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Review Article

Critical review on biological effects and mechanisms of amide alkaloids in *Piper nigrum* and *Piper longum*

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Abstract: *Piper nigrum* and *Piper longum* are globally popular spices, listed in the catalog of medicinal food homology. Their fruits are abundant in amide alkaloids, exhibiting a wide range of biological activities. This paper provides a comprehensive review of the research on amide alkaloids from those two edible species, focusing on their activities and mechanisms of action. 239 amide alkaloids are summarized in this review, of which 97 exhibit anti-inflammatory, anti-tumor, and neuroprotective effects. The anti-inflammatory properties of amide alkaloids are associated with the ERK and NF-κB signaling pathways. Their anti-tumor effects are mediated through the Src/ERK/STAT3, ERK1/2, p38 MAPK, and Akt pathways. Additionally, the neuroprotective benefits are linked to the NGF/Trka/Akt/GSK3β signaling pathway. These findings suggest that *P. nigrum* and *P. longum* could be valuable for promoting human health care.

Keywords: *Piper nigrum*; *Piper longum*; amide alkaloids; biological activity; mechanism; medicinal food homology

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1 Introduction

Piper nigrum and *Piper longum* are globally popular spices, listed in the medicinal food homology catalog issued by China's National Health Commission[1-3]. *P. nigrum*, a perennial climbing herb, is native to the Malabar Coast of India, and now grows all over the world[4]. Their fruits, known as black pepper, are used not only as a household spices for cooking steak, chicken, and so on, but are also applied as folk medicines to treat ailments, gastrointestinal disorders, and epilepsy[5]. *P. longum,* also known as Javanese, Indian, or Indonesian long pepper, is a flowering vine of the family Piperaceae[6], grown in the hot regions of India and parts of Indonesia as well as in some subtropical regions[7]. Its fruits are consumed as special spices when cooking, and also applied as traditional medicines for the treatment of stomach ailments, leprosy, fever, parasitic infections, influenza, muscular pain, and migraine[8,9].

Previous phytochemical studies have indicated that those two spices are rich in amide alkaloids[10,11] and essential oils[12-14], which exhibited a wide range of bioactivities, such as anti-inflammatory, neuroprotective, immunomodulatory, cardioprotective, anticancer[10-14], antiplatelet[15,16], antispasmodic, antidiarrheal, antiasthmatic, antimicrobial, antifungal, and antioxidant properties[17-22]. Among them, amide alkaloids are the main constituents in *P. nigrum* and *P. longum.* Herein, we included the amide alkaloids from two edible species of *Piper* in this review for the first time. A total of 239 amide alkaloids with diverse bioactivities and mechanistic insights are summarized in this review.

2 Amide alkaloids in *P. nigrum* and *P. longum*

The review summarizes a total of 239 amide alkaloids from *P. nigrum* and *P. longum*, with 176 identified in *P. nigrum* and 89 in *P. longum*. These alkaloids are categorized into six types: piperidine alkamides (Type I), pyrrolidine alkamides (Type II), *N*-alkylamide alkaloids (Type III), tyramide-type alkaloids (Type IV), aporphine alkaloids (Type V), and dimeric amide alkaloids (Type VI), as depicted in Fig. 1. Notably, 26 amide alkaloids are found in both species, which is crucial for the classification of *Piper* species. Furthermore, certain dimeric amide alkaloids are synthesized through biomimetic [4 + 2] or [2 + 2] cycloaddition reactions of monomeric amide alkaloids, as illustrated in Fig. 2[23,24].

2.1 Piperidine alkamides (Type I)

Piperidine alkamides are the major components with a total of

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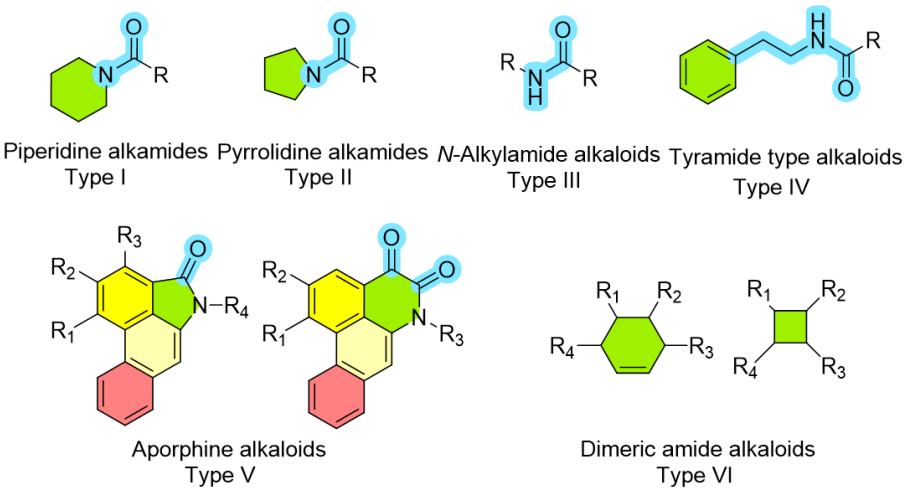


Figure 1 Six structural types of amide alkaloids.

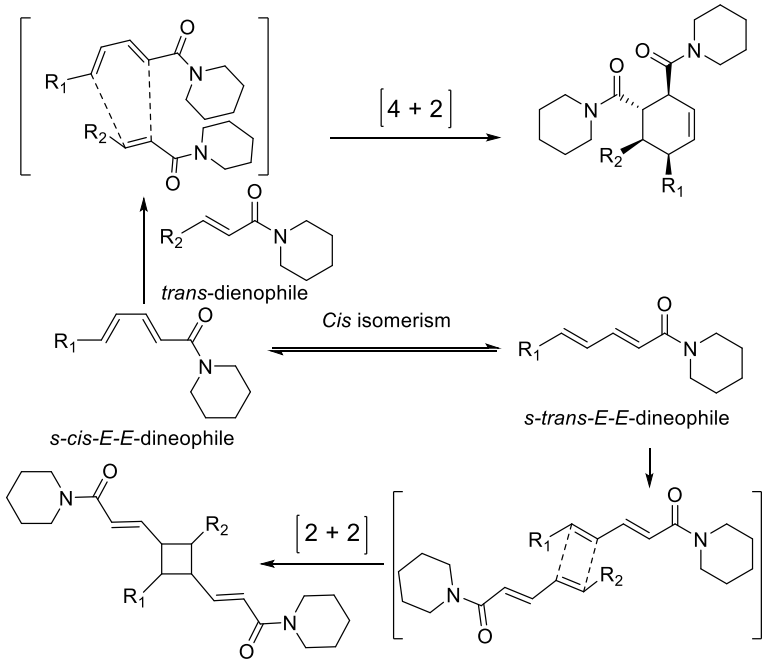


Figure 2 The monomeric amide alkaloids convert to dimeric amide alkaloids.

67 alkamides of this type (**1**–**67**) identified in the fruits of both species (Table 1). Among them, piperine (compound **2**) is one of the most important amide alkaloids. Compounds **1**–**30** feature a 1,3-benzodioxole group, where a 1,3-benzodioxole group and piperidine amide are linked by various groups, including double bonds or oxidized long-chain alkanes. In addition, compounds **31**–**57** mainly possess long-chain acyl groups decorated with double bonds, hydroxyl, or aldehyde groups. Compounds **58**–**65** consist of two parts, a piperidine ring and phenylacetyl, linked by various double bonds and long-chain alkanes. Interestingly, only two piperidin-2-one derivatives (**66** and **67**) were obtained.

2.2 Pyrrolidine alkamides (Type II)

Twenty-eight pyrrolidine alkamides (**68**–**95**) with a common 1-(pyrrolidin-1-yl) ethenone group are summarized in Table 2. These alkamides predominantly contain a 1,3-benzodioxole group, long-chain acyl, or phenyl groups, akin to those of piperidine alkamides (Type II). Only a single pyrrolidin-2-one derivative (**95**) was isolated.

2.3 *N*-Alkylamide alkaloids (Type III)

There are 60 *N*-alkylamide alkaloids (**96**–**155**), characterized by common groups such as *N*-isobutylamide, *N*-isovaleramide, or aminoamide (Table 3). Of these, 27 compounds (**96**–**121**) contain a 1,3-benzodioxole group, while 34 compounds (**122**–**155**) feature long-chain acyl groups modified with double bonds or hydroxyl groups.

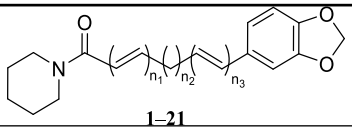
2.4 Tyramide type alkaloids (Type IV)

So far, only five tyramide-type alkaloids (**156**–**160**) have been reported in *P. nigrum* and *P. longum*, which were substituted with a benzoyl group or a long-chain acyl group. (Table 4)

2.5 Aporphine alkaloids (Type V)

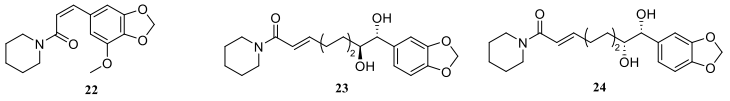
Aporphine alkaloids consist of 13 compounds (**161**–**173**, Table 5), including aristolactam and dehydroaporphine type

Table 1 Piperidine alkamides (Type I)



1–21

No.	Name	Groups	Source
1	Piperanine[25]	$n_1 = 1, n_2 = 2, n_3 = 0$	*P. nigrum*
2	Piperine[26, 27]	$n_1 = 0, n_2 = 0, n_3 = 2$	*P. nigrum* *P. longum*
3	Piperettine[26, 28]	$n_1 = 0, n_2 = 0, n_3 = 3$	*P. nigrum* *P. longum*
4	Piperolein B[26, 29]	$n_1 = 0, n_2 = 6, n_3 = 1$	*P. nigrum* *P. longum*
5	Piperolein A[30]	$n_1 = 0, n_2 = 4, n_3 = 1$	*P. nigrum*
6	*N-trans*-Cinnamoylpiperidine[30] (1-(3-phenyl-2*E*-propenyl)-piperidine)[29]	$n_1 = 0, n_2 = 0, n_3 = 1$	*P. nigrum* *P. longum*
7	Piptigrine[31]	$n_1 = 0, n_2 = 2, n_3 = 3$	*P. nigrum*
8	Pipernonaline[27, 32]	$n_1 = 1, n_2 = 4, n_3 = 1$	*P. nigrum* *P. longum*
9	Dehydropipernonaline[32, 33]	$n_1 = 2, n_2 = 2, n_3 = 1$	*P. nigrum* *P. longum*
10	Pipernigramide B[34]	$n_1 = 0, n_2 = 8, n_3 = 1$	*P. nigrum*
11	Piperchabamide C[34]	$n_1 = 2, n_2 = 8, n_3 = 1$	*P. nigrum*
12	(2*E*,4*E*,12*E*)-13-(3,4-Methylenedioxyphenyl)-1-(1-piperidinyl)-2,4,12-tridecatrien-1-one[34]	$n_1 = 2, n_2 = 6, n_3 = 1$	*P. nigrum*
13	Piperolactam[35] (Piperderdine[27])	$n_1 = 2, n_2 = 2, n_3 = 0$	*P. nigrum* *P. longum*
14	(2*E*,4*E*,10*E*)-*N*-11-(3,4-Methylenedioxyphenylhmdecatrienoyl)-piperidine[35] (Piperundecalidine[27])	$n_1 = 2, n_2 = 4, n_3 = 1$	*P. nigrum* *P. longum*
15	(2*E*,4*Z*,8*E*)-*N*-[9-(3,4-Methylenedioxyphenyl)-2,4,8-nonatrienoyl]-piperidine[36]	$n_1 = 2, n_2 = 2, n_3 = 1$	*P. longum*
16	$\Delta^{\alpha,\beta}$-Dihydropiperine[32]	$n_1 = 1, n_2 = 2, n_3 = 0$	*P. longum*
17	1-(3-Phenylpropionyl)-2*E*-piperidine[29]	$n_1 = 0, n_2 = 2, n_3 = 0$	*P. longum*
18	(2*E*,12*E*)- Pipertridecadienamide[29]	$n_1 = 1, n_2 = 8, n_3 = 1$	*P. longum*
19	Piperlongumamide D[29]	$n_1 = 2, n_2 = 8, n_3 = 1$	*P. longum*
20	Isopiperine[29]	$n_1 = 0, n_2 = 0, n_3 = 2$	*P. longum*
21	Isochavicine[29]	$n_1 = 0, n_2 = 0, n_3 = 2$	*P. longum*



