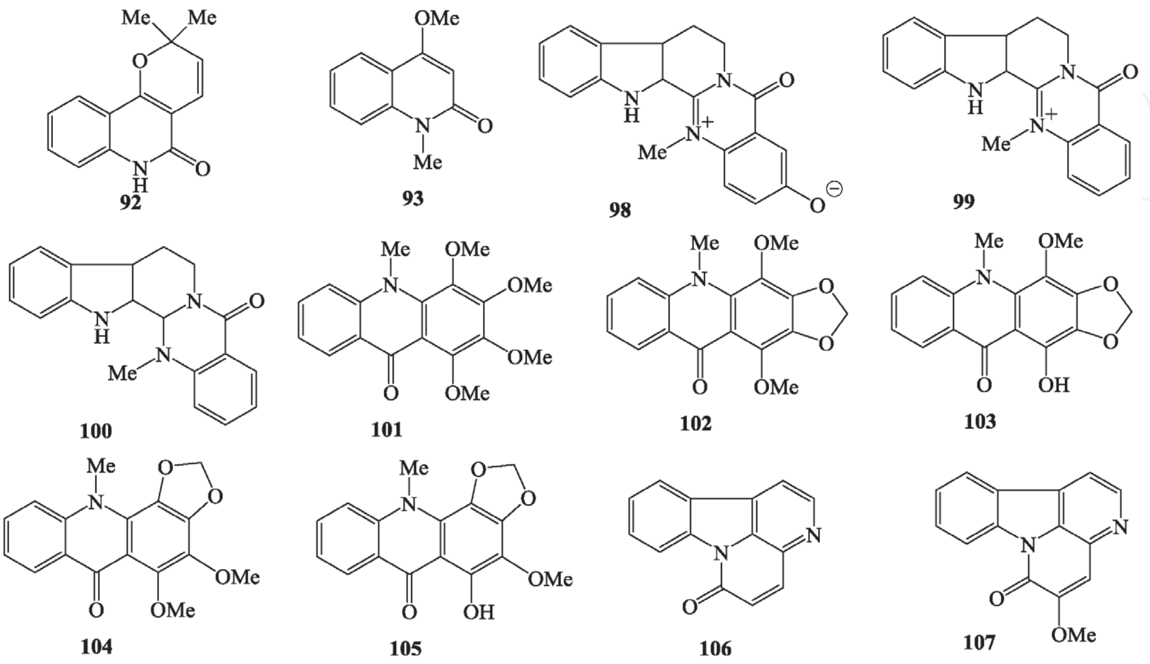

Figure 5.
*The structures of alkaloids **98–107**.*

No.	Compound names	Sources	Ref.
	Indolopyridoquinazolines		
98	3-Hydroxydehydroevodiamine	*Z. atchoum*	[17]
99	Dehydroevodiamine	*Z. atchoum*	[17]
100	Evodiamine	*Z. atchoum*	[17]
	Acridones		
101	Normelicopidine	*Z. simulans*	[40]
102	Normelicopine	*Z. simulans*	[40]
103	Melicopine	*Z. simulans*	[40]
104	Melicopidine	*Z. simulans*	[40]
105	Melicopicine	*Z. simulans*	[40]
	Canthinones		
106	6-Canthinone	*Z. ovalfolium*	[10, 41]
107	5-Methoxycanthin-6-one	*Z. chiloperone*	[42]

Table 4.
Indolopyridoquinazolines, acridones, and canthinones from Zanthoxylum *species.*

from *Z. simulans* showed the cytotoxic activities against PC-3M, LNCaP, and Dd2 with the IC_{50} values of 12.5, 21.1, and 18.9 μg/ml respectively.

Acridone alkaloid derivatives isolated from the roots and fruits of *Z. leprieurii* showed the selective moderately active against two cancer cell lines, A549 and DLD-1 in comparison to normal cell line, WS1 [60]. Liriodenine (**60**) was also isolated from *Z. nitidum* and showed significant cytotoxic activity against three human cancer cell lines, MCF-7, NCI-H460, and SF-268 with IC_{50} values of 2.19, 2.38, and 3.19 μg/ml, respectively. A series of benzo[c]phenanthridine alkaloids isolated from *Zanthoxylum* species showed significant cytotoxic activities: huajiaosimuline (**90**) and zanthosimuline (**89**) isolated from *Z. simulans* showed significant antiplatelet aggregation activity and induced terminal differentiation with cultured HL-60 cells [61], 7,8-dehydro-1-methoxyrutaecarpine, norchelerythrine (**13**), ethoxychelerythrine (**39**), 6-acetonyldihydrochelerythrine (**29**), γ-fagarine (**70**), skimmianine (**69**), (−)-matairesinol, and canthin-6-one (**106**) isolated from the roots of *Z. integrifoliolum* exhibited cytotoxic activities on two human cancer cell lines, P-388 and HT-29 (IC_{50} values < 4 μg/ml) [62]. A new benzophenanthridine-*type* alkaloid, rutaceline isolated from the stem bark powder of *Z. madagascariense* and induced cell cycle arrest in the GO/G1 phase, decreased of cells in S phase as well as induced DNA fragmentation in both cancer cell lines (human colorectal adenocarcinoma (Caco-2) and the African green monkey kidney (Vero) cell lines) [63]. Three others alkaloids isolated from the rhizome of *Z. capense* exhibited strong anticancer activity in HCT-116 colon carcinoma cell line [64].

Nitidine (**1**), a specific compound in *Zanthoxylum* species: *Z. myriacanthum*, *Z. williamsii*, *Z. clava-herculis*, *Z. americanum*, *Z. bouetense*, *Z. nitidum*, *Z. usambarense*, *Z. ovalifolium*, *Z. lemairei*, *Z. atchoum* inhibited gastric tumor cell growth, induced tumor cell apoptosis *in vitro* and effectively suppressed the volume, weight, and microvessel density of human SGC-7901 gastric solid tumors at a dosage of 7 mg/kg/d (intraperitoneal injection) [15], suppressed the growth and pro-apoptotic effects on renal cancer cells both *in vitro* and *in vivo* [16]. Nitidine could inhibit breast cancer cell migration and invasion both *in vitro* and *in vivo* [65]. Chelerythrine (**2**) was found in *Z. williamsii*, *Z. monophyllum*, *Z. clava-herculis*,

