Phytochemical Analysis, Anti-inflammatory, and Anticancer Activities of the Halophyte Herb

*Bassia indica*

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Abstract

*Bassia indica* (Wight) A.J. Scott, family Amaranthaceae, is a halophyte herb growing in extreme environments and hence deemed as a potential economic source of bioactive chemicals with functional properties. In our study, 25 compounds were obtained from *B. indica*. We aimed to assess the inhibitory effect of the methanol extract of *B. indica* and its isolated compounds on COX-2 and cytotoxicity activity against MCF-7, OVK-18, HepG2, and HCT116 tumor cells. Among the isolates, the triterpene oleanane saponin (23) displayed promising anti-inflammatory activity with an IC₅₀ = 3.05 ± 0.15 μg/mL. Additionally, *N*-trans-feruloyl tyramine (11) exhibited significant cytotoxicity to OVK-18 with IC₅₀ = 1.74 ± 1.56 μg/mL, whereas 6,7-dihydroxy coumarin (7) exhibited potent inhibition against the MCF-7 cell line with IC₅₀ = 1.47 ± 0.22 μg/mL. Interestingly, compounds 1 and 25 exhibited remarkable cytotoxicity against HepG2 and HCT116 cells with IC₅₀ < 0.1 μg/mL, while compounds 2, 4, 5, 6, and 9 exerted potent cytotoxicity against HepG2. Finally, *B. indica* is a potential source of candidate compounds for the development of anti-inflammatory and anti-tumor therapies.

Keywords

halophytes, *Bassia indica*, alkaloids, lignanamides, saponins, cytotoxicity, anti-inflammatory

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Introduction

Cancer is a great burden to public health and a serious cause of death worldwide.¹⁻³ Recently, it has been reported that cancer-related mortality is due to lung, colorectal, breast, and liver cancers.⁴ The currently available drugs for cancer treatment are conventional chemotherapy; however, the development of drug resistance is one of the complications caused by chemotherapy.⁵ It is worth noting that a wide variety of plant-based anticancer therapies are in clinical use, and they have exhibited significant efficacy.⁶ On the other hand, inflammation has played a key role in cancer metastasis. Many studies have demonstrated that the possibility of cancer occurrence and development is associated with inflammation.⁷ Currently, there is a growing demand for anti-inflammatory and anticancer drugs that are highly safe with good effects.

Halophytes are plants with salt-tolerant capacity and well-known adaptation to extreme environments.⁸ They have been reported as potential sources of bioactive compounds with substantial economic value.⁹ The halophytic plants have also been deemed to possess antitumor,¹⁰,¹¹ anti-inflammatory,¹²,¹³ anticholinesterase,¹⁴ and anti-tyrosinase¹⁵ properties. Previous research on halophytes revealed their content of various classes of biologically interesting lead compounds, such as steroids,¹⁶ saponins,¹¹,¹⁷ flavonoids, and alkaloids.¹⁸

*Bassia indica* (Wight) A.J. Scott (Amaranthaceae) is a halophytic herb widely grown in the Egyptian ecosystem and other regions of the world.¹⁹ In relation to ethnomedicine, the plant has been traditionally reported as an antitumor, cardiotoxic, and anti-oxidant.²⁰ Till now, the research work on *B. indica* has been very limited particularly regarding its use as an antitumor remedy, and thus there is still a need to explore the
chemicals and biological properties of this plant. Although several effective strategies are available for cancer and inflammation treatment, halophytic plants are deemed significant in providing a variety of chemical entities possessing bioactivities. To emphasize the utilization of halophyte extracts as potential sources of pharmaceutical candidates, this study was conducted to provide a more detailed view of the anti-inflammation and antitumor activities of B. indica. Thus, we evaluated the possibility of cytotoxicity and anti-inflammatory activities of 25 compounds obtained from this species.

Considering the revealed biological properties of halophytes, the methanol extract of B. indica was screened for anti-inflammatory activity against COX-2 and cytotoxic activity toward MCF-7, OVK-18, HepG2, and HCT-116. As a result, the methanol extract exhibited pronounced anti-inflammatory activity. Moreover, the extract displayed cytotoxic activity in OVK-18 cell lines. Hence, the isolates from B. indica were also investigated for their capacity as anti-inflammatory and antitumor candidates. In this context, the isolation, structural elucidation, and evaluation of anti-inflammatory and cytotoxicity properties of isolated compounds are reported.