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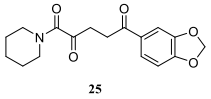

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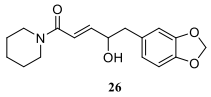

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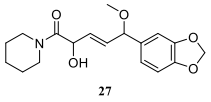

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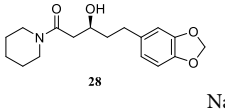

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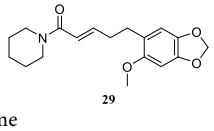

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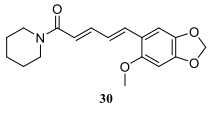

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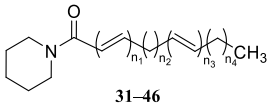
No.	Name	Groups	Source
22	1-[1-Oxo-3(3,4-methylenedioxy-5-methoxyphenyl)-2*Z*-propenyl]piperidine[37]		*P. nigrum*
23	Erythro-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2*E*-nonenyl]-piperidine[38]		*P. longum*
24	Threo-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2*E*-nonenyl]-piperidine[38]		*P. longum*
25	Piperodione[33]		*P. longum*
26	5-(Benzo[d][1, 3]dioxol-5-yl)-4-hydroxy-1-(piperidin-1-yl)pent-2-en-1-one[39]		*P. nigrum*
27	5-(Benzo[d][1, 3]dioxol-5-yl)-2-hydroxy-5-methoxy-1-(piperidin-1-yl)pent-3-en-1-one[39]		*P. nigrum*
28	(*S*)-5-(Benzo[d][1, 3]dioxol-5-yl)-3-hydroxy-1-(piperidin-1-yl)pentan-1-one[39]		*P. nigrum*
29	$\Delta^{\alpha,\beta}$-Dihydrowisanine[40]		*P. nigrum*
30	Wisanine[40]		*P. nigrum*



31–46

No.	Name	Groups	Source

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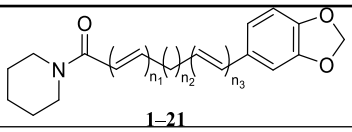
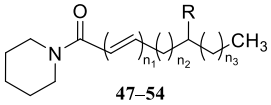


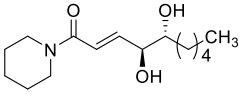
1–21

No.	Name	Groups	Source
31	(2*E*,4*E*)-1-(1-Piperidinyl)-2,4-decadien-1-one[29, 30]	$n_1 = 2, n_2 = 4, n_3 = 0, n_4 = 0$	*P. nigrum* *P. longum*
32	[(2*E*,4*E*)-Octadecadienoyl]-*N*-isobutylamide[41] ((2*E*,4*E*)-1-(1-Piperidinyl)-2,4-octadecadien-1-one[29])	$n_1 = 2, n_2 = 12, n_3 = 0, n_4 = 0$	*P. nigrum* *P. longum*
33	2,4-(*E*,*E*)-Dodecadienylpiperidide[34]	$n_1 = 2, n_2 = 6, n_3 = 0, n_4 = 0$	*P. nigrum*
34	1-(Tetradace-2*E*-monoenyl) piperidine[35]	$n_1 = 1, n_2 = 10, n_3 = 0, n_4 = 0$	*P. nigrum*
35	1-(Tetradace-2*E*,4*E*-dienyl) piperidined ((2*E*,4*E*)-1-(1-Piperidinyl)-2,4-tetradecadien-1-one)[29, 35]	$n_1 = 2, n_2 = 8, n_3 = 0, n_4 = 0$	*P. nigrum* *P. longum*
36	1-(Hexadeca-2*E*,4*E*-dienyl) piperidine[35]	$n_1 = 2, n_2 = 10, n_3 = 0, n_4 = 0$	*P. nigrum*
37	1-(Eicosa-2*E*,4*E*- dienyl) piperidine[35]	$n_1 = 2, n_2 = 14, n_3 = 0, n_4 = 0$	*P. nigrum*
38	Piperlongimin B[42]	$n_1 = 1, n_2 = 12, n_3 = 0, n_4 = 0$	*P. longum*
39	(2*E*,4*E*)-1-(1-Piperidinyl)-2,4-dodecadien-1-one[29]	$n_1 = 2, n_2 = 6, n_3 = 0, n_4 = 0$	*P. longum*
40	1-(Hexadeca-2*E*,4*E*,10*E*-tirenyl) piperidine[35]	$n_1 = 2, n_2 = 4, n_3 = 1, n_4 = 5$	*P. nigrum*
41	1-(Octadeca-2*E*,4*E*,12*E*-tirenyl) piperidine[35]	$n_1 = 2, n_2 = 6, n_3 = 1, n_4 = 5$	*P. nigrum*
42	1-(Eicosa-2*E*,4*E*,14*E*-tirenyl) piperidine[35]	$n_1 = 2, n_2 = 8, n_3 = 1, n_4 = 5$	*P. nigrum*
43	1-(Tetradace-2*E*,4*E*,8*E*-irenyl) piperidine[35]	$n_1 = 2, n_2 = 2, n_3 = 1, n_4 = 5$	*P. nigrum*
44	(2*E*,4*E*,14*Z*)-1-(1-Piperidinyl)-2,4,14-eicosatrien-1-one[29]	$n_1 = 2, n_2 = 8, n_3 = 1, n_4 = 4$	*P. longum*
45	Piperlongumamide F[29]	$n_1 = 1, n_2 = 8, n_3 = 1, n_4 = 4$	*P. longum*
46	1-(Eicosa-2*E*,14*Z*-dienoyl)piperidine[29]	$n_1 = 1, n_2 = 10, n_3 = 1, n_4 = 4$	*P. longum*



47–54

No.	Name	Groups	Source
47	6-Hydroxy-1-(piperidin-1-yl)octa-2,4-dien-1-one[39]	$n_1 = 2, n_2 = 2, n_3 = 1$, R = β-OH	*P. nigrum*
48	(*R*,2*E*,4*E*)-9-Hydroxy-1-(piperidin-1-yl)deca-2,4-dien-1-one[39]	$n_1 = 2, n_2 = 3, n_3 = 0$, R = α-OH	*P. nigrum*
49	(*R*,2*E*,4*E*)-8-Hydroxy-1-(piperidin-1-yl)deca-2,4-dien-1-one[39]	$n_1 = 2, n_2 = 2, n_3 = 1$, R = β-OH	*P. nigrum*
50	1-(1,6-Dioxo-2*E*,4*E*-decadienyl)piperidine[37]	$n_1 = 2, n_2 = 0, n_3 = 2$, R = C=O	*P. nigrum*
51	1-(1-Oxo-6-hydroxy-2*E*,4*E*-decadienyl)-piperidine[43]	$n_1 = 2, n_2 = 0, n_3 = 3$, R = OH	*P. longum*
52	1-(1-Oxo-8-hydroxy-2*E*,4*E*-decadienyl)-piperidine[43]	$n_1 = 2, n_2 = 2, n_3 = 1$, R = OH	*P. longum*
53	1-(1-Oxo-8-hydroxy-2*E*,4*E*-nonadienyl)-piperidine[43]	$n_1 = 2, n_2 = 2, n_3 = 0$, R = OH	*P. longum*
54	1-(1-Oxo-7-hydroxy-2*E*,4*E*-decadienyl)-piperidine[38]	$n_1 = 2, n_2 = 1, n_3 = 2$, R = OH	*P. longum*



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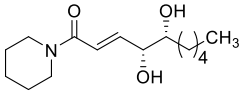

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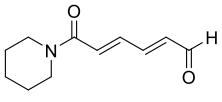

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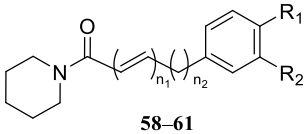
No.	Name	Groups	Source
55	Erythro-1-(1-oxo-4,5-dihydroxy-2*E*-decaenyl)piperidine[37]		*P. nigrum*
56	Threo-1-(1-oxo-4,5-dihydroxy-2*E*-decaenyl)piperidine[37]		*P. nigrum*
57	Pipernigramide A[34]		*P. nigrum*



58–61

No.	Name	Groups	Source
58	1-Cinnamoylpiperidine[34]	$n_1 = 1, n_2 = 0, R_1 = R_2 = H$	*P. nigrum*
59	*N-trans*-Feruloyl piperidine[34]	$n_1 = 1, n_2 = 0, R_1 = OMe, R_2 = OH$	*P. nigrum*
60	1-[1-Oxo-5(3-methoxyl-4-hydroxyphenyl)-2*E*-pentenyl]-piperidine[38]	$n_1 = 1, n_2 = 2, R_1 = OMe, R_2 = OH$	*P. longum*
61	Coumaperine[34]	$n_1 = 2, n_2 = 0, R_1 = OH, R_2 = H$	*P. nigrum*

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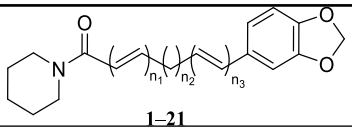

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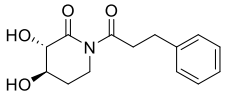
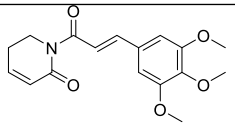
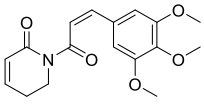
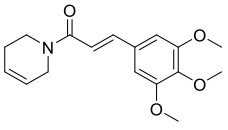
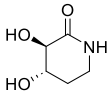
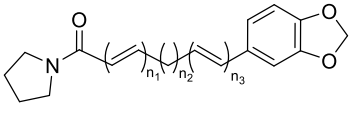
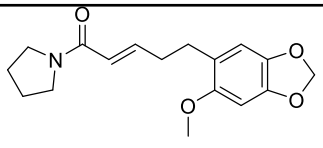
No.	Name	Groups	Source
	 62		
	 63		
	 64		
	 65		
	 66		
	 67		
No.	Name	Groups	Source
62	3*β*,4*α*-Dihydroxy-1-(3-phenylpropanoyl)-piperidine-2-one[44]		*P. longum*
63	(*E*)-Piperlongumine[45]		*P. longum*
64	(*Z*)-Piperlongumine[46]		*P. longum*
65	Piperlongumine A[34]		*P. longum*
66	3*β*,4*α*-Dihydroxy-2-piperidinone[38]		*P. longum*
67	5,6-Dihydro-2(1*H*)-pyridinone[38]		*P. longum*

Table 2 Pyrrolidine alkamides (Type II)