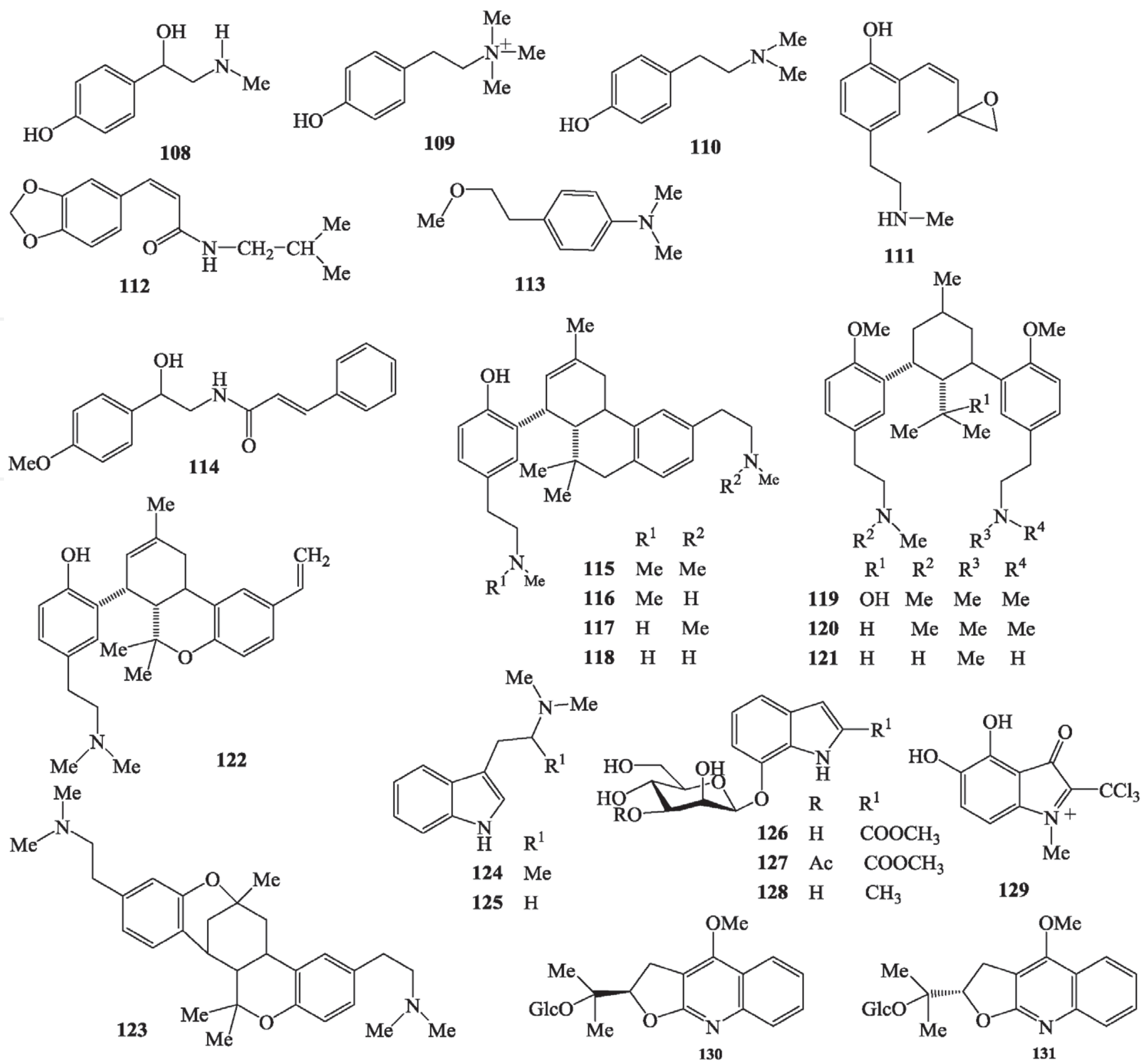

Figure 6.
*The structures of alkaloids **108–131**.*

No.	Compound names	Sources	Ref.
108	Synephrine	*Z. fagara*, *Z. culantrillo*	[4]
109	Candicine	*Z. clava-herculis*, *Z. americanum*	[4]
110	Hordenine	*Z. coriaceum*	[28]
111	4-(2-*N*-methyltyraminyl)-(*Z*)-1,2-epoxy-2-ethylbut-3-ene	*Z. coriaceum*	[28]
112	Fagaramide	*Z. rubescens*	[5]
113	-(2-methoxyethyl)-*N*,*N*-dimethyl benzenamine	*Z. nitidum*	[43]
114	(+)-Aegiline	*Z. coriaceum*	[28]
115	Alfileramine	*Z. coriaceum*, *Z. integrifoliolum*	[28, 44]
116	*N*′-demethylalfileramine	*Z. coriaceum*	[28]
117	*N*-demethylalfileramine	*Z. coriaceum*	[28]
118	*N*,*N*′-demethylalfileramine	*Z. coriaceum*	[28]
119	Culantraraminol	*Z. procerom*, *Z. colantrillo*	[45]
120	Culantraramine	*Z. coriaceum*	[28]
121	*N*,*N*′-demethylculantraramine	*Z. coriaceum*	[28]

No.	Compound names	Sources	Ref.
122	Integramine	*Z. integrifoliolum*	[44]
123	Isoalfileramine	*Z. coriaceum*	[28]
124	*N*,*N*,*N*-trimethyltryptamine	*Z. nitidum*	[8]
125	*N*-trimethyltryptamine	*Z. nitidum*	[8]
126	Methyl 7-(β-D-mannopyranosyloxy)-1H-indole-2-carboxylate	*Z. nitidum*	[46]
127	Methyl 7-[(3-*O*-acetyl-β-D-mannopyranosyl)oxy]-1H-indole-2-carboxylate	*Z. nitidum*	[46]
128	2-Methyl-1H-indol-7-yl *β*-D mannopyranoside	*Z. nitidum*	[46]
129	4,5-Dihydroxy-1-methyl-3-oxo-2-(trichloromethyl)-3H-indolium chloride	*Z. nitidum*	[43]
130	Zanthonitiside A	*Z. nitidum*	[47]
131	Zanthonitiside B	*Z. nitidum*	[47]

Table 5.
Other alkaloids from Zanthoxylum *species.*

Z. americanum, *Z. bouetense*, *Z. nitidum*, *Z. usambarense*, *Z. simulans*, *Z. lemairei*, and *Z. atchoum.* Chelerythrine increased cellular ROS level, leading to endoplasmic reticulum stress, inactivating STAT3 activities and inducing apoptosis in RCC cells which were suppressed by NAC, a special ROS inhibitor [66]. Chelerythrine significantly reduced the gastric ulcer index, myeloperoxidase activities, macroscopic and histological score in a dose-dependent manner [67].

Magnoflorine (**52**) could inhibit the apoptosis of the cells stimulated with TNF-α/IFN-γ. Further animal experiments confirmed that magnoflorine significantly attenuated the AD-like symptom and inhibited the AD-induced increases in IgE/IL-4, as compared with positive control [68]. Doxorubicin effects on the inhibition of migration and invasion of breast cancer cells was significantly promoted by magnoflorine. Doxorubicin-induced cell distribution in G2/M phase was markedly elevated when co-treated with magnoflorine. It is observed that apoptosis process were enhanced through doxorubicin/magnoflorine combinatory treatment rather than using doxorubicin alone through inducing Caspase-3 cleavage. In addition, magnoflorine markedly promoted the role of doxorubicin in autophagy induction by elevating light chain 3 (LC3)-II expression [69].

Liriodenine (**60**) was commonly found in *Zanthoxylum* genus. The effect of liriodenine induced significant apoptosis and suppression of cell growth of the MCF-7 cell line. The results indicated that the anticancer effects of liriodenine suppress cell growth and induce the apoptosis of human breast cancer MCF-7 cells through inhibition of Bcl-2, cyclin D1 and VEGF expression, and upregulation of p53 expression [70].

Skimmianine (**69**) significantly inhibit the growth of non-small cell lung cancer cells and markedly induce apoptosis in non-small cell lung cancer cells [71].