**Results and Discussion**

**Identification of the Isolated Compounds**

The chemical investigation of the 80% aqueous MeOH extract obtained from B. indica afforded 25 compounds (Figure 1). Notably, the isolated chemicals were categorized into various chemical classes including lignans, steroids, amide alkaloids, coumarins, nucleic acid derivatives, phenolic glycosides, flavonoids, and triterpene oleanane saponins (Figure 2). The isolated compounds were identified based on comparison of their spectral data with those reported in the literature, and they were identified as β-sitosterol (1), syringaresinol (2), N-trans-feruloyl-3-methoxy tyramine (3), vanillic acid (4), o-hydroxybenzoic acid (5), p-hydroxybenzoic acid (6), 6,7-dihydroxy coumarin (7), methyl caffeate (8), caffeic acid (9), quercetin (10), N-trans-feruloyl tyramine (11), uracil (12), thymidine (13), tachioside (14), S(-)-N-trans-feruloyl normetanephrine (15), S(-)-N-trans-feruloyl octopamine (16), R(+)-N-trans-feruloyl octopamine (17), isorhamnetin-3-O-β-D-glucoside (18), kaempferol-3-O-rutinoside (19), kaempferol-3-O-β-D-glucopyranosyl-(1→6)-O-[β-D-galactopyranosyl-(1→3)]-2-O-trans-feruloyl-
Figure 2. Chemical structure of compounds 1-25.
α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (20), 21 isorhamnetin-3-O-β-D-glucopyranosyl-(1→6)-O-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (21), 21 N-[(3-(3-methyl-1-oxo-6-butylamino)propyl)-3-(3,4-dihydroxyphenyl)prop-2-enamide (22), 22 3-O-[2′-O-glycolyl]-glyoxylxy-β-D-glucuronopyranosyl]-28-O-β-D-glucopyranosyl-olean-12-en-3β-ol-28-oic acid (23), 21 (2′R,3′S)-3-O-[(2′-O-glycolyl)-oxy-propionic acid]-β-D-glucuronopyranosyl]-28-O-β-D-glucopyranosyl-olean-12-en-3β-ol-28-oic acid (24), 21 and chikusetsusaponin V (25), 42,43 as shown in Supplemental Tables S1 to S5.

**Anti-inflammatory Activity of B. indica and Isolated Compounds**

The formation of prostaglandins is regulated by either COX-1 or COX-2 from arachidonic acid and subsequently leads to the inflammatory process. COX-2 is upregulated in inflammatory conditions. 44 Thus, the discovery of potent anti-inflammatory compounds from natural plant sources through the inhibition of COX-2 is an effective approach in the pharmaceutical field. In the present study, the COX-2 enzyme inhibiting activity of crude extract of B. indica, as well as the isolated triterpenoid saponins, were evaluated. Based on previously published literature data, the saponin content of the s-butanol extract of halophytes is responsible for the anti-inflammatory potential. 12 Therefore, the isolated saponins (23-25) from B indica were investigated for their possible anti-inflammatory activity via inhibition of the COX-2 enzyme. The methanol extract of B. indica exhibited promising anti-inflammatory activity by inhibiting COX-2 with an IC₅₀ = 7.97 ± 0.40 µg/mL. Importantly, compound 23 exhibited significant inhibitory activity on COX-2 with an IC₅₀ value of 3.05 ± 0.15 µg/mL compared to the activity of celecoxib (IC₅₀ = 1.75 ± 0.09 µg/mL). Furthermore, compounds 24 and 25 showed moderate inhibition activities against COX-2 with IC₅₀ values of 24.89 ± 1.26, and 19.65 ± 0.99 µg/mL, respectively.

By reviewing the literature, previous reports demonstrated that saponins could contribute to the anti-inflammatory potential of plant crude extracts. Previously triterpene oleanane saponins isolated from the halophyte Anabasis setifera displayed a potential anti-inflammatory activity. 12 Also, phenolics and flavonoids are suggested to contribute to anti-inflammatory activity.12,45,46 The extract of the herb *Suanda fruticosa* exhibited high activity against inflammation by inhibiting the release of nitric oxide (NO) owing to its phenolic content. 45 Additionally, polyphenols, mainly flavonoids, have anti-inflammatory modifying properties by modulating the expression of the iNOS gene and consequently inhibiting the production of NO. 47 Thus, the anti-inflammatory potential of B. indica might be explained due to its content of saponins and phenolic derivatives.

