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Constituents of carbazole alkaloids and anti-cancer properties of extracts, mahanine, isomahanine, mahanimbine, and girinimbine from *Bergera koenigii*

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ABSTRACT

The new name of *Murraya koenigii* (L.) Spreng. is *Bergera koenigii* L., the Indian curry leaf tree. Constituents of carbazole alkaloids from different plant parts of *B. koenigii* are compiled. Based on the number of reports, mahanimbine (MNB) and koenimbine are the two most dominant carbazole alkaloids from the leaf of *B. koenigii*. Carbazole alkaloids selected for review are mahanine (MN), isomahanine (IMN), MNB, and girinimbine (GNB) which are pyranocarbazoles as they possess the pyranocarbazole skeleton. MN, IMN, and MNB have 23 carbons and four methyl groups, while GNB has 18 carbons and three methyl groups. The anti-cancer properties of extracts and carbazole alkaloids from *B. koenigii* are tabulated with information on cancer types, cancer cell lines, effects, and mechanisms. Other pharmacological properties are briefly mentioned. Findings on the anti-cancer properties of extracts and carbazole alkaloids that will generate interest for further research are included as concluding remarks. Eight areas for future research were suggested.

INTRODUCTION

The genus *Murraya* has been split into *Bergera* and *Murraya* based on morphological and phytochemical differences [1]. *Murraya koenigii* (L.) Spreng. is now *Bergera koenigii* L., a small evergreen tropical tree of the family Rutaceae that is native to South, East, and Southeast Asia [2]. Fresh leaflets emit a unique sulphury and burnt aroma due to 1-phenylethanethiol, and are a compulsory spice for nearly all Indian curries and chutneys. Commonly known as the curry leaf tree, *B. koenigii* should be more appropriately called an Indian curry leaf tree.

The species is a shrub or small tree with a dark-brown stem and root bark. Leaves are pinnate, with individual leaflets having wavy margins and emitting a distinctive aroma (Fig. 1b). Inflorescences are axillary or terminal cymes, each bearing 60−90 flowers. Each flower is bisexual, white, funnel-shaped, and sweetly scented. Petals are five and whitish (Fig. 1a). Fruits are in close clusters, small berries, ovoid or sub-globose, turning purplish–black on ripening (Fig. 1c), and contain one or two green-colored seeds [1,3,4].

Alkaloids are a class of compounds containing at least one nitrogen atom. Carbazole alkaloids are characterized by a tricyclic aromatic basic skeleton with a central pyrrole ring fused between two benzene rings [5,6]. Carbazole alkaloids can broadly be divided into halogenated carbazole alkaloids, oxygenated carbazole alkaloids, carbazolequinone alkaloids, pyranocarbazole alkaloids, furocarbazole alkaloids, pyridocarbazole alkaloids, indolocarbazole alkaloids, dimeric carbazole alkaloids, tetrahydrocarbazole alkaloids, and other substituted carbazole alkaloids [6]. Carbazole alkaloids can also be divided into sub-classes based on the number of carbons. They include those with 13, 18, and 23 carbons; dimeric and trimeric carbazoles; and carbazoles with other moieties [5].

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Figure 1. Flowers (a), leaves (b), and fruits (c) of *Bergera koenigii*.

In this article, the constituents of carbazole alkaloids in different plant parts of *B. koenigii*, and the anti-cancer properties of extracts, mahanine (MN), isomahanine (IMN), mahanimbine (MNB), and girinimbine (GNB) are reviewed. Other pharmacological properties of these carbazole alkaloids are briefly mentioned. The anti-cancer and other pharmacological properties of these four carbazole alkaloids have not been reviewed before. This short review is therefore justified. References for this article are mostly procured on databases such as Google, Google Scholar, Science Direct, PubMed, and J Stage. Search terms were based on the article title and keywords.