3.2 Inflammatory effects

Inflammation defines as the immune system responses to injury or infection with foreign organisms such as bacteria and viruses. However, excessive chronic inflammation represents the basis of inflammatory diseases including rheumatoid arthritis, diabetes, and chronic hepatitis. Several research groups have reported the inflammatory activity of *Zanthoxylum* genus. In LPS-induced endotoxemic mice, nitidine (**1**) increased IL-10 production, suppressed inflammatory responses, and reduced mortality remarkably. In LPS-stimulated RAW264.7 cells and in peritoneal macrophages from endotoxemic mice, nitidine significantly enhanced the activation of Akt, a critical signal transducer for IL-10 production, and inhibition of Akt prevented nitidine from enhancing IL-10 production and ameliorating endotoxemia [72]. Chelerythrine (**2**) markedly suppressed TNF-α, IL-6, and IL-1β production and oxidative LPS-induced [73]. Chelerythrine was found to inhibit NO production, pro-inflammatory IL-6 and TNF-α level in serum and gastric mucosal in the mice exposed to ethanol induced ulceration in a dose-dependent manner [67]. Skimmianine (**69**) significanly decreased in the mRNA levels of TNF-α and IL-6, which are upstream events of the inflammatory cascade. The levels of PGE2 and NO and the activities of COX-2 and 5-LOX were also significantly reduced after skimmianine treatment [71].

3.3 Antifungal and antibacterial activities

Besides cytotoxic activities, the *Zanthoxylum* species has also showed antifungal and antibacterial activities. In traditional medicine, many *Zanthoxylum* species are used commonly to treat skin diseases, purulent dermatitis, diarrhea, hepatitis and nephritis. Aqueous-ethanol 90% extracts of leaves, roots, and stem barks of *Z. leprieurii* and *Z. xanthoxyloides* inhibited the *in vitro* growth of *Candida albicans*, *Cryptococcus neoformans* and seven filamentous fungi tested [74]. Ethanolic extracts of the *Z. fagara*, *Z. elephantiasis*, and *Z. martinicense* showed antifungal activity [75]. Antifungal activity was also found in all extracts of leaves, fruits, twigs, bark, and roots of *Z. americanum* [76, 77]. Canthin-6-one (**106**) and 5-methoxycanthin-6-one (**107**) are major components in *Z. chiloperone* showed the broad-spectrum antifungal activity [78, 79]. In addition, benzophenanthridines such as dictamnine (**71**), γ-fagarine (**70**), 5-methoxydictamnine from *Z. nitidum* [29], liriodenine from *Z. tetraspermum* showed significant antifungal activity [80].

The screening *in vitro* and *in vivo* activity against the tuberculosis bacterium of compounds isolated from *Z. capense* showed that a benzophenanthridine alkaloid, decarine (**14**) and a *N*-isobutylamide *N*-isobutyl-(2E,4E)-2,4-tetradecadienamide exhibited antibacterial activity against *Mycobacterium tuberculosis* H37Rv (MIC value of 1.6 μg/ml) [81]. 6-Acetonyldihydronitidine (**26**) and 6-acetonyldihydroavicine (**27**) isolated from the stem bark of *Z. tetraspermum* [80] and from the bark and twigs of *Z. rhoifolium* and *Z. tetraspermum* [26], showed significant antibacterial activity.

In particular, benzophenanthridine alkaloids from *Zanthoxylum* genus exhibited strong activity against methicillin-resistant *Staphylococcus aureus* (MRAS) such as: dihydrochelerythrine (**24**) from *Z. rhetsa* [82], decarine (**14**), norchelerythrine (**13**), dihydrochelerythrine (**24**), 6-acetonyldihydrochelerythrine (**28**), tridecanonchelerythrine, and 6-acetonyldihydronitidine (**26**) from Z. *capense* [83], bis-[6-(5,6-dihydro-chelerythrinyl)] ether, 6-ethoxy-chelerythrine, and 4-methoxy-*N*-methyl-2-quinolone from *Z. monophyllum* [83], chelerythrine (**2**) from *Z. clava-herculis* [31]. The polymeric proanthocyanidins from *Z. piperitum* also showed antibacterial activity against MRAS [84]. 4-Methoxy-*N*-methyl-2-quinolone from *Z. monophyllum* exhibited significant inhibitory activity against MRSA bacteria with the IC_{50} value of 1.5 μg/ml [1].

Chelerythrine showed strong antibacterial activities against Gram-(+) bacteria, *Staphylococcus aureus*, Methicillin-resistant *S. aureus*, and extended spectrum β-lactamase *S. aureus*. Chellerythrine experiments on three bacteria resulted in

MICs were all 0.156 mg/ml. It suggest the primary anti-bacterial mechanism of this compound could be originated from the destruction of the channels across the bacterial cell membranes which lead to protein leakage to the outside of the cell and its inhibition on protein biosynthesis [85].

3.4 Other biological effect

Besides above mentioned biological activities, the alkaloid from *Zanthoxylum* plants also showed antivirus, cardioprotective, liver protective, antidiabetic, and antimalarial activities. Benzophenanthridine alkaloids, 5,6-dihydro-6-methoxynitidine, skimmianine, and 5-methoxydictamnine from *Z. nitidum* showed significant antiviral activities against hepatitis B virus [29], decarine, γ-fagarine, (+)-tembamide from the root bark of *Z. ailanthoides* against HIV with EC_{50} values < 0.1 μg/ml [86]. Nitidine showed similar *in vitro* activity in CQ-sensitive and resistant strains, and also a satisfying selectivity index (>10) when compared with a non-cancerous cells line. Nitidine can be considered a potential anti-malarial lead compound [87].

4. Structure elucidation of benzophenanthridine alkaloids from *Zanthoxylum* genus

4.1 NMR methods

Benzophenanthridine alkaloids are the most popular class of compounds isolated from *Zanthoxylum* genus. Structures of benzophenanthridines were elucidated by ^{1}H-, ^{13}C-NMR, DEPT, COSY, HSQC, HMBC, NOESY, and ROESY. The absolute configurations of these compounds were also determined by XRAY, and experimental CD as well as calculated CD.

Study on the structures of benzophenanthridine from *Zanthoxylum* genus, we found some following specifics: dioxymethylene group at C-2 and C-3, unsaturated and saturated bond at N/C-6; some substitutions at C-6 such as sesquiterpenes. **Tables 6** and 7 summarized ^{13}C-NMR characteristics of benzophenanthridine as follows:

1. When dioxymethylene group at C-2/C-3, ^{13}C-NMR chemical shift was about 102.0 ppm.

2. The *N*-methyl group at N was confirmed by chemical shift about 50.1–53.0 ppm when the presence of double bond at N/C-6; chemical shift about 41.1–41.2 ppm when the presence of single bond at N/C-6.

3. When C-substitution at C-6, chemical shifts at C-6 appeared around 57.3–66.7 ppm (methine carbon).

4. The positions of methoxy groups at benzophenanthridines normally appear at C-6, C-7, C-8, and C-9 with chemical shift around 55.7–62.8 ppm. Especially when the presence of single bond at N/C-6, the chemical shift of methoxy group at C-6 as 40.9–41.2 ppm.