**Cytotoxic Activity of B. indica and Isolated Compounds**

The isolated chemicals (1-25) were tested for their antitumor activity by MTT assay 48 against 4 cancer cell lines (human breast adenocarcinoma [MCF-7], human ovarian endometrioid carcinoma [OVK-18], colorectal carcinoma [HCT116], human liver carcinoma [HepG2], normal human dermal fibroblast, and human colon epithelial cells [NHDF and CCD841] cell lines). Neither the tested samples (1-25) nor 5-FU exhibited cytotoxic activity to the normal cell lines NHDF and CCD841, indicating their selectivity, except for compound 9, as shown in Table 1.

Against OVK-18, the methanol extract, and compounds 11, 2, and 3 showed good cytotoxicity with IC₅₀ = 7.27±0.1, 1.74±1.56, 4.03±0.21, and 4.00±0.26 µg/mL, respectively, while compounds 14 and 17 displayed moderate activities with IC₅₀ = 21.50±10.67 and 16.33±1.95, respectively, when compared to the positive drug as seen in Table 1. Regarding MCF-7, compound 13 displayed potent inhibition activity with an IC₅₀ < 0.1 µg/mL, while compounds 7 and 3 displayed good activities with IC₅₀ = 1.47±0.22 and 4.55±0.38 µg/mL, respectively. Importantly, compound 1 showed significant activity against human colorectal carcinoma and liver adenocarcinoma with an IC₅₀ less than 0.1 µg/mL. Additionally, compounds 2, 4, 5, and 6 have a promising cytotoxic activity against the HepG2 cell line with an IC₅₀ < 0.1 µg/mL, while compound 9 showed moderate activity with an IC₅₀ = 2.88±0.81 µg/mL. Moreover, compounds 2, 3, and 9 showed moderate activity against the HCT116 cell line with IC₅₀ = 26.95±4.38, 18.16±2.20, and 19.80±8.05 µg/mL, respectively.

Among the isolated triterpene saponins, compound 25 displayed potent cytotoxic activity against HCT116 with an IC₅₀ less than 0.1 µg/mL, while compound 23 showed moderate activity with an IC₅₀ = 44.31±5.79 µg/mL. It is worth mentioning that among the tested lignanamides (3, 11, 15, 16, and 17), compound 11 displayed the highest potential activity toward OVK-18 with an IC₅₀ = 1.74±1.56 µg/mL, while 3 showed activity to MCF-7 and OVK-18 with IC₅₀ = 4.00±0.26 and 4.55±0.38 µg/mL, respectively. Also, the rare occurring R-isomer amide derivative (17) showed moderate activity against OVK-18 with an IC₅₀ = 16.33±1.95 µg/mL. Consequently, the hydroxyl group at position C-7′ markedly decreases the activity, except when the configuration of C-7′ is the R-isomer. Furthermore, the presence of the methyl group in compound 9 markedly enhances the activity when compared to compound 8.

By reviewing the literature, it is to be noted that β-sitosterol stimulates apoptosis and inhibits proliferation through induction of caspase-3 and the Bax/Bcl-2 ratio. 49 The furofuran lignan (syringaresinol) showed cytotoxicity to a number of cell lines including Hep-2 (larynx epidermoid carcinoma), HeLa (human cervix carcinoma), and C6 (rat glioma) cell lines with IC₅₀ values ranging from 0.23 to 0.63 µg/mL. 50 The amide alkaloid, N-trans-furaloyl tyramine, showed cytotoxic activity against human lung (A549 and K562) cancer cell lines with IC₅₀ = 37.20 and 41.52 µmol/L, respectively. Also, aesculetin (6,7-dihydroxy coumarin) induced apoptosis in HeLa cells through a ROS-mediated mitochondrial dysfunction pathway. 51 Moreover, the stimulation of the mitochondrial pathway and induction of DNA damage produced by methyl caffeate lead to apoptosis. 52 Therefore, the cytotoxic activity of B. indica might be attributed to its content of diverse metabolites with significant antitumor activities.
To sum up, the halophyte herb *B. indica* has been deemed a promising and cheap source of bioactive compounds. Importantly, the current study marks the first report of the anti-inflammatory and antitumor activity of the constituents of *B. indica* growing in Egypt. Besides, the findings of our study highlight the potential utilization of halophytes as a source of pharmaceutical candidates through the determination of key candidate compounds from *B. indica* responsible for antitumor and anti-inflammatory activities. In the future, further studies to elucidate the exact mechanisms of *B. indica* as an anti-inflammatory and antitumor will be needed.