CHEMICAL CONSTITUENTS

A total of 101 carbazole alkaloids have been reported from different plant parts of *B. koenigii* (Table 1). They include carbazoles with 13 carbons and 2 methyl groups (e.g., murrayafoline A and murrayaquinone A); carbazoles with 18 carbons and 3 methyl groups (e.g., GNB and koenimbine); carbazoles with 23 carbons and 4 methyl groups (e.g., MN, IMN, and MNB); and dimeric carbazoles (e.g., bismahanine, bismurrayaquinone A, and bikoeniquinone A). From the leaf of *B. koenigii*, MNB (22) and koenimbine (16) are the two most dominant carbazole alkaloids, based on the number of reports. Most reports of these two compounds are from the leaf.

Carbazole alkaloids from *B. koenigii* selected for review are MN, IMN, MNB, and GNB (Fig. 2). They are classified as pyranocarbazoles because of their pyranocarbazole skeleton [7,8]. The pyranocarbazole is a tricyclic hetero-aromatic unit comprising two benzene rings A and C fused by a pyrrole ring B [9]. MN, IMN, and MNB are carbazoles with 23 carbons and four methyl groups [5]. MN ($C_{23}H_{25}NO_2$ and 347.4 g/mol) was first isolated from the leaf of *B. koenigii* [10]. IMN ($C_{23}H_{25}NO_2$ and 347.4 g/mol) was first isolated from the stem bark of *M. euchrestifolia* [11] and later from the leaf of *B. koenigii* [12]. MNB ($C_{23}H_{25}NO$, 331.4 g/mol) was first isolated from the leaf of *B. koenigii* [10]. GNB is another pyranocarbazole but with 18 carbons and three methyl groups. GNB ($C_{18}H_{17}NO$, 263.3 g/mol) was first isolated from the stem bark of *B. koenigii* [13].

From six climatic zones of India, 11 carbazole alkaloids were identified from the leaf of *B. koenigii* [14]. The contents of MN, GNB, MNB, and IMN were 0.01–7.34, 0.05–5.29, 0.01–1.67, and 0.01–0.11 mg/g, respectively. The contents

Table 1. Carbazole alkaloids from different plant parts of *Bergera koenigii*.

No.	Compound class (name)	Plant part	Reference
	Carbazole alkaloids		
2	*N*-Benzylcarbazoles A & B	Whole plant	[29]
3	Bicyclomahanimbine	Leaf	[9,30]
		Aerial part	[31]
		Stem bark	[12,32]
4	Bismahanine	Stem bark	[33–35]
		Root	[33–35]
5	9-Carbethoxy-3-methylcarbazole	Root	[36]
6	Clauraila A	Aerial part	[31]
7	Currayangine	Aerial part	[31]
8	*O*-Demethylmurrayanine	Whole plant	[29]
9	6,7-Dimethoxy-1-hydroxy-3-methylcarbazole	Leaf	[37]
10	Euchrestine B	Leaf	[12,33,38–40]
11	3-Formylcarbazole	Stem bark	[12]
12	1-Formyl-3-methoxy-6-methylcarbazole	Leaf	[37]
13	9-Formyl-3-methylcarbazole	Root	[36]
14	3-Geranyl 8-hydroxy 6,7-di methoxy 3′,3′-dimethyl 1,2-pyranocarbazole	Seed	[41]
15	Girinimbilol	Stem bark	[42]
16	GNB	Leaf	[30,35,40,43]
		Whole plant	[29]
		Aerial part	[31]
		Stem bark	[12,34,43–46]
		Seed	[34,41,47]
		Root	[44,45,48]
17	1-Hydroxy-7-methoxy-8-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carbaldehyde	Aerial part	[31]
18	1-Hydroxy-3-methylcarbazole	Stem bark	[49]
19	2-Hydroxy-3-methylcarbazole	Stem bark	[12]
20	3-Hydroxymethyl-9-*H*-carbazole	Whole plant	[29]
21	7-Hydroxymurrayazolinine	Leaf	[31]
22	Isokoenidine	Whole plant	[29]
23	Isokoenigine	Whole plant	[29]
24	Isomahanimbine	Leaf	[9,34,40,48]
		Root	[34]
24	IMN	Leaf	[12,34]

(Conitnued)