5. When substitution groups at C-6 appear, they will have additional signals such as sesquiterpene.

C	1	7	11	12	13	14	19	20	22	24
1	107.3	108.0	104.7	106.2	104.4	104.4	104.7	104.7	104.5	104.2
2	151.0	154.0	147.6	150.4	148.2	147.9	147.6	147.4	147.4	147.1
3	150.5	153.5	147.1	150.3	148.2	148.1	147.0	147.0	145.9	147.7
4	103.9	106.0	102.6	104.7	100.7	100.8	100.6	102.6	101.4	100.6
4a	132.6	123.0	121.1	121.2	126.9	128.3	120.8	121.0	120.0	126.2
4b	152.2	138.0	135.7	132.7	136.9	138.7	152.4	135.8	128.0	142.6
6	134.6	155.0	162.7	163.4	145.5	145.7	164.0	164.3	162.7	48.6
6a	134.5	122.0	119.8	129.2	120.6	121.4	135.9	119.0	126.4	126.1
7	109.7	110.0	150.3	147.0	144.1	142.1	106.6	108.6	145.7	146.0
8	154.2	155.0	152.8	151.1	149.4	147.5	148.2	149.6	148.1	152.2
9	161.4	160.0	118.0	127.0	120.5	123.5	131.1	153.5	126.4	110.9
10	105.6	105.0	117.9	119.1	118.6	118.5	102.6	102.7	118.6	118.6
10a	121.6	133.0	129.0	120.2	127.3	126.4	132.0	128.9	118.1	126.2
10b	128.3	119.0	117.3	126.4	120.0	120.0	116.8	116.7	123.7	123.7
11	120.0	144.0	118.5	117.9	118.4	118.5	118.5	118.3	118.7	120.0
12	131.9	128.0	123.4	132.1	127.6	127.0	123.2	123.2	127.1	123.6
12a	122.3	132.0	131.8	133.9	129.5	129.2	120.9	131.8	129.1	130.8
2,3-OCH_2O	104.4	103.0	101.6	103.4	101.4	101.4	101.5	101.5	101.8	100.9
7,8-OCH_2O				102.3						
8,9-OCH_2O							101.9			
NCH_3	52.2	53.0		50.1						41.2
6-OCH_3			40.9	49.7			41.1	41.2	41.2	
7-OCH_3			61.8		61.5	61.1				60.9
8-OCH_3	57.2	58.0	56.7		56.7			56.2	59.9	55.7
9-OCH_3	57.9	58.0						56.1		
Solv.	**m**	**m**	**m**	**m**	**d**	**d**	**c**	**c**	**m**	**c**
Ref.	[71]	[17]	[9]	[19]	[72]	[72]	[26]	[26]	[19]	[72]

c, recorded in chloroform-d_1; d, DMSO-d_6; m, methanol-d_4.

Table 6.
^{13}C-NMR data of benzophenanthridine alkaloids.

4.2 Circular dichlorism

Circular dichroism (CD), a spectroscopic technique based on differential absorption of left- and right-handed circularly polarized light, is ideally disposed to analyze molecular structure, composition and interactions of chiral systems. Quantum mechanical calculations based on density functional theory (DFT) and its time-dependent formulation theory (TD-DFT) could be used to determine the theoretical chiroptical response of all the possible conformations of complexed-structures;

C	26	29	36	37	38	40	41	42	43	44
1	123.3	106.9	106.0	101.2	104.0	105.2	105.1	105.0	104.9	105.0
2	148.7	149.9	152.5	147.6	147.5	148.4	148.4	148.3	148.3	148.4
3	149.0	150.9	152.0	147.9	146.5	148.9	148.8	148.5	148.5	148.8
4	104.3	101.6	101.0	104.2	99.3	101.9	102.0	102.6	102.7	102.4
4a	123.8	128.8	130.5	131.0	123.1	132.1	132.1	132.0	132.0	132.1
4b	130.9	140.0	141.0	140.0	137.8	141.3	141.1	141.1	141.1	141.1
6	60.0	66.7	92.0	56.2	54.3	58.5	57.4	56.6	56.3	57.4
6a	123.5	126.0	121.0	126.2	121.3	131.1	131.1	131.5	131.4	131.3
7	100.4	149.3	112.0	146.7	149.5	147.0	147.0	147.0	147.0	147.1
8	147.5	154.4	150.0	151.9	143.8	153.0	153.0	153.0	153.0	153.0
9	148.2	114.4	150.0	111.3	116.0	112.1	111.8	112.0	112.0	111.9
10	106.4	121.4	110.0	119.1	118.7	119.3	119.3	119.3	119.3	119.2
10a	139.0	127.2	127.0	125.3	130.1	125.8	125.8	125.9	125.9	125.8
10b	127.0	126.7	119.0	123.2	127.4	124.8	124.8	124.8	124.8	124.9
11	119.6	121.9	144.0	119.6	119.5	120.7	120.7	120.8	120.7	120.7
12	110.4	126.7	121.0	123.5	123.6	124.4	124.5	124.4	124.3	124.4
12a	127.3	133.4	130.0	127.4	126.4	128.7	128.7	128.7	128.7	128.6
2,3-OCH_2O	101.3	103.4	104.0	101.0	101.0	101.2	101.3	101.3	101.3	101.3
NCH_3	42.4	44.2	40.0	42.3	42.4	43.3	43.2	43.2	43.1	43.2
6-OCH_3			55.0							
7-OCH_3		62.8		60.8	60.0	60.9	60.9	61.0	61.0	61.0
8-OCH_3	56.1	57.9	57.0	55.7		55.8	55.6	55.7	55.7	55.7
9-OCH_3	56.0		57.0							
1′	148.4	69.3		53.3	47.2	48.2	42.6	50.7	47.9	47.3
2′	207.9	20.4		211.9	206.1	21.7	21.6	23.6	23.4	23.6
3′	31.5			41.8	30.0	30.8	30.8	29.9	29.5	29.4
4′				28.9		135.7	134.6	135.5	136.4	136.3
5′				23.8		128.2	128.2	126.0	125.2	125.9
6′				30.4		35.2	35.0	38.0	40.3	40.3
7′						44.6	44.6	46.7	46.5	47.1
8′						20.0	20.0	20.4	17.7	22.3
9′						32.4	32.8	34.5	36.3	36.2
10′						76.1	76.1	74.3	76.3	76.3
11′						43.1	43.0	44.1	44.2	43.4
12′						27.4	27.3	26.6	26.2	26.4
13′						15.9	15.8	15.6	15.4	15.4
14′						22.4	22.2	21.8	21.8	22.0
15′						23.0	23.1	23.2	22.3	18.2
10′-OCH_3						48.1	48.3	48.7	48.4	48.3
Solv.	**c**	**m**	**m**	**c**	**d**	**p**	**p**	**p**	**p**	**p**
Ref.	[30]	[9]	[17]	[31]	[14]	[33]	[33]	[33]	[33]	[33]

c, recorded in chloroform-d_1; d, DMSO-d_6; m, methanol-d_4; p, pyridine-d_5.

Table 7.
^{13}C-NMR data of benzophenanthridine alkaloids (continued).

by comparison with the experimental CD spectra. This approach can lead to the elucidation of possible absolute structure in the absence of X-ray crystallography or NMR data.

Van et al. isolated four new compounds from *Z. nitidum*. Of these compounds **130** and **131** have the same constitution. This suggested the aglycone could be enantiomer. Thus, the absolute configuration at C-11 of **130** and **131** were elucidated by the comparison of its experimental ECD spectra with those calculated spectra. The TD-DFT calculated ECD spectra [47] of a pair of epimers (**130a** and **131a**) are shown in **Figure 7**. The CD spectra of **130** and **131** were found to be similar to **130a** and **131a** indicating the absolute configuration at C-11 as *R* and S, respectively.

Yang et al., isolated five novel dihydrobenzo[*c*]phenanthridine alkaloids, zanthomuurolanine (**40**), *epi*-zanthomuurolanine (**41**), zanthocadinanine A (**42**), zanthocadinanine B (**43**), and *epi*-zanthocadinanine B (**44**) from *Z. nitidum* [33]. The absolute configurations of these compounds were determined by XRAY and also CD spectra.