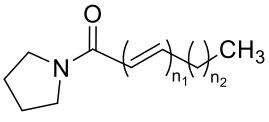


68–80



81

No.	Name	Groups	Source
68	1-[(2*E*)-5-(3,4-Methylenedioxyohenyl)-2-pentenoyl]pyrrolidine[26]	$n_1 = 1, n_2 = 2, n_3 = 0,$	*P. nigrum*
69	1-[(*E*)-7-(3,4-Methylenedioxyohenyl)-6-pentenoyl]pyrrolidine[26, 43]	$n_1 = 0, n_2 = 4, n_3 = 1$	*P. nigrum* *P. longum*
70	1-[(2*E*,6*E*)-7-(3,4-Methylenedioxyohenyl)-2,6-pentenoyl]pyrrolidine[26]	$n_1 = 1, n_2 = 2, n_3 = 1,$	*P. nigrum*
71	1-[(*E*)-9-(3,4-Methylenedioxyohenyl)-8-nonenyl]pyrrolidine[26]	$n_1 = 0, n_2 = 6, n_3 = 1,$	*P. nigrum*
72	1-[(2*E*,8*E*)-9-(3,4-Methylenedioxyohenyl)-2,8-nonadienoy]pyrrolidine[26]	$n_1 = 1, n_2 = 4, n_3 = 1,$	*P. nigrum*
73	1-[(2*E*,4*E*,8*E*)-9-(3,4-Methylenedioxyohenyl)-2,4,8-nonadienoy]pyrrolidine[26] ((*E*,*E*,*E*)-1-{[9-[3,4-(Methylenedioxy)phenyl-nona-2,4,8-trienoylpyrrolidine)[40]	$n_1 = 2, n_2 = 2, n_3 = 1,$	*P. nigrum* *P. longum*
74	1-[1-Oxo-5(3,4-methylenedioxyphenyl)-2*Z*,4*E*-pentadienyl]-yrrolidine[37]	$n_1 = 0, n_2 = 0, n_3 = 2,$	*P. nigrum*
75	Piperylin[37]	$n_1 = 0, n_2 = 0, n_3 = 2,$	*P. nigrum*
76	Isopiperolein B[47]	$n_1 = 0, n_2 = 7, n_3 = 1,$	*P. nigrum*
77	Brachyamide A[30]	$n_1 = 2, n_2 = 6, n_3 = 1,$	*P. nigrum*
78	1-[(2*E*,10*E*)-11-(3,4-Methylenedioxyphenyl)-2,10-undecenoyl]pyrrolidine[34]	$n_1 = 1, n_2 = 6, n_3 = 1,$	*P. nigrum*
79	1-[(2*E*,4*E*,10*E*)-11-(3,4-Methylenedioxyphenyl)-2,4,10-undecatrienoyl]pyrrolidine[34]	$n_1 = 2, n_2 = 4, n_3 = 1,$	*P. nigrum*
80	Tricholein[43]	$n_1 = 0, n_2 = 6, n_3 = 2,$	*P. longum*
81	$\Delta^{\alpha,\beta}$-Dihydrowisanidine[41]		*P. nigrum*



82–88

No.	Name	Groups	Source
82	1-[(2*E*,4*E*)-2,4-Decadienoyl]pyrrolidine[26]	$n_1 = 2, n_2 = 4$	*P. nigrum*
83	1-[(2*E*,4*E*)-2,4-Dodecadienoyl]pyrrolidine[26]	$n_1 = 2, n_2 = 6$	*P. nigrum*
84	Hexadecanoylpyrrolidine[48]	$n_1 = 0, n_2 = 14$	*P. nigrum*

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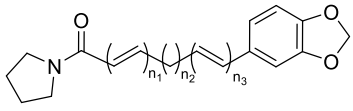
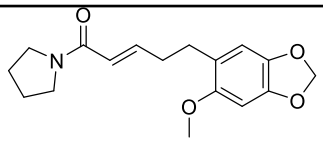
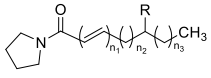


68–80

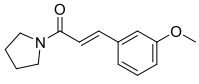


81

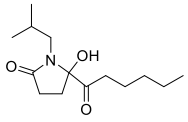
85	[(2*E*)-Octadecanoyl]pyrrolidine[48]	$n_1 = 1, n_2 = 14$	*P. nigrum*
86	[(2*E*)-Hexadecanoyl]pyrrolidine[41]	$n_1 = 1, n_2 = 12$	*P. nigrum*
87	Pipyaqubine[49]	$n_1 = 2, n_2 = 12$	*P. nigrum*
88	Sarmentine[50]	$n_1 = 2, n_2 = 5$	*P. longum*



89-93



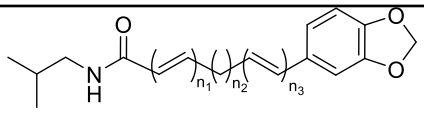
94



95

No.	Name	Groups	Source
89	6-Hydroxy-1-(pyrrolidin-1-yl)deca-2,4-dien-1-one[39]	$n_1 = 2, n_2 = 2, n_3 = 3$, R = α-OH	*P. nigrum*
90	(*R*,2*E*,4*E*)-7-Hydroxy-1-(pyrrolidin-1-yl)deca-2,4-dien-1-one[39]	$n_1 = 2, n_2 = 1, n_3 = 2$, R = α-OH	*P. nigrum*
91	(*R*,2*E*,4*E*)-8-Hydroxy-1-(pyrrolidin-1-yl)deca-2,4-dien-1-one[39]	$n_1 = 2, n_2 = 2, n_3 = 1$, R = β-OH	*P. nigrum*
92	(*R*,2*E*,4*E*)-9-Hydroxy-1-(pyrrolidin-1-yl)deca-2,4-dien-1-one[39]	$n_1 = 2, n_2 = 3, n_3 = 0$, R = α-OH	*P. nigrum*
93	1-(1,6-Dioxo-2*E*,4*E*-decadienyl)-pyrrolidine[43]	$n_1 = 2, n_2 = 0, n_3 = 3$, R = C=O	*P. longum*
94	*N*-(*m*-Methoxy-cinnamoyl)-pyrrolidine[43]		*P. longum*
95	*N*-isobutyl-4-Hexanoyl-4-hydroxypyrrolidin-1-one[37]		*P. nigrum*

Table 3 *N*-Alkylamide alkaloids (Type III)



96-118

No.	Name	Groups	Source
96	(*E*,*E*,*E*)-11-(1,3-Benzodioxol-5-yl)-*N*-(2-methylpropyl)-2,4,10-undecatrienamide[51] (Piercide[27])	$n_1 = 2, n_2 = 4, n_3 = 1$	*P. nigrum* *P. longum*
97	(*E*,*E*,*E*)-13-(1,3-Benzodioxol-5-yl)-*N*-(2-methylpropyl)-2,4,12-tridecatrienamid[51] (Guineensine[45])	$n_1 = 2, n_2 = 6, n_3 = 1$	*P. nigrum* *P. longum*
98	Retrofractamide A[52]	$n_1 = 2, n_2 = 2, n_3 = 1$	*P. nigrum* *P. longum*
99	Pipgulzarine[29, 53]	$n_1 = 2, n_2 = 7, n_3 = 1$	*P. nigrum* *P. longum*
100	1-[7-(3,4-Methylenedioxyphenyl)-(2*E*,4*E*)-heptadienoyl]-*N*-isobutylamide[48]	$n_1 = 2, n_2 = 2, n_3 = 0$	*P. nigrum*
101	Pipercallosine[35]	$n_1 = 2, n_2 = 4, n_3 = 0$	*P. nigrum*
102	Retrofractamide D[41]	$n_1 = 2, n_2 = 3, n_3 = 1$	*P. nigrum*
103	Retrofractamide C[32]	$n_1 = 1, n_2 = 4, n_3 = 1$	*P. nigrum* *P. longum*
104	Dehydroretrofractamide C[54]	$n_1 = 0, n_2 = 6, n_3 = 1$	*P. nigrum*
105	Piperchabamide D[33, 55]	$n_1 = 1, n_2 = 6, n_3 = 1$	*P. nigrum* *P. longum*
106	4,5-Dihydroguineensine[55]	$n_1 = 1, n_2 = 8, n_3 = 1$	*P. nigrum*
107	Brachystamide B[34]	$n_1 = 2, n_2 = 8, n_3 = 1$	*P. nigrum*
108	Retrofractamide B[34]	$n_1 = 2, n_2 = 4, n_3 = 1$	*P. nigrum*
109	Dihydropipericided[35]	$n_1 = 2, n_2 = 6, n_3 = 0$	*P. nigrum*
110	Piperlonguminine[43]	$n_1 = 0, n_2 = 2, n_3 = 0$	*P. longum*
111	Dihydropiperlonguminine[27]	$n_1 = 1, n_2 = 2, n_3 = 0$	*P. longum*
112	Brachystamide[27]	$n_1 = 2, n_2 = 8, n_3 = 1$	*P. longum*
113	Pergumidiene[52]	$n_1 = 2, n_2 = 9, n_3 = 1$	*P. longum*
114	Isodihydropiperlonguminine[56]	$n_1 = 0, n_2 = 2, n_3 = 1$	*P. longum*
115	Piperlongumide[36]	$n_1 = 2, n_2 = 14, n_3 = 0$	*P. longum*
116	*trans*-Fagaramide[57]	$n_1 = 0, n_2 = 0, n_3 = 1$	*P. longum*

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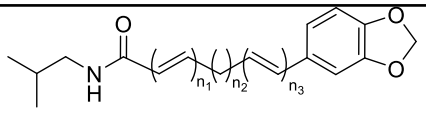
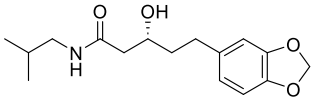
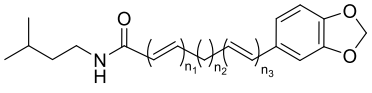


96-118

117	*cis*-Fagaramide[33]	$n_1 = 0, n_2 = 0, n_3 = 1$	*P. longum*

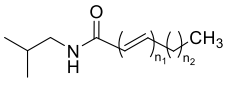


118

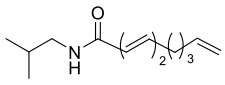


119–121

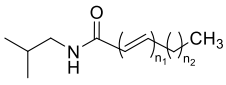
No.	Name	Groups	Source
118	(*R*)-5-(Benzo[d][1, 3]dioxol-5-yl)-3-hydroxy-*N*-isobutylpentanamide[39]		*P. nigrum*
119	Pipyahyine[48]	$n_1 = 2, n_2 = 5, n_3 = 1$	*P. nigrum*
120	Pipwaqarine[41]	$n_1 = 2, n_2 = 6, n_3 = 1$	*P. nigrum*
121	*N*-2′-Methylbutyl-2*E*,4*E*-decadienamide[29]	$n_1 = 2, n_2 = 2, n_3 = 0$	*P. longum*



122–130

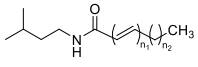


131

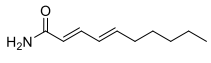


132–133

No.	Name	Groups	Source
122	*N*-Isobutyl-eicosa-*trans*-2-*trans*-4-dienamid[27, 58]	$n_1 = 2, n_2 = 14$	*P. nigrum* *P. longum*
123	(2*E*,4*E*)-*N*-Isobutyl-decadienamide[51] (Pellitorine[29]) *N*-Isobutyl-2*E*,4*E*-decadienamid[59])	$n_1 = 2, n_2 = 4$	*P. nigrum* *P. longum*
124	Pipericine[60] ((2*E*,4*E*)-N-Isobutyl-octadeca-2,4-dienamide[27])	$n_1 = 2, n_2 = 12$	*P. nigrum* *P. longum*
125	(2*E*,4*E*)-Dodecadienoyl]-*N*-isobutylamide[40] ((*E*,*E*)-*N*-(2-Methylpropyl)dodeca-2,4-dienamide[27])	$n_1 = 2, n_2 = 6$	*P. nigrum* *P. longum*
126	(2*E*,4*E*)-Octadienoyl]-*N*-isobutylamide[48]	$n_1 = 2, n_2 = 2$	*P. nigrum*
127	2,4-Tetradecadienoic acid isobutyl amide[61]	$n_1 = 2, n_2 = 8$	*P. nigrum*
128	*N*-Isobutyl-(2*E*,4*E*)-exadecadienamide[34]	$n_1 = 2, n_2 = 10$	*P. nigrum*
129	Hexacosanoic acid isobutyl amide[62]	$n_1 = 2, n_2 = 24$	*P. longum*
130	Piperlongimin A[63]	$n_1 = 1, n_2 = 12$	*P. longum*
131	*N*-Isobutyl-(2*E*,4*E*)-octadienamide[29]		*P. longum*
132	*N*-Isobutyl-(2*E*,4*E*)-undeca-2,4-dienamide[29]	$n_1 = 2, n_2 = 5$	*P. longum*
133	*N*-Isobutyl-(2*E*,4*E*)-hexadeca-2,4- dienamide[29]	$n_1 = 2, n_2 = 9$	*P. longum*