No.	Compound class (name)	Plant part	Reference
		Seed	[34,35,47]
25	Koenidine	Leaf	[39,43,50,51]
		Whole plant	[29]
		Stem bark	[43]
26	Koenigicine	Leaf	[9,34]
		Aerial part	[31]
27	Koenigine	Leaf	[9,35,39,52,53]
		Whole plant	[29]
28	Koenimbidine	Leaf	[48]
		Root	[34]
29	Koenimbine	Leaf	[9,12,30,33–35,39,40,46,50,51]
		Whole plant	[29]
		Aerial part	[31]
		Root	[34]
		Seed	[34,47]
30	Koenine	Leaf	[9,39,40,53]
		Whole plant	[29]
		Stem bark	[35,53]
31	Koenoline	Whole plant	[29]
		Stem bark	[12,53]
		Root bark	[35,53,54]
32	Kurryam	Leaf	[40]
		Seed	[55]
33	Mahanimbicine	Leaf	[34,38,56]
34	Mahanimbilol	Stem bark	[12,32,42]
35	MNB	Leaf	[9,30,38–40,43,46,48,50,51,56,57,14]
		Whole plant	[29]
		Aerial part	[31]
		Stem bark	[12,43–45]
		Seed	[41,47]
		Root	[44,45]
36	Mahanimbinine	Aerial part	[31]
37	Mahanimbinol	Stem bark	[34,38]
38	MN	Leaf	[9,12,33,35,38,39,56,57]
		Whole plant	[29]
		Seed	[47]
39	Mahaninebicine T	Leaf	[33]
40	Mahaninebine	Leaf	[12,33]
41	2-Methoxycarbazole-3-methylcarboxylate	Stem bark	[49]
42	*N*-Methoxy-3-hydroxymethyl-9-*H*-carbazole	Whole plant	[29]
43	2-Methoxy-3-methyl-9*H*-carbazole	Aerial part	[31]
44	7-Methoxymurrayacine	Leaf	[9]
45	Methylcarbazole	Root	[61]
46	*O*-Methylmahanine	Leaf	[33]
47	*O*-Methylmurrayamine A	Leaf	[9,33,43,46,50,51]
		Aerial part	[31]
		Stem bark	[43]
48	Mukoeic acid	Stem bark	[34,38]
51	Mukoenines A−C	Stem bark	[12,58]
		Root	[58]
52	Mukoline	Root	[34,35,53]
53	Mukolidine	Stem bark	[34,38
		Root	[34,35,38]
54	Mukonal	Stem bark	[34,35]
55	Mukonicine	Leaf	[9,34,40,59]
		Aerial part	[31]
56	Mumunine	Stem bark	[60]
57	Murrastanine A	Stem bark	[12]
60	Murrastinines A−C	Stem bark	[12]
61	Murrayacine	Leaf	[35,48]
		Stem bark	[12,45,53]
		Root	[45]
62	Murrayafoline A	Stem bark	[12,44]
		Root	[44,61]
63	Murrayakoeninol	Leaf	[46]
		Stem bark	[12,32]
67	Murrayakonines A–D	Aerial part	[31]
	Murayakonine D	Leaf	[9]
68	Murrayamine A	Whole plant	[29]
70	Murrayamines B & D	Leaf	[12,30]
71	Murrayamine C	Leaf	[9]
72	Murrayamines C & J	Aerial part	[31]
		Stem bark	[12,32]
73	Murrayanine	Leaf	[43]
		Whole plant	[29]
		Aerial part	[31,62]
		Stem bark	[12,34,43–45,63]
		Root	[44,45]
		Root bark	[54]

(Conitnued)