Zhao et al. isolated a pair of new enantiomeric furoquinoline alkaloids, zanthonitidine A (77) from *Z. nitidum.* There is no obvious absorption of electronic circular dichroism indicated that zanthonitidine A was proposed to be a racemate

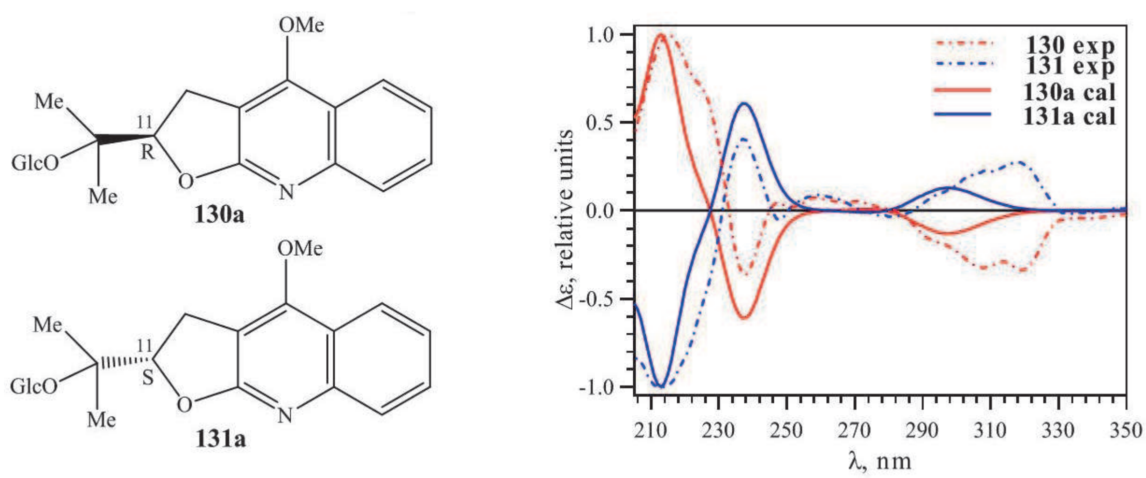

Figure 7.
Experimental CD and calculated ECD spectra of ***130*** *and* ***131*** *(calculated spectra are shifted by −8 nm). The figure was cited from Van et al [47].*

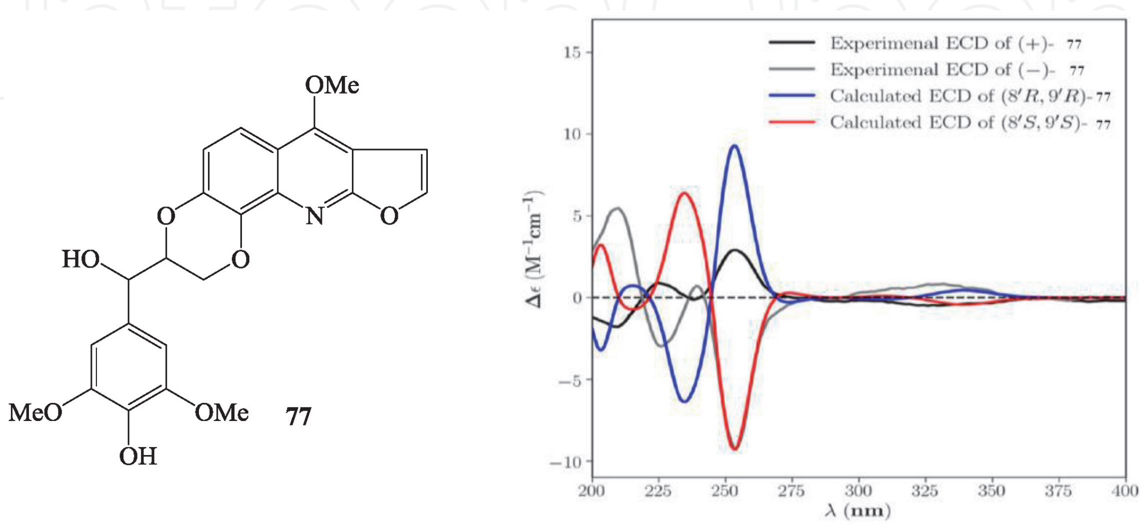

Figure 8.
*Two possible stereochemical structures of 77; experimental ECD spectra of (+)-77/(−)-77 and calculated ECD spectra of (8′*R*, 9′*R*)/(8′*S*, 9′*S*) of* ***77****. The figure was cited from Zhao et al [24].*

mixture. Thus, they used Chiralpak ID column chromatography to separate the mixtures to obtain the enantiomers, (+) and (-)-zanthonitidine A. The absolute configurations of the enantiomers were then determined by comparing the experimental CD to the calculated ECD using TD-DFT of the Gaussian 9.0. By analyzing ECD spectra at the same theory level, the absolute configurations of (+) and (−)-zanthonitidine A were evaluated as ($8'R,9'R$)-zanthonitidine A and ($8'S,9'S$)-zanthonitidine A [24] (**Figure 8**).

Overall, experimental and calculated ECD spectra could play an important role for determine absolute configurations of alkaloids from *Zanthoxylum* species.

5. Conclusions

Alkaloids are the main constituents of *Zanthoxylum* species, present in the fruits, leaves, bark and root of plants. There are different types of skeletons of these alkaloids, including benzophenanthridines, aporphines, benzylisoquinolines, furoquinolines, quinolines, quinolones, quinazolines, indolopyridoquinazolines, acridones, canthinones, amines and tryptamines; in which benzophenanthridines are the main ingredient. Alkaloids from *Zanthoxylum* species have been displayed a variety of valuable biological activities, such as antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, cardiovascular protect and especially anti-cancer effects. Some alkaloids of which shown their potential to become natural healing agents, this has increasingly attracted scientists' interest in the genus *Zanthoxylum*. The data collected in this chapter has clearly shown that *Zanthoxylum* alkaloids with abundance of chemical structures and a wide range of cytotoxic activities on many the cancer cell lines. These could be good sources of potential cancer chemo-preventive agents. Further studies should be carried out to know more clearly the anticancer mechanisms of these alkaloids.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this book chapter.