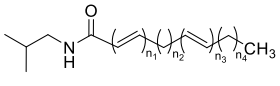


134–137

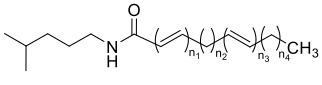


138

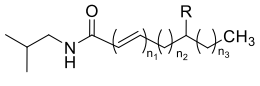
No.	Name	Groups	Source
134	Pipkirine[64]	$n_1 = 2, n_2 = 14$	*P. nigrum*
135	Pipilyasine[49]	$n_1 = 2, n_2 = 7$	*P. nigrum*
136	Pipzubedine[49]	$n_1 = 2, n_2 = 11$	*P. nigrum*
137	Pellitorine[49] (*N*-2′-Methylbutyl-2*E*,4*E*-decadienamide[29])	$n_1 = 2, n_2 = 4$	*P. nigrum* *P. longum*
138	(2*E*,4*E*)-Deca-2,4-dienamide[29]		*P. longum*



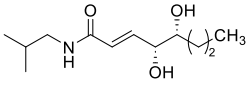
140–147



148–149



150–153



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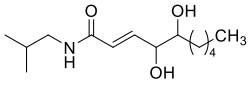

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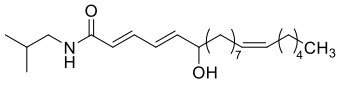

156

No.	Name	Groups	Source
139	1-[(2*E*,4*E*,12*Z*)-Octadecatrienoyl]-*N*-isobutylamide[48]	$n_1 = 2, n_2 = 6, n_3 = 1, n_4 = 5$	*P. nigrum*

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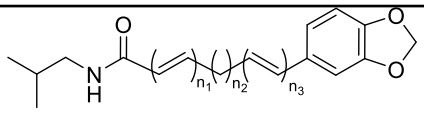
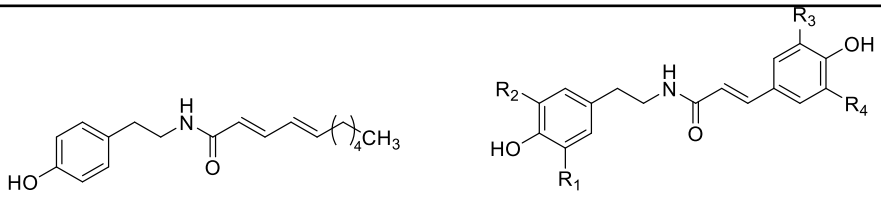


96-118

140	*N*-Isobutyl-(2*E*,4*E*,14*Z*)-eicosa-2,4,14-trienamide[34]	$n_1 = 2, n_2 = 8, n_3 = 1, n_4 = 5$	*P. nigrum*
141	(2*E*,4*E*,8*E*)-*N*-Isobuyl-tetradace-2,4,8-trienamide[35]	$n_1 = 2, n_2 = 2, n_3 = 1, n_4 = 5$	*P. nigrum*
142	(2*E*,4*E*,10*E*)-*N*-isobuyl-Hexadeca-2,4,10- trienamide[35]	$n_1 = 2, n_2 = 4, n_3 = 1, n_4 = 5$	*P. nigrum*
143	(2*E*,4*E*,8*Z*)-*N*-isobutyleicosa-2,4,8-trienamide[27]	$n_1 = 2, n_2 = 2, n_3 = 1, n_4 = 10$	*P. longum*
144	(2*E*,4*E*,12*Z*)-*N*-isobutylocatadeca-2,4,12-trienamide[65]	$n_1 = 2, n_2 = 6, n_3 = 1, n_4 = 4$	*P. longum*
145	(2*E*,4*E*,14*Z*)-*N*-isobutyleicosa-2,4,14-trienamide[29]	$n_1 = 2, n_2 = 8, n_3 = 1, n_4 = 4$	*P. longum*
146	(2*E*,4*E*,16*Z*)-*N*-isobutyldocosa-2,4,16-trienamide[29]	$n_1 = 2, n_2 = 10, n_3 = 1, n_4 = 4$	*P. longum*
147	Pipzorine[53]	$n_1 = 1, n_2 = 8, n_3 = 1, n_4 = 5$	*P. nigrum*
148	Pipnoohine[48]	$n_1 = 2, n_2 = 6, n_3 = 1, n_4 = 5$	*P. nigrum*
149	Piptahsine[53]	$n_1 = 1, n_2 = 0, n_3 = 1$, R = β-OH	*P. nigrum*
150	(*R*,2*E*,4*E*)-8-Hydroxy-*N*-isobutyldeca-2,4-dienamide[39]	$n_1 = 2, n_2 = 2, n_3 = 1$, R = β-OH	*P. nigrum*
151	(*S*,2*E*,4*E*)-7-Hydroxy-*N*-isobutyldeca-2,4-dienamide[39]	$n_1 = 2, n_2 = 1, n_3 = 2$, R = β-OH	*P. nigrum*
152	6-Hydroxypellitorine	$n_1 = 2, n_2 = 0, n_3 = 3$, R = OH	*P. longum*
153	Threo-*N*-isobutyl-4,5-dihydroxy-2E-octaenamide[37]		*P. nigrum*
154	Sylvamide[61]		*P. nigrum*
155	Deca-2*E*,4*E*-dienoicacid-4-hydroxy-2-phenylethylamide[43]		*P. longum*

Table 4 Tyramide type alkaloids (Type Ⅳ)



156 157–160

No.	Name	Groups	Source
156	(2*E*,4*E*,14*Z*)-6-Hydroxyl-*N*-isobutyleicosa-2,4,14-trienamide[44]		*P. longum*
157	*N-trans*-Feruloylmethoxytyramine[30]	R_1 = H, R_2 = OMe, R_3 = H, R_4 = OMe	*P. nigrum*
158	*N-trans*-Feruloyltyramine[30]	R_1 = H, R_2 = H, R_3 = H, R_4 = OMe	*P. nigrum*
159	Paprazine[61]	R_1 = H, R_2 = H, R_3 = H, R_4 = H	*P. nigrum*
160	*N-trans*-Feruloyldopamine[61]	R_1 = OH, R_2 = H, R_3 = H, R_4 = OMe	*P. nigrum*

alkaloids. Aristolactam alkaloids (**161**–**168**) feature a structure containing a 5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline core with a *γ*-lactam group[66], commonly occurring in plants from the Annonaceae, Aristolochiaceae, and Piperaceae families[67]. Dehydroaporphine alkaloids, which contain a *δ*-lactam group (**169**–**173**)[68], have been reported in plants from the Nymphaeaceae, Ranunculaceae, and Annonaceae families[69].

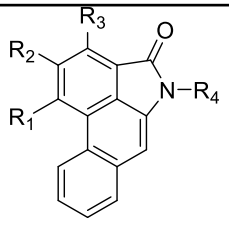
2.6 Dimeric amide alkaloids (Type Ⅵ)

Sixty-six Dimeric amide alkaloids (**174**–**239**) were obtained in *P. nigrum* and *P. longum* (Table 6 and Fig. 3). The dimers can be categorized into three types: cyclohexene-type, cyclobutene-type, and long-chain type. Cyclohexene-type dimeric amide alkaloids (**174**–**217**) and cyclobutene-type dimeric amide alkaloids (**218**–**237**) are biosynthesized from monomeric amide alkaloids through biomimetic [4 + 2] or [2 + 2] cycloaddition reactions (Fig. 2)[23,24]. Additionally, compounds **238** and **239** are long chain-type dimeric amide alkaloids, created by linking piperanine (**1**) and piperine (**2**) through a carbon-carbon bond within the benzene ring structure.

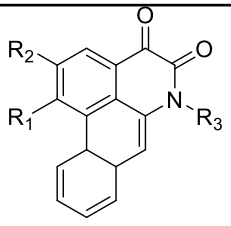
3 Bioactivity and mechanistic study of amide alkaloids

This article summarizes the biological activities of amide alkaloids in *P. nigrum* and *P. longum*. A total of 97 compounds exhibited 12 types of bioactivities (Table 7), including anti-inflammatory, anti-tumor, insecticidal, neuroprotective, etc. Anti-tumor activity is the most frequently reported (Fig. 4). As shown in Fig. 5, the network illustrates relationships between 97 compounds and their bioactivities. Among these active compounds, 97 amide alkaloids primarily consist of six structural types: piperidine alkamides, pyrrolidine alkamides, *N*-alkylamide alkaloids, tyramide type alkaloids, aporphine alkaloids, and dimeric amide alkaloids. The dimeric amide alkaloids have the highest number of compounds compared to other types.

Table 5 Aporphine alkaloids (Type Ⅴ)



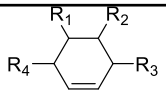
161–168



169–173

No.	Name	Groups	Source
161	Piperolactam D[61]	$R_1 = R_2 = OMe$, $R_3 = OH$, $R_4 = H$	*P. nigrum*
162	Piperolactam A[70]	$R_1 = OH$, $R_2 = OMe$, $R_3 = R_4 = H$	*P. nigrum*
163	Piperolactam B[70]	$R_1 = OH$, $R_2 = R_3 = OMe$, $R_4 = H$	*P. nigrum*
164	Piperolactam C[71]	$R_1 = R_2 = R_3 = OMe$, $R_4 = H$	*P. nigrum*
165	Cepharanone B[72]	$R_1 = R_2 = OMe$, $R_3 = R_4 = H$	*P. longum*
166	Anstolactam A Ⅱ[72]	$R_1 = OMe$, $R_2 = OH$, $R_3 = R_4 = H$	*P. longum*
167	Piperolactam A[72]	$R_1 = OH$, $R_2 = OMe$, $R_3 = R_4 = H$	*P. longum*
168	Piperolactam B[72]	$R_1 = OH$, $R_2 = R_3 = OMe$, $R_4 = H$	*P. longum*
169	Cepharadlone A[61, 72]	$R_1 = R_2 = OCH_2O$, $R_3 = Me$	*P. nigrum* *P. longum*
170	Cepharadione B[72]	$R_1 = R_2 = OMe$, $R_3 = Me$	*P. longum*
171	Norcepharadione B[72]	$R_1 = R_2 = OMe$, $R_3 = H$	*P. longum*
172	Piperadione[72]	$R_1 = OMe$, $R_2 = OH$, $R_3 = Me$	*P. longum*
173	2-Hydroxy-1-methoxy-4*H*-dlbenzo[*de*,*g*]quinohne-4,5-(6*H*)-dione[72]	$R_1 = OMe$, $R_2 = OH$, $R_3 = H$	*P. longum*

Table 6 Dimeric amide alkaloids (Type Ⅵ)



174–217

No.	Name	Groups	Source
174	Nigramide A[24]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
175	Nigramide B[24]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
176	Nigramide C[24]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
177	Nigramide D[24]	R_1 = β-PhE, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
178	Nigramide E[24]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhB	*P. nigrum*
179	Nigramide F[24]	R_1 = β-PhB, R_2 = α-AmF, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
180	Nigramide G[24]	R_1 = β-PhC, R_2 = α-AmD, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
181	Nigramide H[24]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AM, R_4 = β-AmF	*P. nigrum*
182	Nigramide I[24]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AM, R_4 = β-AmF	*P. nigrum*
183	Nigramide J[24]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-AM	*P. nigrum*
184	Nigramide K[24]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AmO, R_4 = β-AM	*P. nigrum*
185	Nigramide L[24]	R_1 = β-AM, R_2 = α-AmG, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
186	Nigramide M[24, 43]	R_1 = β-AmE, R_2 = α-AM, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum* *P. longum*
187	Nigramide N[24]	R_1 = β-HpE, R_2 = α-AmO, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
188	Nigramide O[24]	R_1 = β-AmP, R_2 = α-AM, R_3 = β-AmO, R_4 = β-AM	*P. nigrum*
189	Chabamide[24]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
190	Pipernigramide A[70]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AM, R_4 = β-AmD	*P. nigrum*
191	Pipernigramide B[70]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AM, R_4 = β-AmD	*P. nigrum*
192	(*E*)-3-(2,6-Bis(benzo[d][1, 3]dioxol-5-yl)-5-(piperidine-1-carbonyl)cyclohex-3-en-1-yl)-1-(piperidin-1-yl)prop-2-en-1-one[70]	R_1 = β-AmG, R_2 = α-PhA, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
193	Chabamide I[70]	R_1 = β-PhA, R_2 = α-AmO, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
194	Nigrunoid A[23]	R_1 = β-HpA, R_2 = α-AmF, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*