No.	Compound class (name)	Plant part	Reference
74	Murrayanol	Leaf	[34,48,53,57]
		Root	[34,48]
		Seed	[34,35,47]
76	Murrayaquinones A & B	Stem bark	[12]
77	Murrayatanine A	Stem bark	[12]
78	Murrayazolidine	Aerial part	[31]
		Seed	[47]
79	Murrayazoline	Leaf	[50,51]
		Aerial part	[31]
		Stem bark	[34]
80	Murrayazolinine	Leaf	[46]
		Stem bark	[53]
81	Murrayazolinol	Stem bark	[12,32,34]
82	Pyrayafoline D	Leaf	[39]
	Dimeric carbazole alkaloids		
83	Bikoeniquinone A	Stem bark	[58]
		Root	[58]
86	Bisgerayafolines A−C	Fruit	[64]
87	Bisisomahanine	Leaf	[12]
88	8,8′-Biskoenigine	Leaf	[62]
		Aerial part	[31]
		Whole plant	[29]
89	8,8″-Biskoenigine	Aerial part	[50,62]
90	Bismahanimboline	Stem bark	[12]
91	Bismahanine	Leaf	[33,40]
		Stem bark	[58]
		Root	[58]
92	Bismurrayafoline E	Leaf	[12,33,38]
93	Bismurrayaquinone A	Stem bark	[58]
		Root	[58]
94	Bispyrayafoline	Leaf	[12,33]
95	*bis*-2-Hydroxy-3-methycarbazole	Stem bark	[58]
		Root	[58]
96	Mahabinine A	Leaf	[39]
97	Murrafoline I	Leaf	[39]
98	Murrastifoline F	Stem bark	[58]
		Root	[58]
99	3,3′-[Oxy*bis*(methylene)]*bis*(9-methoxy-9*H*-carbazole)	Stem bark	[65]
100	3,3′,5,5′,8-Pentamethyl-3,3′-*bis*(4-methylpent-3-en-1-yl)-3,3′,11,11′-tetrahydro-10,10′-bipyrano[3,2-α]carbazole	Leaf	[66]
101	8,10′-[3,3′,11,11′-Tetrahydro-9,9′-dihydroxy-3,3′,5,8′-tetramethyl-3,3′-*bis*(4-methyl-3-pentenyl)] bipyrano[3,2-α]carbazole	Leaf	[33]

of MN and MNB in the leaf of *B. koenigii* from Tamil Nadu were 9.6% and 4.3% *w*/*w* [15]. From the ethanol root extract of *B. koenigii*, the total phenolic content and total flavonoid content were reported to be 51.2 mg of gallic acid equivalent/g and 43.6 mg of catechin equivalent/g [16].

ANTI-CANCER PROPERTIES

Extracts

An earlier study reported that the aqueous methanol leaf extract of *B. koenigii* was cytotoxic against Caco2 colon, HeLa cervical, HepG2 liver, and LNCaP prostate cancer cells, with IC_{50} values of 8.07, 4.80, 17.5, and 16.4 µg/ml, respectively [17]. In terms of proteasome inhibition, a promising strategy for cancer therapy, their IC_{50} values were 12.5, 7.99, 43.4, and 12.4 µg/ml, respectively. With regard to the anti-cancer properties of *B. koenigii* extracts, breast cancer cells were the most commonly reported tumor cells. Glioma, colon, and cervical were the other cancer cells (Table 2). Five studies involved breast cancer cells [18–22] while the other cancer types were represented by single studies [23–25].

Carbazole alkaloids

MN is cytotoxic to leukemic, colon, lung, oral squamous, pancreatic, and breast cancer cells. The IC_{50} values of MN after 48 hours were 10.6 and 13.0 µM for MOLT-3 and K562 leukemic cells, respectively [26]. Against HCT116 ($p53^{wt}$), HCT ($p53^{null}$), and SW480 ($p53^{mut}$) colon cancer cells, its IC_{50} values were 12.6, 13.9, and 16.6 µM [27]. The IC_{50} values of MN against A549, A549-TR, and H1299 lung cancer cells were 12.5, 12.5, and 10.0 µM, respectively [28]. IC_{50} values against A549 and H1299 lung cancer cells were 40.2 and 42.6 µM at 24 hours and 28.0 and 26.7 µM at 48 hours [28]. Against CLS-354 oral squamous carcinoma cells, the IC_{50} values of MN and IMN were 15.1 and 15.0 µM, respectively [67]. These values were slightly stronger than that of cisplatin, the anticancer drug, which has an IC_{50} value of 16.3 µM. MN enhanced cisplatin-induced apoptosis and reduced its effective concentration by 5–8 fold. IC_{50} values of MNB against CAPAN and SW119 pancreatic cancer cells were both 3.5 µM [68]. IC_{50} values against Hs172.T bladder and MCF-7 breast cancer cells were 32.5 µM [69] and 14 µM [70], respectively.