Author details

Nguyen Xuan Nhiem[1], Pham Minh Quan[2] and Nguyen Thi Hong Van[2]*

1 Institute of Marine Biochemistry, Vietnam Academy of Science and Technology, Hanoi, Vietnam

2 Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology, Hanoi, Vietnam

*Address all correspondence to: van762004@yahoo.com

References

[1] Rodriguez-Guzman R, Radwan MM, Burandt CL, Williamson JS, Ross SA. Xenobiotic biotransformation of 4-methoxy-N-methyl-2-quinolone, isolated from *Zanthoxylum monophyllum*. Natural Product Communications. 2010;**5**:1463-1464

[2] Hu J, Zhang WD, Liu RH, Zhang C, Shen YH, Li H-L, et al. Benzophenanthridine alkaloids from *Zanthoxylum nitidum* (ROXB.) DC, and their analgesic and anti-inflammatory activities. Chemistry & Biodiversity. 2006;**3**:990-995

[3] Waterman PG. Alkaloids from the root bark of *Zanthoxylum myriacanthum*. Phytochemistry. 1975;**14**:2530

[4] Stermitz FR, Caolo MA, Swinehart JA. Chemistry of *Zanthoxylum*. Part 5. Alkaloids and other constituents of *Zanthoxylum williamsii*, *Z. monophyllum*, and *Z. fagara*. Phytochemistry. 1980;**19**:1469-1472

[5] Moody JO, Sofowora A. Leaf alkaloids of *Zanthoxylum rubescens*. Planta Medica. 1984;**50**:101-103

[6] Fang SD, Wang LK, Hecht SM. Inhibitors of DNA topoisomerase I isolated from the roots of *Zanthoxylum nitidum*. Journal of Organic Chemistry. 1993;**58**:5025-5027

[7] Kato A, Moriyasu M, Ichimaru M, Nishiyama Y, Juma FD, Nganga JN, et al. Examination of alkaloidal constituents of *Zanthoxylum usambarense* by a combination of ion-pair extraction and ion-pair chromatography using sodium perchlorate. Phytochemical Analysis. 1995;**6**:89-95

[8] Moriyasu M, Ichimaru M, Nishiyama Y, Kato A, Wang J, Zhang H, et al. (R)-(+)-Isotembetarine, a quaternary alkaloid from *Zanthoxylum nitidium*. Journal of Natural Products. 1997;**60**:299-301

[9] Patino-Ladino OJ, Cuca-Suarez LE. Benzophenanthridine alkaloids from *Zanthoxylum quinduensis*. Actualidades Biologicas. 2005;**27**:53-58

[10] Halstead CW, Forster PI, Waterman PG. Alkaloids from the stem bark of an Australian population of *Zanthoxylum ovalifolium*. Natural Product Research. 2006;**20**:940-945

[11] Liang M, Zhang W, Hu J, Liu R, Zhang C. Simultaneous analysis of alkaloids from *Zanthoxylum nitidum* by high performance liquid chromatography-diode array detector-electrospray tandem mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis. 2006;**42**:178-183

[12] Cai M, Zhou Y, Wang X, Li R, Liao X, Ding L. Rapid structural characterization of isomeric benzo[c] phenanthridine alkaloids from the roots of *Zanthoxylum nitidium* by liquid chromatography combined with electrospray ionization tandem mass spectrometry. Rapid Communications in Mass Spectrometry. 2007;**21**: 1931-1936

[13] Hu J, Zhang W-D, Shen Y-H, Zhang C, Xu L, Liu R-H, et al. Alkaloids from *Zanthoxylum nitidum* (Roxb.) DC. Biochemical Systematics and Ecology. 2007;**35**:114-117

[14] Talontsi FM, Matasyoh JC, Ngoumfo RM, Chepkorir R. Mosquito larvicidal activity of alkaloids from *Zanthoxylum lemairei* against the malaria vector Anopheles gambiae. Pesticide Biochemistry and Physiology. 2011;**99**:82-85

[15] Chen J, Wang J, Lin L, He L, Wu Y, Zhang L, et al. Inhibition of STAT3 signaling pathway by nitidine chloride

suppressed the angiogenesis and growth of human gastric cancer. Molecular Cancer Therapeutics. 2012;**11**:277-287

[16] Fang Z, Tang Y, Jiao W, Xing Z, Guo Z, Wang W, et al. Nitidine chloride induces apoptosis and inhibits tumor cell proliferation via suppressing ERK signaling pathway in renal cancer. Food and Chemical Toxicology. 2014;**66**: 210-216

[17] Akoua Yao-Kouassi P, Caron C, Ramiarantsoa H, Prost E, Harakat D, Le Magrex-Debar E, et al. New nitro-benzo[c]phenanthridine and indolopyridoquinazoline alkaloids from *Zanthoxylum atchoum*. Comptes Rendus Chimie. 2015;**18**:891-897

[18] Tuyen TT, Van NTH, Quan PM, Inh CT, Minh PTH, Thuy TTT, et al. Non-alkaloid compounds isolated from *Zanthoxylum nitidum* plant. Vietnam Journal of Chemistry. 2018;**56**:396-400

[19] Cui XG, Zhao QJ, Chen QL, Xu L, Song Y, Jin YS, et al. Two new benzophenanthridine alkaloids from *Zanthoxylum nitidum*. Helvetica Chimica Acta. 2008;**91**:155-158

[20] Deyun K, Gray AI, Hartley TG, Waterman PG. Alkaloids from an Australian accession of *Zanthoxylum nitidum* (Rutaceae). Biochemical Systematics and Ecology. 1996;**24**:87-88

[21] Chen I-S, Tsai I-W, Teng C-M, Chen J-J, Chang Y-L, Ko F-N, et al. Pyranoquinoline alkaloids from *Zanthoxylum simulans*. Phytochemistry. 1997;**46**:525-529

[22] Yang CH, Cheng MJ, Lee SJ, Yang CW, Chang HS, Chen IS. Secondary metabolites and cytotoxic activities from the stem bark of *Zanthoxylum nitidum*. Chemistry & Biodiversity. 2009;**6**:846-857

[23] Wang CF, Fan L, Tian M, Du SS, Deng ZW, Feng JB, et al. Cytotoxicity of benzophenanthridine alkaloids from the roots of *Zanthoxylum nitidum* (Roxb.) DC. var. *fastuosum* How ex Huang. Natural Product Research. 2015;**29**: 1380-1383

[24] Zhao L-N, Guo X-X, Liu S, Feng L, Bi Q-R, Wang Z, et al. (±)-Zanthonitidine A, a pair of enantiomeric furoquinoline alkaloids from *Zanthoxylum nitidum* with antibacterial activity. Natural Products and Bioprospecting. 2018;**8**:361-367

[25] Sukari MA, Salim WSW, Ibrahim NH, Rahmani M, Aimi N, Kitajima M. Phenantridine alkaloids from *Zanthoxylum myriacanthum*. Fitoterapia. 1999;**70**:197-199

[26] Gonzaga WA, Weber AD, Giacomelli SR, Dalcol II, Hoelzel SCS, Morel AF. Antibacterial alkaloids from *Zanthoxylum rhoifolium*. Planta Medica. 2003;**69**:371-374

[27] Hu J, Shi X, Mao X, Chen J, Zhu L, Zhao Q. Antinociceptive activity of Rhoifoline A from the ethanol extract of *Zanthoxylum nitidum* in mice. Journal of Ethnopharmacology. 2013;**150**:828-834

[28] Marcos M, Villaverde MC, Riguera R, Castedo L, Stermitz FR. *Zanthoxylum coriaceum* alkaloids related to bishordeninyl terpenes. Phytochemistry. 1990;**29**:2315-2319

[29] Yang G, Chen D. Alkaloids from the roots of *Zanthoxylum nitidum* and their antiviral and antifungal effects. Chemistry & Biodiversity. 2008;**5**: 1718-1722

[30] Wang XL, Yu KB, Li QF, Peng SL, Ding LS. 8-Acetonyldihydronitidine. Archive of Acta Crystallographica Section E. 2006;**62**:o2247-o2248

[31] Geng D, Li D-X, Shi Y, Liang J-Y, Min Z-D. A new benzophenanthridine alkaloid from *Zanthoxylum nitidum*. Zhongguo Tianran Yaowu. 2009;**7**: 274-277

[32] Liu H, Feng J, Feng K, Lai M. Optimization of the extraction conditions and quantification by RP-LC analysis of three alkaloids in *Zanthoxylum nitidum* roots. Pharmaceutical Biology. 2014;**52**:255-261