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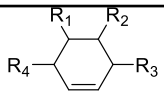
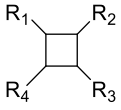


174–217

195	Nigrunoid B[23]	R_1 = α-HpE, R_2 = β-AmF, R_3 = α-PhA, R_4 = α-AmF	*P. nigrum*
196	Nigrunoid C[23]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AM, R_4 = β-AmF	*P. nigrum*
197	Nigrunoid D[23]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-AM	*P. nigrum*
198	Nigrunoid E[23]	R_1 = β-HpE, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
199	Nigrunoid G[23]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AmO, R_4 = β-AM	*P. nigrum*
200	Nigrunoid H[23]	R_1 = β-PhB, R_2 = α-AmF, R_3 = β-AmO, R_4 = β-AM	*P. nigrum*
201	Nigrunoid F[23]	R_1 = β-HpE, R_2 = α-AmO, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
202	Nigrunoid I[23]	R_1 = α-PhC, R_2 = β-AmF, R_3 = α-AmF, R_4 = α-AM	*P. nigrum*
203	Pipernigramide C[71]	R_1 = β-AmP, R_2 = α-AM, R_3 = β-AmF, R_4 = β-PhA	*P. nigrum*
204	Pipernigramide D[71]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-AM	*P. nigrum*
205	Pipernigramide E[71]	R_1 = β-PhD, R_2 = α-AmF, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
206	Pipernigramide F[71]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AmO, R_4 = β-AM	*P. nigrum*
207	Pipernigramide G[71]	R_1 = β-Ph, R_2 = α-AmF, R_3 = β-PhA, R_4 = β-AmF	*P. nigrum*
208	Pipernigramide H[71]	R_1 = β-PhB, R_2 = α-AmF, R_3 = β-PhA, R_4 = β-AmD	*P. nigrum*
209	Pipernigramide I[71]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AmD, R_4 = β-PhA	*P. nigrum*
210	Pipernigramide J[71]	R_1 = β-PhC, R_2 = β-AmF, R_3 = α-AmF, R_4 = β-PhA	*P. nigrum*
211	Piperidin-1-ylmethanone[73]	R_1 = α-PhC, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhE	*P. nigrum*
212	Piperidin-1-ylmethanone[73]	R_1 = β-PhE, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhC	*P. nigrum*
213	Piperidin-1-ylmethanone[73]	R_1 = α-PhE, R_2 = α-AmF, R_3 = β-AmF, R_4 = β-PhC	*P. nigrum*
214	Piperlongramide A[39]	R_1 = AmF, R_2 = PhA, R_3 = AmF, R_4 = PhA	*P. longum*
215	Piperlongramide B[43]	R_1 = PhC, R_2 = AmF, R_3 = AmD, R_4 = PhA	*P. longum*
216	Piperlongramide C[43]	R_1 = PhD, R_2 = AmF, R_3 = AmF, R_4 = PhA	*P. longum*
217	Piperlongramide D[43]	R_1 = PhC, R_2 = AmD, R_3 = AmF, R_4 = PhA	*P. longum*



218–237

No.	Name	Groups	Source
218	Dipiperamide A[74]	R_1 = β-AmG, R_2 = α-PhA, R_3 = β-AmG, R_4 = α-PhA	*P. nigrum*
219	Dipiperamide B[74]	R_1 = β-AmG, R_2 = β-PhA, R_3 = α-AmG, R_4 = α-PhA	*P. nigrum*
220	Dipiperamide C[74]	R_1 = β-PhC, R_2 = β-AmD, R_3 = α-AmF, R_4 = α-PhC	*P. nigrum*
221	Dipiperamide D[30]	R_1 = β-PhC, R_2 = α-AmG, R_3 = α-AmF, R_4 = β-PhC	*P. nigrum*
222	Dipiperamide E[30]	R_1 = β-AmF, R_2 = α-PhC, R_3 = α-AmG, R_4 = β-PhA	*P. nigrum*
223	Pipernigramide E[34]	R_1 = PhA, R_2 = AmM, R_3 = AmN, R_4 = PhA	*P. nigrum*
224	Pipernigramide F[34]	R_1 = α-AmG, R_2 = β-PhC, R_3 = β-AmM, R_4 = α-PhA	*P. nigrum*
225	Pipercyclobutanamide D[75]	R_1 = β-AmF, R_2 = α-PhC, R_3 = β-AmM, R_4 = α-PhA	*P. nigrum*
226	Nigramide P[24]	R_1 = α-AmG, R_2 = β-PhA, R_3 = β-AmF, R_4 = α-PhA	*P. nigrum*
227	Nigramide Q[24]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AmF, R_4 = α-PhA	*P. nigrum*
228	Nigramide R[24]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AmF, R_4 = α-PhC	*P. nigrum*
229	Nigramide S[24]	R_1 = β-PhC, R_2 = α-AmF, R_3 = β-AmF, R_4 = α-PhE	*P. nigrum*
230	Pipercyclobutamide C[73]	R_1 = β-PhE, R_2 = β-AmF, R_3 = β-AmM, R_4 = α-PhE	*P. nigrum*
231	(2*E*,4*E*)-5-(3-(Benzo[d][1, 3]dioxol-5-yl)-2-((*E*)-2-(benzo[d][1, 3]dioxol-5-yl)vinyl)-4-(piperidine-1-carbonyl)cyclobutyl)-1-(piperidin-1-yl)penta-2,4-dien-1-one[73]	R_1 = α-PhA, R_2 = β-AmF, R_3 = β-AmM, R_4 = β-PhC	*P. nigrum*
232	(*E*)-3-(3-(Benzo[d][1, 3]dioxol-5-yl)-2-((1*E*,3*E*)-4-(benzo[d][1, 3]dioxol-5-yl)buta-1,3-dien-1-yl)-4-(piperidine-1-carbonyl)cyclobutyl)-1-(piperidin-1-yl)prop-2-en-1-one[73]	R_1 = β-PhA, R_2 = α-AmF, R_3 = β-AmM, R_4 = α-PhE	*P. nigrum*
233	(2*Z*,4*E*)-5-(3-(Benzo[d][1, 3]dioxol-5-yl)-2-((1*E*,3*E*)-4-(benzo[d][1, 3]dioxol-5-yl)buta-1,3-dien-1-yl)-4(piperidine-1-carbonyl)cyclobutyl)-1-(piperidin-1-yl)penta-2,4-dien-1-one[73]	R_1 = β-PhA, R_2 = α-AmF, R_3 = α-AmN, R_4 = β-PhE	*P. nigrum*

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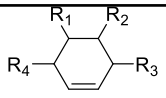
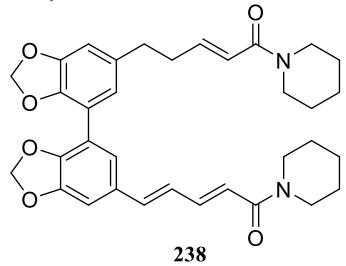
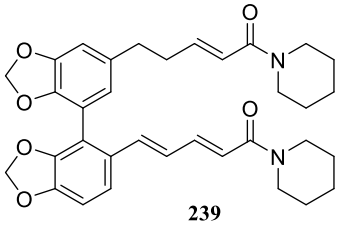


174–217

234	(3-((1*E*,3*E*)-4-(Benzo[d][1, 3]dioxol-5-yl)buta-1,3-dien-1-yl)-4-((1*Z*,3*E*)-4-(benzo[d][1, 3]dioxol-5 ylbuta-1,3-dien-1-yl)cyclobutane-1,2-diyl)bis(piperidin-1-ylmethanone)[73]	R_1 = *β*-PhE, R_2 = *α*-AmF, R_3 = *β*-AmF, R_4 = *α*-PhF	*P. nigrum*
235	(2*E*,4*E*)-5-(2-(Benzo[d][1, 3]dioxol-5-yl)-4-((*E*)-2-(benzo[d][1, 3] dioxol-5-yl)vinyl)-3 (pyrrolidine-1-carbonyl)cyclobutyl)-1-(pyrrolidin-1-yl)penta-2,4-dien-1-one[73]	R_1 = *α*-PhC, R_2 = *β*-AmD, R_3 = *β*-AmQ, R_4 = *α*-PhA	*P. nigrum*
236	3,4-Bis((1*E*,3*E*)-4-(benzo[d][1, 3]dioxol-5-yl)buta-1,3-dien-1-yl)cyclobutane-1,2-diyl)bis(piperidin-1-ylmethanone)[73]	R_1 = *α*-PhE, R_2 = *β*-AmF, R_3 = *α*-AmF, R_4 = *α*-PhE	*P. nigrum*
237	(2*Z*,4*E*)-5-(2,3-Bis(benzo[d][1, 3]dioxol-5-yl)-4-((*E*)-3-oxo-3-(piperidin-1-yl)prop-1-en-1-yl cyclobutyl)-1-(piperidin-1-yl)penta-2,4-dien-1- one[73]	R_1 = *α*-PhA, R_2 = *β*-AmG, R_3 = *α*-AmN, R_4 = *α*-PhA	*P. nigrum*



238



239

No.	Name	Groups	Source
238	Pipsaeedine[40]		*P. nigrum*
239	Pipbinine[40]		*P. nigrum*

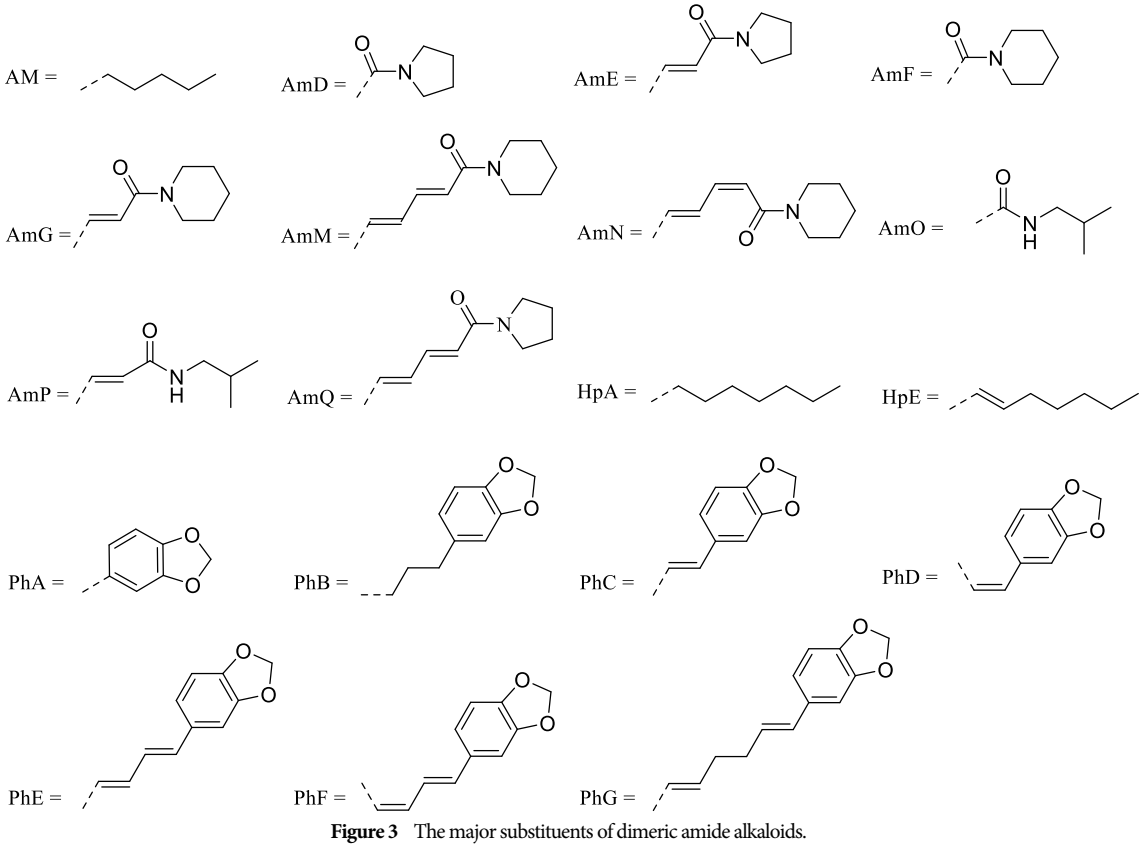


Figure 3 The major substituents of dimeric amide alkaloids.