### Material and Methods

**Material for Chromatography Experiments**

Normal-phase silica (75-150 μm), reversed-phase silica (38-63 μm), and solvents for the extraction and isolation of phytochemicals were obtained from Wako Pure Chemical Corporation, Osaka, Japan. Sephadex LH-20 was used for purification and obtained from Sigma Aldrich, USA. Diaion HP-20 was purchased from Mitsubishi Chemical Corporation, Japan. Biotage selekt operated with a RP-C18 (Sfär C18 D Duo column, 30 μm, 30, and 60 g) was used for fractionation and purification of compounds (obtained from Biotage Japan Ltd, a subsidiary of Biotage Uppsala, Sweden). The medium-pressure liquid chromatograph was connected to an UV and ELSD detector used for further purification (obtained from Buchi, Switzerland). A HPLC preparative column (ODS-3, 5 μm, 20 × 250 mm), obtained from GL Sciences Inc., Japan was used to achieve further purification of compounds.

**Analysis of the Isolated Compounds**

A JASCO P-2000 polarimeter obtained from JASCO, Tokyo, Japan, was used for measurement of optical rotations. 1D and 2D NMR spectra were obtained from a DRX-600 spectrometer (Bruker Daltonics, USA). The high-resolution mass of isolates was detected on an Agilent QTOF-LC-MS, Agilent Technologies, USA.

**Plant Material**

The aerial parts of *B. indica* were collected from desert areas of Egypt near 6th October City (El-Wahat Road; 29°58′16″N 31°01′25″E) in September 2019, and identified by Prof. Ibrahim A. El-Garf, Department of Botany, Faculty of Science, Cairo University, Egypt. A voucher specimen (BIC-2019-2) has

### Table 1. Cytotoxic Activities of Compounds 1-25 Against MCF-7, OVK-18, HCT-116, HepG2, NHDF, and CCD841.

| Compound | IC₅₀ (μg mL⁻¹) |
|----------|----------------|
|          | MCF-7 | OVK-18 | HCT-116 | HepG2 | NHDF | CCD841 |
| MeOH extract | > 200 | 7.27 ± 1.08 | > 200 | > 200 | > 400 | > 400 |
| 1        | 49.78 ± 4.88 | > 400 | < 0.1 | < 0.1 | > 400 | > 400 |
| 2        | 22.95 ± 6.22 | 4.03 ± 0.21 | 26.95 ± 4.38 | < 0.1 | > 400 | > 400 |
| 3        | 4.55 ± 0.38 | 4.00 ± 0.26 | 18.16 ± 2.20 | > 400 | > 400 | > 400 |
| 4        | > 400 | > 400 | > 400 | < 0.1 | > 400 | > 400 |
| 5        | > 400 | > 400 | > 400 | < 0.1 | > 400 | > 400 |
| 6        | > 400 | > 400 | < 200 | < 0.1 | > 400 | > 400 |
| 7        | 1.47 ± 0.22 | 82.42 ± 1.18 | > 400 | > 400 | > 400 | > 400 |
| 8        | > 400 | > 400 | 19.80 ± 8.05 | 2.88 ± 0.81 | 143.92 ± 4.90 | > 400 |
| 9        | > 400 | > 400 | 1.74 ± 1.56 | ND | > 400 | > 400 |
| 10       | > 400 | > 400 | 16.33 ± 1.95 | > 400 | ND | > 400 |
| 11       | 224.59 ± 12.11 | 1.74 ± 1.56 | ND | > 400 | > 400 | > 400 |
| 12       | 55.92 ± 23.79 | > 400 | ND | > 400 | > 400 | > 400 |
| 13       | < 0.1 | > 400 | ND | > 400 | > 400 | > 400 |
| 14       | 129.14 ± 5.91 | 21.50 ± 10.67 | > 400 | ND | > 400 | > 400 |
| 15       | > 400 | > 400 | > 400 | > 400 | > 400 | > 400 |
| 16       | > 400 | > 400 | > 400 | > 400 | > 400 | > 400 |
| 17       | > 400 | 16.33 ± 1.95 | > 400 | 151.60 ± 5.54 | > 400 | > 400 |
| 18       | > 400 | > 400 | > 400 | > 400 | > 400 | > 400 |
| 19       | > 400 | > 400 | > 400 | > 400 | > 400 | > 400 |
| 20       | > 400 | 141.79 ± 16.33 | > 400 | 284.22 ± 6.60 | > 400 | > 400 |
| 21       | > 400 | > 200 | > 400 | 159.87 ± 19.08 | > 400 | > 400 |
| 22       | > 200 | > 200 | > 200 | > 200 | > 200 | > 200 |
| 23       | 136.64 ± 3.51 | 44.31 ± 5.79 | > 400 | 178.45 ± 9.01 | > 400 | > 400 |
| 24       | > 400 | > 400 | > 400 | > 400 | > 400 | > 400 |
| 25       | > 400 | > 400 | < 0.1 | > 400 | > 400 | > 400 |
| 5-FU     | 93.7 ± 1.56 | 70.6 ± 2.28 | 44.6 ± 0.22 | > 100 | > 100 | > 100 |