[33] Yang CH, Cheng MJ, Chiang MY, Kuo YH, Wang CJ, Chen IS. Dihydrobenzo[*c*]phenanthridine alkaloids from stem bark of *Zanthoxylum nitidum*. Journal of Natural Products. 2008;**71**:669-673

[34] Dreyer DL, Brenner RC. Chemotaxonomy of the Rutaceae. Part XIII. Alkaloids of some Mexican *Zanthoxylum* species. Phytochemistry. 1980;**19**:935-939

[35] Samita FN, Sandjo LP, Ndiege IO, Hassanali A, Lwande W. Zanthoxoaporphines A-C: Three new larvicidal dibenzo[de,g]quinolin-7-one alkaloids from *Zanthoxylum paracanthum* (Rutaceae). Beilstein Journal of Organic Chemistry. 2013;**9**: 447-452, No. 447

[36] Liu Y-C, Chen Z-F, Liu L-M, Peng Y, Hong X, Yang B, et al. Divalent later transition metal complexes of the traditional chinese medicine (TCM) liriodenine: Coordination chemistry, cytotoxicity and DNA binding studies. Dalton Transactions. 2009:10813-10823

[37] Yang Z-D, Zhang D-B, Ren J, Yang M-J. Skimmianine, a furoquinoline alkaloid from *Zanthoxylum nitidum* as a potential acetylcholinesterase inhibitor. Medicinal Chemistry Research. 2012;**21**: 722-725

[38] Ruangrungsi N, Tantivatana P, Borris RP, Cordell GA. Traditional medicinal plants of Thailand. III. Constituents of *Zanthoxylum budrunga* (Rutaceae). Journal of the Science Society of Thailand. 1981;7:123-127

[39] Ahmad MU, Rahman MA, Huq E, Chowdhury R. Alkaloids of *Zanthoxylum budrunga*. Fitoterapia. 2003;**74**:191-193

[40] Wang C, Wan J, Mei Z, Yang X. Acridone alkaloids with cytotoxic and antimalarial activities from *Zanthoxylum simulans* Hance. Pharmacognosy Magazine. 2014;**10**:73-76, 76a

[41] Talapatra SK, Dutta S, Talapatra B. Alkaloids and terpenoids of *Zanthoxylum ovalifolium*. Phytochemistry. 1973;**12**:729-730

[42] Ferreira ME, Rojas de Arias A, Torres de Ortiz S, Inchausti A, Nakayama H, Thouvenel C, et al. Leishmanicidal activity of two canthin-6-one alkaloids, two major constituents of *Zanthoxylum chiloperone* var. *angustifolium*. Journal of Ethnopharmacology. 2002;**80**:199-202

[43] Hu J, Zhang W-D, Shen Y-H, Zhang C, Liu R-H, Xu X-K, et al. Two novel alkaloids from *Zanthoxylum nitidum*. Helvetica Chimica Acta. 2007; **90**:720-722

[44] Liu S-L, Tsai I-L, Ishikawa T, Harayama T, Chen I-S. Bishordeninyl terpene alkaloids from *Zanthoxylum integrifoliolum*. Journal of the Chinese Chemical Society. 2000;**47**:571-574

[45] Schroeder DR. 1985

[46] Hu J, Shi X, Mao X, Chen J, Li H. Cytotoxic mannopyranosides of indole alkaloids from *Zanthoxylum nitidum*. Chemistry & Biodiversity. 2014;**11**: 970-974

[47] Van NTH, Tuyen TT, Quan PM, Long PQ, Nhiem NX, Tai BH, et al. Alkaloid glycosides and their cytotoxic constituents from *Zanthoxylum nitidum*. Phytochemistry Letters. 2019;**32**:47-51

[48] Ochwang'i DO, Kimwele CN, Oduma JA, Gathumbi PK, Mbaria JM, Kiama SG. Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya. Journal of Ethnopharmacology. 2014;**151**: 1040-1055

[49] Lee J, Lim KT. Inhibitory effect of phytoglycoprotein (24 kDa) on hepatocarcinogenesis in N-nitrosodiethylamine-treated ICR mice. Journal of Pharmacy and Pharmacology. 2011;**63**:840-848

[50] Rajamani P, Banerjeet S, Rao AR. Chemoprotective influence of *Zanthoxylum* sps. on hepatic carcinogen metabolizing and antioxidant enzymes and skin papillomagenesis in murine model. Indian Journal of Experimental Biology. 2011;**49**:857-863

[51] Misra LN, Wouatsa NAV, Kumar S, Venkatesh Kumar R, Tchoumbougnang F. Antibacterial, cytotoxic activities and chemical composition of fruits of two Cameroonian *Zanthoxylum* species. Journal of Ethnopharmacology. 2013; **148**:74-80

[52] Tokita Y, Yuzurihara M, Sakaguchi M, Satoh K, Kase Y. The pharmacological effects of daikenchuto, a traditional herbal medicine, on delayed gastrointestinal transit in rat postoperative Ileus. Journal of Pharmacological Sciences. 2007;**104**: 303-310

[53] Chou ST, Chan HH, Peng HY, Liou MJ, Wu TS. Isolation of substances with antiproliferative and apoptosis-inducing activities against leukemia cells from the leaves of *Zanthoxylum ailanthoides* Sieb. & Zucc. Phytomedicine. 2011;**18**:344-348

[54] Ozkan M, Mutiso PB, Nahar L, Liu P, Brown S, Wang W, et al. *Zanthoxylum usambarense* (Engl.) Kokwaro (Rutaceae) extracts inhibit the growth of the breast cancer cell lines MDA-MB-231 and MCF-7, but not the brain tumour cell line U251 in vitro. Phytotherapy Research. 2013;**27**:787-790

[55] Walker TM, Vogler B, Moriarity DM, Haber WA, Setzer WN. A phytochemical investigation of *Zanthoxylum setulosum*. Natural Product Communications. 2011;**6**:1807-1808

[56] Dung TD, Feng CC, Kuo WW, Pai P, Chung LC, Chang SH, et al. Suppression of plasminogen activators and the MMP-2/-9 pathway by a *Zanthoxylum avicennae* extract to inhibit the HA22T human hepatocellular carcinoma cell migration and invasion effects in vitro and in vivo via phosphatase 2A activation. Bioscience, Biotechnology, and Biochemistry. 2013; **77**:1814-1821

[57] Karmakar I, Haldar S, Chakraborty M, Chaudhury K, Dewanjee S, Haldar PK. Regulation of apoptosis through bcl-2/bax proteins expression and DNA damage by *Zanthoxylum alatum*. Pharmaceutical Biology. 2016;**54**:503-508

[58] Chon SU, Heo BG, Park YS, Kim DK, Gorinstein S. Total phenolics level, antioxidant activities and cytotoxicity of young sprouts of some traditional Korean salad plants. Plant Foods for Human Nutrition. 2009;**64**: 25-31

[59] Jang KH, Chang YH, Kim DD, Oh KB, Oh U, Shin J. New polyunsaturated fatty acid amides isolated from the seeds of *Zanthoxylum piperitum*. Archives of Pharmacal Research. 2008;**31**:569-572

[60] Ngoumfo RM, Jouda JB, Mouafo FT, Komguem J, Mbazoa CD, Shiao TC, et al. In vitro cytotoxic activity of isolated acridones alkaloids from Zanthoxylum leprieurii Guill. et Perr. Bioorganic & Medicinal Chemistry. 2010;**18**:3601-3605