Additionally, compound **2**, a piperidine alkamide alkaloid, exhibited the broadest range of activities, encompassing lipid-lowering, anti-allergic, anti-hypertensive, antioxidant, anti-tumor, anti-viral, insecticidal, neuroprotective, lowering blood sugar, and anti-inflammatory activities. This may explain its high content in both *P. nigrum* and *P. longum*, and, given its abundance, it has been extensively screened for various bioactivities.

3.1 Anti-tumor activity

Forty-two amide alkaloids exhibited inhibitory effects on

Table 7 Active amide alkaloids in *Piper nigrum* and *Piper longum*

NO.	Compound	Activities	Ref.
1	Piperanine	1. Neuroprotection	[35]
		2. Anti-inflammatory	[71]
2	Piperine	1. Lipid-lowering	[76-78]
		2. Anti-allergy	[38]
		3. Anti-hypertension	[79]
		4. Antioxidant	[49]
		5. Anti-tumor	[33, 35, 63, 80-85]
		6. Anti-viral	[70]
		7. Insecticidal activity	[86]
		8. Neuroprotection	[61, 87-89]
		9. Reduce blood sugar	[76, 90]
		10. Anti-inflammatory	[91]
3	Piperettine	Neuroprotection	[92]
4	Piperettine B	Insecticidal activity	[26]
6	Ilepcimide	1. Anti-tumor	[61]
		2. Anti-inflammatory	[29, 71]
8	Pipernonaline	1. Insecticidal activity	[93]
		2. Lipid-lowering	[32]
		3. Neuroprotection	[35]
		4. Anti-tumor	[94]
9	Dehydropipernonaline	1. Lipid-lowering	[54]
		2. Anti-inflammatory	[32, 95]
		3. Neuroprotection	[35]
10	Pipernigramide B	Anti-tumor	[70]
12	2*E*,4*E*,12*E*,13-(3,4-Methylenedioxy-phenyl)-trideca-trienoic acid isobutyl amide	Insecticidal activity	[57]
15	(2*E*,4*Z*,8*E*)-*N*-[9-(3,4-Methylenedioxyphenyl)-2,4,8-nonatrienoyl]-piperidine	1. Lipid-lowering	[32]
		2. Anti-inflammatory	[29, 95]
		3. Anti-tumor	
20	Isopiperine	Anti-tumor	[33]
21	Isochavicine	Anti-inflammatory	[29]
23	Erythro-1-[1-oxo-9-(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2*E*-nonenyl]-piperidine	Anti-viral	[38]
24	Threo-1-[1-oxo-9-(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2*E*-nonenyl]-piperidine	Anti-viral	[38]
38	Piperlongimin B	1. Insecticidal activity	[57]
		2. Anti-tumor	[63]
		3. Neuroprotection	[42]
48	(*R*,2*E*,4*E*)-9-Hydroxy-1-(piperidin-1-yl)deca-2,4-dien-1-one	Neuroprotection	[39]
51	1-(1-Oxo-6-hydroxy-2*E*,4*E*-decadienyl)-piperidine	Anti-inflammatory	[43]
52	1-(1-Oxo-8-hydroxy-2*E*,4*E*-decadienyl)-piperidine.	Anti-inflammatory	[43]
53	1-(1-Oxo-8-hydroxy-2*E*,4*E*-nonadienyl)-piperidine	Anti-inflammatory	[43]
54	1-(1-Oxo-7-hydroxy-2*E*,4*E*-decadienyl)-piperidine	Anti-inflammatory	[43]
57	Pipernigramide A	Anti-tumor	[70]
62	3*β*,4*α*-1-(3-phenylpropanoyl)-piperidine-2-one	Anti-viral	[44]
69	1-[(*E*)-(3,4-Methylenedioxy-phenyl)-6-heptenoylpyrrolidine	1. Insecticidal activity	[26]
		2. Anti-inflammatory	[43]
70	1-(2*E*,6*E*)-7-(3,4-Methylenedioxypheny)-2,6-heptaienoyIprrolidine	Insecticidal activity	[26]
71	1-[(*E*)-9-(3,4-Methylenedi-oxyphenyl)-8-nonenoyl] pyrolidine	Insecticidal activity	[26]
72	1-[(2*E*,8*E*)-9-(3,4-Methylenedioxyphenyl)-2,8-nonadienoylpyrrolidine	Insecticidal activity	[26]
73	1-[(2*E*,4*E*,8*E*)-9-(3,4-Methylenedioxyphenyl)-2,4,8-nonatrienoyl] pyrrolidine	Anti-inflammatory	[43]
80	Tricholein	Anti-inflammatory	[43]
82	1-[(2*E*,4*E*)-2,4-Decadienoyl] pyrrolidine	Insecticidal activity	[26]
83	1-[(2*E*,4*E*)-2,4-Dodecadienoyl] pyrrolidine	Insecticidal activity	[26]
87	Pipyaqubine	Insecticidal activity	[49]
88	Sarmentine	Anti-inflammatory	[71]
90	(*R*,2*E*,4*E*)-7-Hydroxy-1-(pyrrolidin-1-yl)deca-2,4-dien-1-one	Neuroprotection	[39]
93	1-(1,6-Dioxo-2*E*,4*E*-decadienyl)-pyrrolidine	Anti-inflammatory	[43]
94	*N*-(M-methoxy-cinnamoyl)-pyrrolidine	Anti-inflammatory	[43]

(Continued)

NO.	Compound	Activities	Ref.
96	Pipercide	1. Insecticidal activity	[51, 96, 97]
		2. Lipid-lowering	[54]
97	Guineesine	1. Anti-viral	[38]
		2. Anti-tumor	[55, 63]
		3. Neuroprotection	[35]
		4. Anti-inflammatory	[98]
		5. Insecticidal activity	[51, 96, 97]
98	Retrofractamide A	1. Anti-diabetic	[54, 99]
		2. Anti-tumor	[33, 96]
		3. Insecticidal	[55]
		4. Lipid-lowering	[100]
101	Pipercallosine	Neuroprotection	[35]
103	Retrofractamide C	1. Anti-inflammatory	[101]
		2. Anti-diabetic	[99, 100]
105	Piperchabamide D	1. Lipid-lowering	[33]
		2. Anti-tumor	[54]
106	4,5-Dihydroguineensine	Anti-tumor	[55]
108	Retrofractamide B	1. Neuroprotection	[55]
		2. Anti-tumor	[35]
		3. Anti-diabetic	[55]
110	Piperlonguminine	1. Anti-hypertension	[100]
		2. Anti-tumor	[80, 102]
		3. Anti-diabetic	[33, 103-107]
		4. Neuroprotection	[100]
		5. Anti-inflammatory	[35]
115	Piperlongumide	1. Insecticidal activity	[108]
		2. Anti-tumor	[57]
116	Pipericine	Insecticidal activity	[29, 109, 110]
119	Pipyahyine	Insecticidal activity	[49]
123	Pellitorine	1. Neuroprotection	[48]
		2. Insecticidal activity	[35]
		3. Anti-inflammatory	[49, 96, 97]
		4. Anti-tumor	[95]
124	2*E*,4*E*-*N*-Isobutyl-octadecenamide	1. Insecticidal activity	[54]
		2. Anti-tumor	[61]
125	2*E*,4*E*-*N*-Isobutyl-dodecenamide	1. Anti-tumor	[57]
		2. Insecticidal activity	[63]
127	2,4-Tetradecadienoic acid isobutyl amide	Anti-tumor	[63]
130	Piperlongimin A	1. Anti-tumor	[57]
		2. Insecticidal activity	[61]
135	Pipilyasine	Insecticidal activity	[63]
138	Pipzubedine	Insecticidal activity	[57]
145	(2*E*,4*E*,14*Z*)-*N*-Isobutyleicosa-2,4,14-trienamide	Anti-hypertension	[49]
147	Pipnoohine	Insecticidal activity	[46, 50] [46, 50]
150	(*R*,2*E*,4*E*)-8-Hydroxy-*N*-isobutyldeca-2,4-dienamide	Neuroprotection	[80]
152	6-Hydroxypellitorine	Anti-inflammatory	[48]
154	Sylvamide	Anti-tumor	[39]
156	Deca-2*E*,4*E*-dienoic acid 4-hydroxy-2-phenylethylamide	Anti-inflammatory	[43]
159	Paprazine	Anti-tumor	[61]
160	*N*-trans-feruloyltyramine	Antioxidant	[92]
161	Piperolactam D	Anti-tumor	[61]
164	Piperolactam C	1. Anti-inflammatory	[71, 95]
		2. Lipid-lowering	[32]
169	Cepharadione A	Anti-tumor	[61]
174	Nigramide A	1. Anti-inflammatory	[71]
		2. Anti-tumor	[71]
175	Nigramide B	Anti-tumor	[70]
179	Nigramide F	Anti-inflammatory	[71]
180	Nigramide G	Anti-inflammatory	[71]
186	Nigramide M	1. Anti-inflammatory	[43]
		2. Anti-tumor	[43]

(Continued)

NO.	Compound	Activities	Ref.
189	Chabamide	Anti-tumor	[55, 70]
192	(*E*)-3-(2,6-Bis(benzo[d][1, 3]dioxol-5-yl)-5-(piperidine-1-carbonyl)cyclohex-3-en-1-yl)-1-(Piperidin-1-yl)prop-2-en-1-one	Anti-tumor	[70]
193	Chabamide I	Anti-tumor	[70]
196	(+)-Nigrunoid C	Anti-inflammatory	[23]
198	Nigrunoid E	Anti-inflammatory	[23]
199	(-)-Nigrunoid F	Neuroprotection	[23]
200	Nigrunoid G	Neuroprotection	[23, 111]
201	Nigrunoid H	Neuroprotection	[111]
203	Pipernigramide C	1. Anti-inflammatory 2. Anti-tumor	[71]
204	Pipernigramide D	1. Anti-inflammatory 2. Anti-tumor	[71] [71]
205	Pipernigramide E	1. Anti-inflammatory 2. Anti-tumor	[71] [71]
206	Pipernigramide F	1. Anti-inflammatory 2. Anti-tumor	[71] [34]
207	Pipernigramide G	1. Anti-inflammatory 2. Anti-tumor	[34] [71]
208	Pipernigramide H	1. Anti-inflammatory 2. Anti-tumor	[71] [71]
209	Pipernigramide I	1. Anti-inflammatory 2. Anti-tumor	[71] [71]
210	Pipernigramide J	1. Anti-inflammatory 2. Anti-tumor	[71] [71]
214	Piperlongramide A	1. Anti-inflammatory 2. Anti-tumor	[43] [43]
215	Piperlongramide B	1. Anti-inflammatory 2. Anti-tumor	[43] [43]
216	Piperlongramide C	1. Anti-inflammatory 2. Anti-tumor	[43] [43]
217	Piperlongramide D	1. Anti-inflammatory 2. Anti-tumor	[43] [43]
218	Dipiperamide A	1. Inhibit CYP3A4 2. Anti-inflammatory	[74] [71]
219	Dipiperamide B	Inhibit CYP3A4	[74]
220	Dipiperamide C	Inhibit CYP3A4	[74]
221	Dipiperamide D	Inhibit CYP3A4	[30]
222	Dipiperamide E	Inhibit CYP3A4	[30]
223	Pipernigramide E	1. Anti-inflammatory 2. Anti-tumor	[34] [34]
225	Pipercyclobutanamide D	1. Reduce blood sugar 2. Anti-tumor	[75] [75]

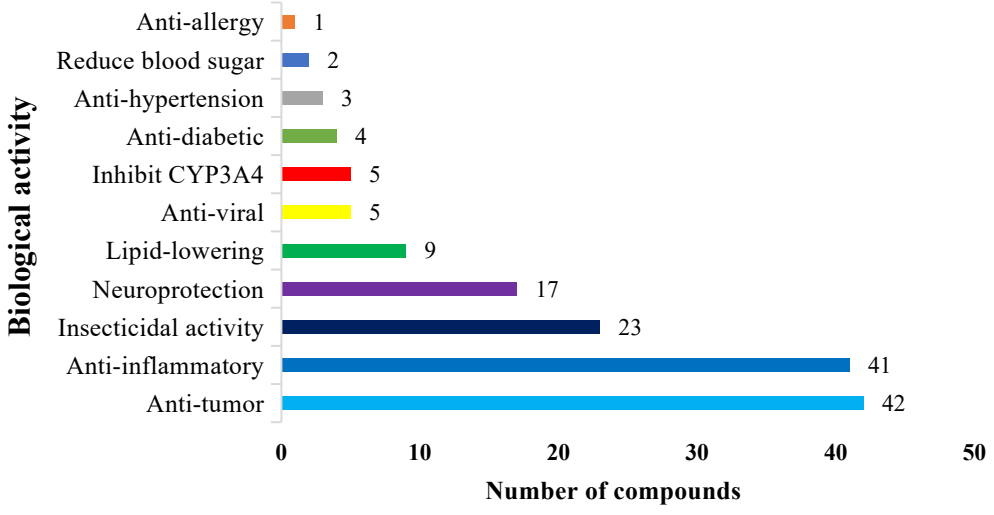


Figure 4 Relationship between the biological activities of amide alkaloids and the number of compounds. The length of the bar represents the number of compounds with activity.