ND = not determined, n = 3 ± S.E.
been kept at the herbarium of Pharmacognosy and Medicinal Plants Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.

**Extraction and Isolation of Compounds**

The aerial parts of *B. indica* were shade-dried and ground into a fine powder (1.3 kg). The powder was then extracted with 80% MeOH (7 L) 4 times to get a crude extract (138.5 g). The crude extract was partitioned into 4 major fractions, *n*-hexane, dichloromethane, ethyl acetate, and *n*-butanol. Part of the CH₂Cl₂ fraction (2 g) was subjected to fractionation with silica gel using a gradient of *n*-hexane-ethyl acetate-methanol to afford 5 fractions (D1-D5). Compound 1 (7.1 mg) was obtained after purification of fraction D1 over Sephadex LH-20 (100% methanol). Fraction D-3 (90 mg) was purified by MPLC using H₂O-MeOH (4:1:1) yielding compounds 2 (3.1 mg), and 3 (6.2 mg). The ethyl acetate fraction (2 g) was fractionated by MPLC with a normal-phase flash column (40 g) using *n*-hexane-ethyl acetate-methanol (4:1:0-0:1:1 v/v) to obtain 5 fractions (E1-E5). E2 was separated over on a Sephadex LH-20 column using methanol to obtain 3 fractions (E2-1 to E2-3). Fraction E-2-1 (46 mg) was purified by NP-TLC with dichloromethane-methanol (4.5:1) to obtain compounds 4 (6 mg), 5 (6.5 mg), 6 (7 mg), and 7 (5.5 mg). Fraction E-2.2 (30 mg) was purified by silica CC eluting with dichloromethane-methanol (4.5:1) to afford 8 (5.2 mg), and 9 (4.5 mg). Compound 10 (2.9 mg) was obtained from fraction E-2.3 following purification on Sephadex LH-20 using 100% methanol. Fraction E4 was separated on a Sephadex LH-20 column with 100% methanol to obtain 11 (2.5 mg). Fraction E5 was separated into 5 fractions (E-5-A to E-5-E) by MPLC with a reverse-phase C18 column (40 µM, 12 g) using H₂O-MeOH. Fraction E-5-A (24 mg) was partitioned over Sephadex LH-20 to obtain compound 12 (4 mg), while 13 (4.2 mg) and 14 (3.5 mg) were obtained after further purification by NP-TLC (CH₃Cl₂-MeOH: 9:1). Fraction E-5-C (89 mg) was purified by preparative HPLC to obtain compounds 15-17 (3.2, 4.5, and 5 mg, respectively). Fraction E-5-E (250 mg) was purified over ODS-18 and Sephadex yielding compounds 18 (5.6 mg) and 19 (3.7). The *n*-butanol extract (12 g) was partitioned on a Diaion HP-20 column using a gradient of H₂O-MeOH (1:0 to 0:1) to yield 5 fractions (BU-1-BU-5). BU-3 (1.1 g) was partitioned by MPLC with a RP-C18 column, followed by purification on a preparative HPLC column using a gradient of H₂O-MeOH to obtain compounds 20 (3 mg), 21 (2.3 mg), and 22 (1.2 mg). BU-4 (1.5 g) was fractionated over Biotage (ODS-18; 30 g column) to obtain 3 fractions. Fraction BU-4-3 was purified by ODS-18 eluted with a gradient of H₂O-ACN-0.1% FA to obtain 23 (8.5 mg), 24 (9.3 mg), and 25 (11.5 mg).

**In Vitro Assays for COX-2 Inhibition and Cytotoxicity**

See Supplemental information.

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**Statement of Human and Animal Rights**

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There are no human subjects in this article and informed consent is not applicable.

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**Supplemental Material**

Supplemental material for this article is available online.

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