[61] Chen I-S, Wu S-J, Tsai I-L, Wu T-S, Pezzuto JM, Lu MC, et al. Chemical and bioactive constituents from *Zanthoxylum simulans*. Journal of Natural Products. 1994;**57**:1206-1211

[62] Chen JJ, Fang HY, Duh CY, Chen IS. New indolopyridoquinazoline, benzo[c]

phenanthridines and cytotoxic constituents from *Zanthoxylum integrifoliolum*. Planta Medica. 2005;**71**: 470-475

[63] Pachon G, Rasoanaivo H, Azqueta A, Rakotozafy JC, Raharisololalao A, De Cerain AL, et al. Anticancer effect of a new benzophenanthridine isolated from *Zanthoxylum madagascariense* (Rutaceline). In Vivo. 2007;**21**:417-422

[64] Mansoor TA, Borralho PM, Luo X, Mulhovo S, Rodrigues CM, Ferreira MJ. Apoptosis inducing activity of benzophenanthridine-type alkaloids and 2-arylbenzofuran neolignans in HCT116 colon carcinoma cells. Phytomedicine. 2013;**20**:923-929

[65] Pan X, Han H, Wang L, Yang L, Li R, Li Z, et al. Nitidine chloride inhibits breast cancer cells migration and invasion by suppressing c-Src/FAK associated signaling pathway. Cancer Letters. 2011;**313**:181-191

[66] He H, Zhuo R, Dai J, Wang X, Huang X, Wang H, et al. Chelerythrine induces apoptosis via ROS-mediated endoplasmic reticulum stress and STAT3 pathways in human renal cell carcinoma. Journal of Cellular and Molecular Medicine. 2020;**24**:50-60

[67] Li WF, Hao DJ, Fan T, Huang HM, Yao H, Niu XF. Protective effect of chelerythrine against ethanol-induced gastric ulcer in mice. Chemico-Biological Interactions. 2014;**208**:18-27

[68] Wu S, Yu D, Liu W, Zhang J, Liu X, Wang J, et al. Magnoflorine from Coptis chinese has the potential to treat DNCB-induced Atopic dermatits by inhibiting apoptosis of keratinocyte. Bioorganic & Medicinal Chemistry. 2019;**28**:115093

[69] Wei T, Xiaojun X, Peilong C. Magnoflorine improves sensitivity to doxorubicin (DOX) of breast cancer cells via inducing apoptosis and autophagy through AKT/mTOR and p38 signaling pathways. Biomedicine & Pharmacotherapy. 2020;**121**:109139

[70] Li ZH, Gao J, Hu PH, Xiong JP. Anticancer effects of liriodenine on the cell growth and apoptosis of human breast cancer MCF-7 cells through the upregulation of p53 expression. Oncology Letters. 2017;**14**:1979-1984

[71] Ratheesh M, Sindhu G, Helen A. Anti-inflammatory effect of quinoline alkaloid skimmianine isolated from *Ruta graveolens* L. Inflammation Research. 2013;**62**:367-376

[72] Yang N, Yue R, Ma J, Li W, Zhao Z, Li H, et al. Nitidine chloride exerts anti-inflammatory action by targeting Topoisomerase I and enhancing IL-10 production. Pharmacological Research. 2019;**148**:104368

[73] Fan L, Fan Y, Liu L, Tao W, Shan X, Dong Y, et al. Chelerythrine attenuates the inflammation of lipopolysaccharide-induced acute lung inflammation through NF-kappaB signaling pathway mediated by Nrf2. Frontiers in Pharmacology. 2018;**9**:1047

[74] Ngane AN, Biyiti L, Zollo PH, Bouchet P. Evaluation of antifungal activity of extracts of two Cameroonian rutaceae: *Zanthoxylum* leprieurii Guill. et Perr. and *Zanthoxylum* xanthoxyloides Waterm. Journal of Ethnopharmacology. 2000;**70**:335-342

[75] Dieguez-Hurtado R, Garrido-Garrido G, Prieto-Gonzalez S, Iznaga Y, Gonzalez L, Molina-Torres J, et al. Antifungal activity of some Cuban *Zanthoxylum* species. Fitoterapia. 2003; **74**:384-386

[76] Smith ML, Gregory P, Bafi-Yeboa NF, Arnason JT. Inhibition of DNA polymerization and antifungal specificity of furanocoumarins present in traditional medicines. Photochemistry and Photobiology. 2004;**79**:506-509

[77] Bafi-Yeboa NF, Arnason JT, Baker J, Smith ML. Antifungal constituents of northern prickly ash, *Zanthoxylum americanum* mill. Phytomedicine. 2005; **12**:370-377

[78] Ferreira ME, Cebrian-Torrejon G, Corrales AS, Vera de Bilbao N, Rolon M, Gomez CV, et al. *Zanthoxylum chiloperone* leaves extract: First sustainable Chagas disease treatment. Journal of Ethnopharmacology. 2011; **133**:986-993

[79] Thouvenel C, Gantier JC, Duret P, Fourneau C, Hocquemiller R, Ferreira ME, et al. Antifungal compounds from *Zanthoxylum chiloperone* var. *angustifolium*. Phytotherapy Research. 2003;**17**: 678-680

[80] Nissanka AP, Karunaratne V, Bandara BM, Kumar V, Nakanishi T, Nishi M, et al. Antimicrobial alkaloids from *Zanthoxylum tetraspermum* and *caudatum*. Phytochemistry. 2001;**56**: 857-861

[81] Luo X, Pires D, Ainsa JA, Gracia B, Duarte N, Mulhovo S, et al. *Zanthoxylum capense* constituents with antimycobacterial activity against *Mycobacterium tuberculosis* in vitro and ex vivo within human macrophages. Journal of Ethnopharmacology. 2013; **146**:417-422

[82] Tantapakul C, Phakhodee W, Ritthiwigrom T, Yossathera K, Deachathai S, Laphookhieo S. Antibacterial compounds from *Zanthoxylum rhetsa*. Archives of Pharmacal Research. 2012;**35**:1139-1142

[83] Luo X, Pedro L, Milic V, Mulhovo S, Duarte A, Duarte N, et al. Antibacterial benzofuran neolignans and benzophenanthridine alkaloids from the roots of *Zanthoxylum capense*. Planta Medica. 2012;**78**:148-153

[84] Hatano T, Kusuda M, Inada K, Ogawa TO, Shiota S, Tsuchiya T, et al. Effects of tannins and related polyphenols on methicillin-resistant *Staphylococcus aureus*. Phytochemistry. 2005;**66**:2047-2055

[85] He N, Wang P, Wang P, Ma C, Kang W. Antibacterial mechanism of chelerythrine isolated from root of *Toddalia asiatica* (Linn) Lam. BMC Complementary Medicine and Therapies. 2018;**18**:261

[86] Cheng MJ, Lee KH, Tsai IL, Chen IS. Two new sesquiterpenoids and anti-HIV principles from the root bark of *Zanthoxylum ailanthoides*. Bioorganic & Medicinal Chemistry. 2005;**13**: 5915-5920

[87] Bouquet J, Rivaud M, Chevalley S, Deharo E, Jullian V, Valentin A. Biological activities of nitidine, a potential anti-malarial lead compound. Malaria Journal. 2012;**11**:67