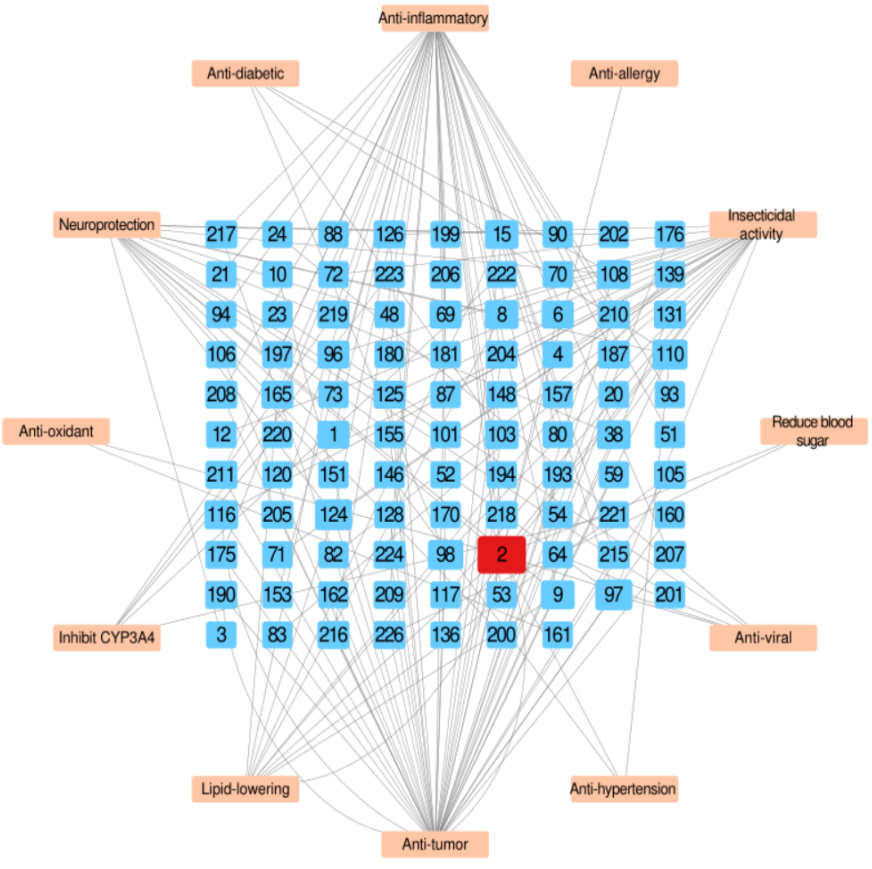


Figure 5 Network of bioactive relationships between compounds and bioactivity in *P. nigrum* and *P. longum*.

tumor cell lines with IC_{50} values ranging from 13.0 to 156.86 μM (Table 8). Moreover, compound **116** could enhance FosB expression by causing reactive oxygen species accumulation, thereby inducing apoptosis in MCF-7 cells[110].

In addition, 21 compounds (**2**, **10**, **57**, **174**, **175**, **186**, **189**, **192**, **193**, **203**–**210**, **214**–**217**) have the ability to enhance sensitivity to overcome drug resistance. Compound **2** synergistically enhanced the cytotoxicity of doxorubicin in Caco-2 and CEM/ADR cells by affecting ERK1/2, p38, MAPK, and AKT signaling pathways[76]. Compounds **174**, **186**, **203**–**210**, **214**–**217**, and **223** also could improve the sensitivity of paclitaxel, vincristine, or adriamycin against multidrug resistance cancer cells[43,71], in which the mechanism of four dimeric amide alkaloids (**186** and **214**–**217**) is related to the Src/ERK/STAT3 signaling pathway[43]. Seven compounds (**2**, **10**, **57**, **175**, **189**, **192**, and **193**) combined with paclitaxel exhibited good MDR activity on HeLa/PTX cells through prohibiting the expression of Mcl-1 and enhancing the expression of Bax, cleaved caspase-3, and cleaved PARP (Fig. 6)[70].

3.2 Anti-inflammatory activity

Forty-one amide alkaloids have been reported to exhibit anti-inflammatory activity. Thirty-four compounds (**1**, **6**, **15**, **21**, **51**–**54**, **57**, **73**, **80**, **88**, **93**, **94**, **152**, **156**, **164**, **174**, **179**, **180**, **186**, **203**–**210**, and **214**–**218**) exhibited anti-inflammatory activity by inhibiting the production of nitrogen monoxide with IC_{50} values ranging from 1.9 to 40.2 μM (Table 9)[29,43,71]. Compounds **4**, **9**, **15**, and **123** inhibited the direct binding between sICAM-1 and LFA-1 of THP-1 cells, to suppress cell adhesion with IC_{50} values of 13.4, 50.6, 10.7, and 13.5 μg/mL, respectively[95].

A series of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α,

Table 8 Cytotoxicity of 13 compounds on several cell lines (IC_{50}).

Com.	Cell lines	IC_{50} (μM)	Ref.
2	MAD-MB-231	156.3	[82]
	MCF-7	121.8	
	MAD-MB-468	156.9	
15	HL-60	42.1	[63]
38	HL-60	26.9	[55]
97	HL-60	46.7	[63]
	Hela	13.0	[63]
98	Hela	40.4	[55]
	MCF-7	49.8	
105	Hela	36.9	[55]
	HL-60	41.0	
106	Hela	54.4	[55]
	HL-60	22.1	
108	Hela	51.6	[55]
	MCF-7	23.1	
	HL-60	55.7	
124	HL-60	51.4	[63]
125	HL-60	29.8	[63]
130	HL-60	43.8	[63]
189	HL-60	45.3	[63]
	Hela	26.9	[55]
	MCF-7	36.0	
	HL-60	16.0	
225	MCF-7	45.6	[75]
	HepG2	63.9	

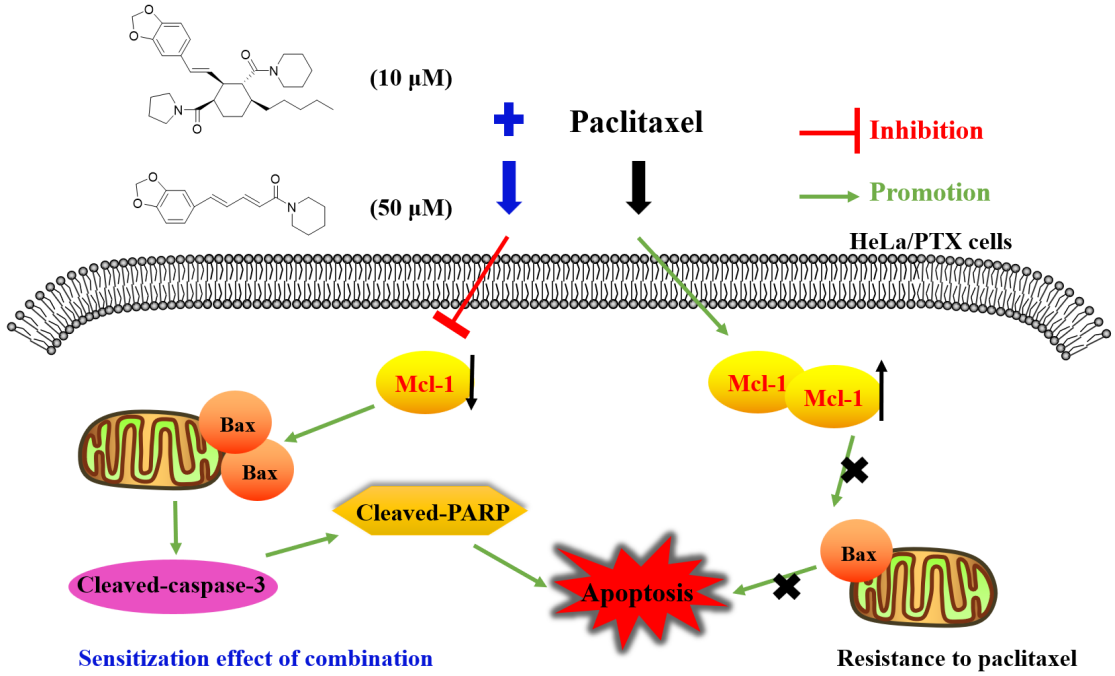


Figure 6 Alkaloids from *P. nigrum* synergistically enhanced the effect of paclitaxel against paclitaxel-resistant cervical cancer cells through the downregulation of Mcl-1[70].

Table 9 33 Anti-inflammatory activity (NO) with IC_{50} values.

Com.	IC_{50} (μM)	Ref.	Com.	IC_{50} (μM)	Ref.
1	28.5	[71]	**180**	23.4	[71]
6	16.1	[71]	**181**	21.7	[71]
21	14.5	[29]	**187**	2.3	[43]
51	5.6	[43]	**204**	5.6	[71]
52	32.0	[43]	**205**	8.8	[71]
53	28.5	[43]	**206**	9.8	[71]
54	13.4	[43]	**207**	16.9	[71]
69	14.6	[43]	**208**	18.9	[71]
73	1.9	[43]	**209**	11.4	[71]
80	35.3	[43]	**210**	13.3	[71]
88	33.2	[71]	**211**	6.3	[71]
93	32.7	[43]	**215**	14.4	[43]
94	25.8	[43]	**216**	5.9	[43]
152	40.2	[43]	**217**	3.5	[43]
156	4.2	[43]	**218**	5.9	[43]
164	16.6	[71]	**219**	7.0	[71]
174	11.3	[71]			

and PGE2) production can be suppressed by compounds **97**, **196**, **198**, and **205–207**[23,83]. In a mouse model of acute and inflammatory pain and endotoxemia, compound **103** alleviated xylene-induced mouse ear edema via inhibiting phosphorylation of ERK and NF-κB[98]. Compound **2** (piperine) inhibited PMA-induced cyclooxygenase-2 expression through downregulating NF-κB, C/EBP and AP-1 signaling pathways in murine macrophages[91]. Moreover, compounds **205–207** could also suppress IκB degradation and further inhibit the p65 subunit cytosol-nucleus translocation by targeting IKK-β[34], resulting in strong anti-inflammatory activity in murine macrophages.