Anti-cancer effects of carbazole alkaloids of *B. koenigii* have been reported in nine types of cancer cells (Table 3). Four studies on MN involved prostate cancer cells [71–74], and two studies involved leukemia [26,75] and breast cancer cells [76,77]. Single studies on MN included colon [27], cervical [78], lung [79], pancreatic [80], and glioma [81] cancer cells. Cancer cells affected by MNB were lung [82], pancreatic [68], bladder [69], and breast [70] cancer cells. There was only one study on IMN involving oral squamous carcinoma cells [67]. Two studies on GNB involved colon cancer cells [83, 84] while one study each included anti-tumor [85], liver [86], lung [87], and breast [88] cancer cells.

The anti-cancer structure-activity relationship (SAR) of MN against five different cancer cell lines has been studied [89]. MN exhibited enhanced apoptosis compared to

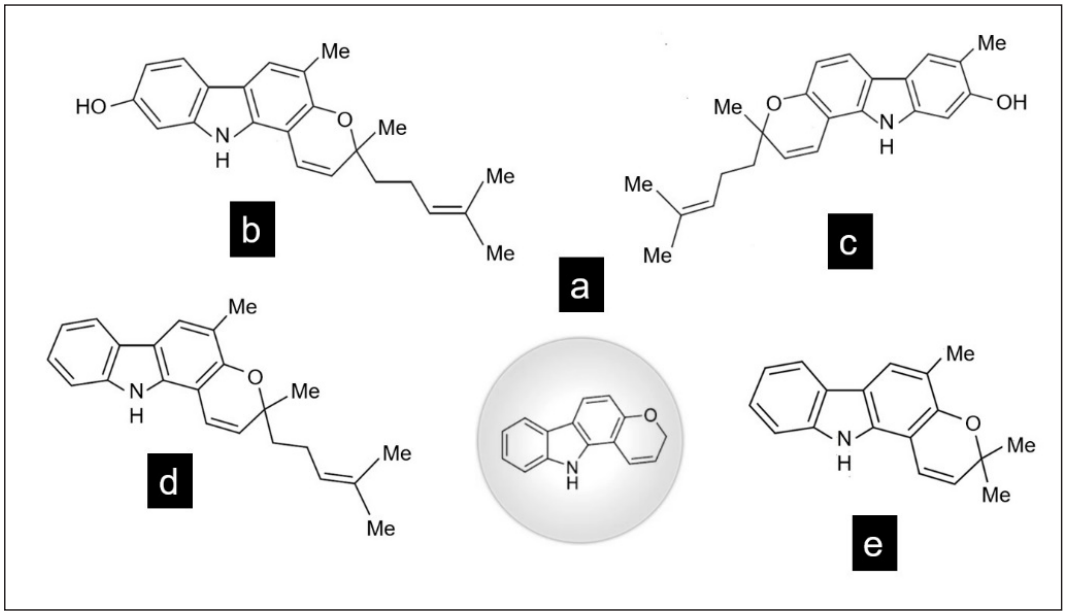

Figure 2. Chemical structures of the pyranocarbazole skeleton (a), MN (b), IMN (c), MNB (d), and GNB (e).

Table 2. Anti-cancer properties of extracts from *Bergera koenigii*.

Cancer type, cancer cell line, extract, & effect	Reference
Breast MCF-7 & MDA-MB-231: Aqueous methanol leaf extract inhibited proteasome leading to cell cycle ar rest and apoptosis. IC_{50} values were 30.0 and 22.5 µg of extract.	[18]
Breast MDA-MB-231 & 4T1: Aqueous leaf extract inhibited cells with IC_{50} values of 0.80 and 0.50 mg/ml at 48 hours of treatment, respectively. The extract checked the progression of 4T1 inoculated mice by its anti-proliferative, anti-inflammatory, and immuno-modulatory effects.	[19]
Breast MDA-MB-231: TAE was cytotoxic with IC_{50} value of 14.4 mg/ml and inhibited proteasome leading to cell death.	[20]
Breast MDA-MB-231: Aqueous exerted proteasome inhibitory effect, induced apoptosis, and reduced tumor growth in a xenograft tumor mouse model.	[21]
HER2: Ethanol leaf extract exerted anti-tumor effect on DMBA-induced mammary carcinoma in rats *via* caspase-3 activation and apoptosis of tumor cells.	[22]
Glioma U373MG: Methanol leaf extract reduced cell viability by exhibiting significant cytotoxicity.	[23]
Colon HT-29: Synthesized silver nanoparticles using aqueous leaf extract exerted potent cytotoxic activity.	[24]
Cervical HeLa: Hexane and ethyl acetate leaf extract showed stronger cytotoxic activity with CD_{50} values <1.0 µg/ml than that of methanol leaf extract with CD_{50} value <2.2 µg/ml.	[25]

Abbreviations: CD_{50} = 50% cytotoxic dilution, DMBA = 7,12-dimethylbenz(α)-anthracene, HER2 = human epidermal growth factor receptor 2, and TAE = total alkaloid extract.

dehydroxymahanine, indicating a significant contribution of the C7−OH group. Methylation of the C7−OH group reduced its antiproliferative activity. The study provided evidence of the contribution of C7−OH and 9−NH groups of MN toward its cytotoxicity [89].

Table 3. Anti-cancer properties of MN, IMN, MNB, and GNB from *Bergera koenigii*.

Alkaloid	Cancer type, cancer cell line, effect, & mechanism	Reference
MN		
	MN induced DR-mediated apoptosis in MOLT-3 and K562 leukemic cells *via* Apo-1/Fas signaling and mitochondrial pathways. MN also inhibited tumor growth in K562 xenograft mice.	[26]
	Against HCT116 and SW480 colon cancer cells, MN synergistically enhanced the cytotoxicity of 5-FU through ROS-mediated activation of PTEN and p53/p73.	[27]
	MN inhibited the proliferation, induced apoptosis and cell cycle arrest, and depolarized mitochondrial membrane of HL-60 leukemia cells.	[76]
	MN inhibited growth and induces apoptosis in PC3 & LNCaP prostate cancer cells *via* the deactivation of Akt and activation of caspases.	[71]
	MN induced the expression of the tumor suppressor gene RASSF1A in PC3 & LNCaP prostate and various other cancer cells by inhibiting DNMT.	[72]
	MN restored RASSF1A expression by down-regulating DNMT1 and DNMT3B in PC3 & LNCaP prostate cancer cells.	[73]
	MN strongly disrupted AR signaling and inhibited the growth of androgen-dependent and -independent LNCaP prostate cancer cells.	[74]
	MN displayed synergistic activity with cisplatin and improved chemosensitivity in HeLa cervical cancer *via* STAT3 inhibition.	[79]
	MN induced apoptosis in A549 and H1299 lung cancer cells by deactivating mTOR and suppressing RICTOR.	[79]
	MN induced apoptosis in MIAPaCa-2 and BxPC-3 pancreatic cancer cells by inducing ER stress, calcium signaling and possibly defective sialylation. MN also inhibited MIAPaCa-2 xenograft tumor in mice.	[80]

(Conitnued)