3.3 Insecticidal activity

Twelve compounds (**2**, **4**, **87**, **96**, **97**, **98**, **116**, **119**, **123**, **135**, **138**, and **147**) exhibited insecticidal activity against *Aedes aegypti*, *Culex pipiens pallens*, and *Aedes togoi* with LC_{50} values ranging from 0.01 to 35.1 ppm (Table 10)[48,49,93,96]. Among them, compound **98** showed the best insecticidal activity with an LC_{50} value of 0.01 ppm. Seven compounds (**4**, **69**, **70**, **71**, **72**, **82**, and **83**) showed larvicidal activity against second-stage larvae of *Toxocara canis* with MIC ranging from 0.05 to 0.30 mM[26]. In addition, compound **8** showed larvicidal activity against *Aedes aegypti*[93]. Six compounds (**12**, **38**, **115**, **124**, **125**, and **130**) had leishmanicidal activity against *Promastigotes* and *Axenic*

Table 10 Insecticidal activity with LC_{50} value

Com.	Insects	LC_{50} (*ppm*)	Ref.
2	*Aedes aegypti*	10	[46]
4	*Aedes aegypti*	31	[46]
87	*Aedes aegypti*	31	[46]
	Culex pipiens pallens	0.004	
96	*Aedes aegypti*	0.1	[93]
	Aedes togoi	0.26	
	Culex pipiens pallens	0.17	
97	*Aedes aegypti*	0.89	[93]
	Aedes togoi	0.75	
	Culex pipiens pallens	0.028	
98	*Aedes aegypti*	0.039	[93]
	Aedes togoi	0.01	
116	*Aedes aegypti*	25	[46]
119	*Aedes aegypti*	30	[45]
	Culex pipiens pallens	0.86	
123	*Aedes aegypti*	0.92	[93]
	Aedes togoi	0.71	
135	*Aedes aegypti*	28	[46]
138	*Aedes aegypti*	22	[46]
147	*Aedes aegypti*	35.1	[45]

amastigotes[57], while compounds **96**, **97**, and **123** were toxic to female *Culex pipiens pallens* and female *Aedes aegypti*[93, 94]. Additionally, compound **97** also had insecticidal properties against *Cowpea weevils* with LD_{50} values of 0.25 μg/insect for males and 1.43 μg/insect for females[51].

3.4 Neuroprotective activity

Seventeen amide alkaloids exhibited good neuroprotective activity. Among them, nine compounds (**1**, **2**, **8**, **9**, **97**, **101**, **108**, **110**, and **123**) can improve cell viability in 6-OHDA-induced SK-N-SH and SH-SY5Y cells[35]. Compound **2** also could suppress the activity of MAO-B with an IC_{50} value of 0.483 μM[78, 90]. In addition, compounds **2**, **3**, **48**, **90**, and **150** revealed inhibitory effects on AChE, BChE, and Aβ aggregation[39, 92]. Compounds **199**–**202** also can inhibit AChE activity with IC_{50} values of 35.64, 8.34, 3.81, and 6.06 μM, respectively[23, 42, 111]. Compound **2** protected hippocampal neurons against KA-induced cytotoxicity by upregulating the NGF/TrkA/Akt/GSK3β signaling pathways[75] (Fig. 7).

3.5 Lipid-lowering activity

Nine amide alkaloids exhibited lipid-lowering activity. Compounds **4**, **8**, **9**, and **15** inhibited diacylglycerol acyltransferase with IC_{50} values of 20.1, 37.2, 21.2, and 29.8 μM[32], respectively. Compounds **96**, **98**, and **105** could suppress the activity of acetyl-CoA acetyltransferase[54].

Compound **115** (piperlongumine) was shown to potently upregulate activation of AMPK via phosphorylation and inactivation of acetyl-CoA carboxylases in cultured HepG2 cells, leading to fatty acid oxidation[109]. Additionally, fat cell differentiation could be inhibited by compound **2** by downregulating transcriptional activity of PPARγ (LXRα), resulting in suppressing the expression of PPARγ (and LXRα)[83, 84]. Compound **2** could also downregulate adiponectin-AMP-activated protein kinase (AMPK) signaling molecules caused by a high-fat diet in mice. In the livers of the Pin50 group, the expression of lipogenic target genes decreased, while the expression of carnitine palmitoyltransferase 1 (CPT1) gene, involved in fatty acid oxidation, increased (Fig. 8)[89].

3.6 Other activities

Some amide alkaloids were found to be active in other bioassay models, such as anti-diabetic, anti- hypertension, antioxidant, inhibiting CYP3A4, anti-virus, etc. As for the anti-diabetic activity, six compounds (**2**, **98**, **103**, **108**, **110**, and **225**) were active. Compounds **98**, **103**, **108**, and **110** exerted anti-diabetic activity via promoting adipogenesis of 3T3-L1 cells and increasing the amount of adiponectin released and the uptake of 2-deoxyglucose into the cells[100]. Compounds **98** and **103** could promote glucose consumption, glucose uptake, glycogen synthesis, and glycolysis, to achieve anti-diabetic effects[99]. In an animal model, compound **2** significantly decreased the phosphorylation of insulin receptor substrate-1 (IRS-1) compared with the HFD-fed mice, resulting in reversing existing HFD-induced hepatic steatosis and insulin resistance[89]. What's more, compound **225** showed weak α-glucosidase activity with an IC_{50} value of 158.5 μM[75].

Three compounds had the potential to combat hypertension. Compound **2** suppressed vasoconstriction in the mesenteric artery, facilitated the influx of extracellular calcium into mesenteric artery smooth muscle cells (MASMC), and functioned via an endothelium-independent mechanism that involved $Ca2^{+}$ entry. Compounds **110** and **145** could also suppress mesenteric artery

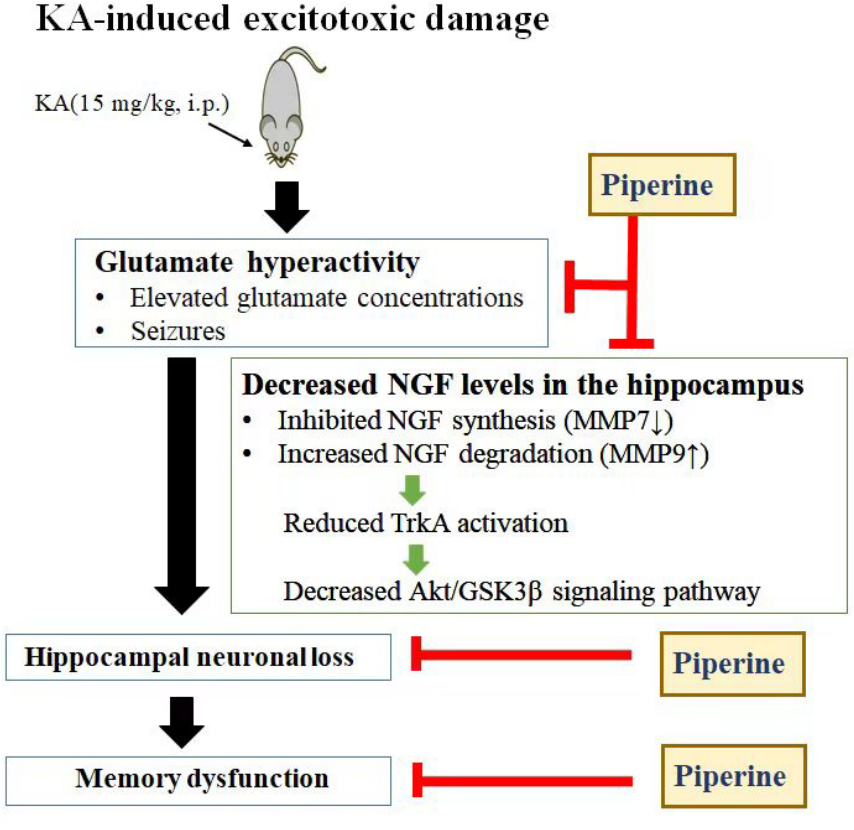


Figure 7 The neuroprotective effects of compound 2 in the hippocampus of rats induced by KA[78].

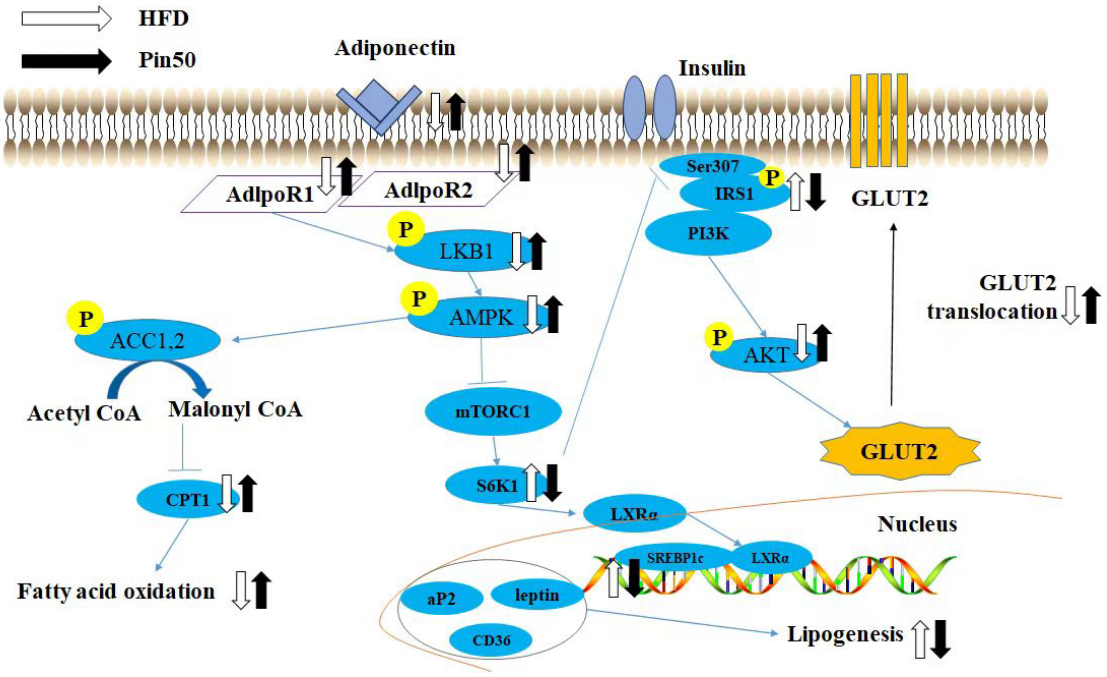


Figure 8 The possible molecular mechanism of compound 2 in treating hepatic steatosis and insulin resistance induced by HFD[89].

vasoconstriction with the relaxation rate of 100% and 80%[80].

Two compounds exhibited anti-oxidation activity. Compound **2** exhibited antioxidant activity via binding with hemoglobin[79]. Compound **160** revealed the DPPH radical-scavenging potency with an EC_{50} of 11.82 μg/mL[92].

Compounds **218**–**222** exhibited CYP3A4 inhibitory activity with IC_{50} values of 0.18, 0.45, 0.48, 0.79, and 0.12 μM, respectively[74]. Compound **2** could suppress IgE-mediated signaling pathway to achieve anti-allergic activity[77]. The secretion of hepatitis B virus surface antigen (HBsAg) was prohibited by five compounds (**2, 23**, **24**, **62**, and **97**) with IC_{50} values of 0.15, 0.13, 0.11, 1.8, and 0.05 mM, respectively[38]. Compounds **2**, **98**, **103**, and **110** exhibited potent ability to increase melanin content and improve tyrosinase activity in a concentration dependent manner[33].

4 Conclusions and Prospects

P. nigrum and *P. longum* are widely used as flavoring agents and healthy supplements in the food industry. Amide alkaloids are one of the main active ingredients in both species, with various biological activities such as anti-inflammatory, anti-tumor, neuroprotective, insecticidal, and lipid-lowering. Some of these active amide alkaloids have been used in food and daily health supplements. For example, piperine is used as a spice additive in brandy to impart a spicy flavor or as a preservative to extend food shelf life. With the advances in experimental techniques, piperine has become relatively easy to obtain and use. Due to the low content of active ingredients and insufficient research on the mechanism of action, the widespread use of other active amide alkaloids requires further research and development.

In addition to the research on amide alkaloids in existing *P. nigrum* and *P. longum*, further exploration is needed into additional compound structures and their associated biological activities. Moreover, the full utilization of black pepper and long pepper also needs to be developed.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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