Alkaloid	Cancer type, cancer cell line, effect, & mechanism	Reference
	MN induced apoptosis, cell cycle arrest, inhibition of cell migration and invasion in HS683 glioma cells *via* the PI3K/Akt/mTOR signaling pathway. MN also inhibited *in vivo* glioma tumor growth in mice.	[81]
	MN inhibited the proliferation of MCF-7 and MDA-MB-231 breast cancer cells. It also repressed the progression of mammary tumor in MNU-induced rats.	[77]
	MN inhibited the proliferation of drug sensitive MCF-7 and MDA-MB-231, and paclitaxel resistant MCF-7TR and MDA-MB-231TR breast cancer cells. It also suppressed mammary tumors in MNU-induced rats.	[77]
MNB		
	MNB synergistically enhanced the efficiency of gefitinib, a cancer drug, by increasing its intracellular accumulation in A549 lung cancer cells.	[67]
	MNB exerted anti-cancer effects on Capan-2 and SW1190 cells pancreatic cancer cells by triggering cell cycle arrest, apoptosis, and modulating Akt/mTOR and STAT3 signalling pathways.	[68]
	Anticancer effects of MNB on Hs172.T bladder cancer cells were due to the induction of G0/G1 cell cycle arrest, apoptosis and autophagy.	[69]
	Cytotoxicity of MNB against MCF-7 breast cancer cells involved mitochondrial apoptosis and anti-angiogenesis. The anti-invasive property of MN was shown by results of the inhibition of wound healing scratch test.	[70]
IMN		
	IMN induced ER stress and triggered p38 MAPK-mediated apoptosis and autophagy in multidrug-resistant CLS-354 oral squamous carcinoma cells.	[78]
GNB		
	GNB displayed its anticancer activity by inducing apoptosis in HCT-15 colon cancer cells, and the mechanism may involve the rapid decrease of △ψm.	[82]
	GNB exhibited anti-tumor promoting activity by inhibiting the expression of early antigen of EBV in Raji cells.	[84]
	The growth inhibition effects of GNB on HepG2 liver cancer cells involved the induction of apoptosis and cell cycle arrest.	[85]
	GNB exerted antiproliferative and apoptotic effects on A549 lung cancer cells *via* up- and down-regulation of apoptotic and anti-apoptotic proteins, and significant involvement of both intrinsic and extrinsic pathways.	[86]
	GNB induced apoptosis in HT-29 colon cancer cells *via* G0/G1 cell cycle arrest and activation of caspases-3 and -9.	[83]
	GNB inhibited the proliferation, migration, and invasion of MDA-MB-453 breast cancer cells *via* the induction of apoptosis, and inhibition of MEK/Erk and STAT3 signaling pathways.	[87]

Abbreviations: Akt = protein kinase B, AR = androgen receptor, CA = carbazole alkaloid, DNA = deoxyribonucleic acid, DNMT = DNA methyltransferase, DR = death receptor, EBV = Epstein-Barr virus, ER = endoplasmic reticulum, 5-FU = 5-fluorouracil, MEK = mitogen-activated Erk kinase, MNU = N-methyl-N-nitrosourea, mTOR = mammalian target of rapamycin, △ψm = mitochondrial transmembrane potential, OSCC = oral squamous cell carcinoma, PI3K = phosphoinositide 3-kinase, PTEN = phosphatase and tensin homolog, RICTOR = rapamycin insensitive companion of mTOR, ROS = reactive oxygen species, and STAT3 = signal transducer and activator of transcription 3.

OTHER PROPERTIES

Other pharmacological properties of MNB include anti-anxiety properties [90], anti-hyperglycemic and anti-lipidemic properties [91], neuroprotective [92], anti-obesity [93], acetylcholinesterase (AChE) inhibition [94], larvicidal [95], and reversal in age-related memory dysfunction [96]. Other pharmacological properties of GNB are anti-inflammatory [84], and anti-angiogenic activity [97], while MN stimulates glucose uptake [98] and promotes lipid-induced insulin resistance [99].

CONCLUSION

As concluding remarks, findings on the anti-cancer properties of extracts and carbazole alkaloids from *B. koenigii* that will generate interest for further research include: a) Extracts of *B. koenigii* inhibited proteasome and this led to cell cycle arrest, apoptosis, and reduced xenograft tumor. b) MN inhibited prostate cancer cells by down-regulating DNA methyltransferase (DNMT). c) Synthesis of silver nanoparticles using aqueous leaf extract of *B. koenigii* exerted potent cytotoxic activity. d) MN inhibited both drug-sensitive A549 and taxol-resistant A549-TR lung cancer cells with cytotoxicity of equal potency. e) Against CLS-354 oral squamous carcinoma cells, MN possessed cytotoxicity that was slightly stronger than cisplatin, and it enhanced cisplatin-induced apoptosis by 5–8 fold. f) GNB-induced apoptosis in HCT-15 colon cancer cells *via* the rapid decrease of mitochondrial transmembrane potential. g) MNB synergistically enhanced the efficiency of gefitinib by increasing its intracellular accumulation in A549 lung cancer cells. h) More in-depth studies on the anti-cancer SAR of MN and other carbazole alkaloids from *B. koenigii* are also needed.

AUTHOR CONTRIBUTIONS

The authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. The authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJEs) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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