|   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|   | 1  | Colchicine | 2  | Dehydroabietic acid | 3  | Pomiferin | 4  | Chartreusin | 5  | Noscapine | 6  | Veratridine | 7  | Aleuritic acid |
|   |   | 757 |   | 2952 |   | 5113 |   | 5159 |   | 5366 |   | 7524 |   | 7668 |
|   | 8  | Khellin | 9  | Fumagillin, alcohol I | 10 | Argemone |   |   |   |   |   |   |   | origin |
|   |   | 8519 |   | 9665 |   | 11440 |   |   |   |   |   |   |   | origin |
|   | 11 | Aristolochic | 12 | Resorufin | 13 | Aureomycin | 14 | Glaucarubine | 15 | Amygdalin | 16 | Pyrethrosin | 17 | Coumestrol |
|   |   | acid |   | 12097 |   | 13252 |   | 14975 |   | 15780 |   | 22070 |   | 22842 |
|   | 18 | Himbaefcine | 19 | Cube | 20 | Lapachone, |   |   |   |   |   |   |   | beta |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   | 26326 |
|   | 21 | Isorescinna- | 22 | Mangostin | 23 | Neohesperidin | 24 | Norlobaric | 25 | Bicuculline | 26 | Isocorydine | 27 | Curcumín |
|   |   | mine, dihydro- |   | 30552 |   | 31048 |   | acid, decarboxy- |   | 32192 |   | 32979 |   | 35611 |
|   | 28 | Solanine | 29 | Canadine (dl-) | 30 | Guercetin, dihydro- |
|   |   |   |   |   |   |   |   | 31867 |   |   |   |   |   | 36398 |
|   | 31 | Santonine, | 32 | Streptonigrin | 33 | Methoxsalen | 34 | Carbomycin | 35 | Aconitine | 36 | Fumagillin dicyclohexylamine salt |
|   | ozime |   |   | 45383 |   | 45923 |   | 51001 |   | 56464 |   | 58368 |
|   | 45 | Fungtalin | 46 | Brefeldin A |   | 89671 |   | 94600 |   | 96911 |   | 96911 |
|   | 47 | Brefeldin | 48 | Camptothecin |   | 96911 |   | 96911 |   | 96911 |   | 96911 |
|   | 49 | Riboflavin lumichrome | 50 | Lagosin |   |   |   |   |   |   |   |   | 153858 |
|   | 50 | Lagosin |   | 105388 |   |   |   |   |   |   |   |   |   | |
|   | 51 | Tirandamycin | 52 | Ascochitine | 53 | Radicin | 54 | Sporidesmolide I | 55 | Teniposide | 56 | Picrotin | 57 | Rifamycin SV |
|   |   | 107067 |   | 114344 |   | 118343 |   | 122224 |   | 122819 |   | 129536 |   | 133100 |
|   | 58 | Lankacidin C | 59 | Nystatin | 60 | Maytansine |   |   |   |   |   |   |   | 153858 |
|   | Name                  |     | Name                      |     | Name                      |     | Name                      |     | Name                      |     | Name                      |     |
|---|-----------------------|-----|---------------------------|-----|---------------------------|-----|---------------------------|-----|---------------------------|-----|---------------------------|-----|
| 61| Parthenolide          | 157035 | Streptoval C              | 169627 | Fastigillin B            | 176503 | Antibiotic X-536A         | 177406 | Staphylococcus S           | 177858 | Vermiculine               | 8140514 |
| 62|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 63|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 64|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 65|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 66|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 67|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 68|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 69|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 70|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 71| NSC250430             | 250430 |                       |     |                           |     |                           |     |                           |     |                           |     |
| 72|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 73|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 74|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 75|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 76|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 77|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 78|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 79|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 80|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 81|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 82|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 83|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 84|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 85|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 86|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 87|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 88|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 89|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 90|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 91|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 92|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 93|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 94|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 95|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 96|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 97|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 98|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 99|                       |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 100|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 101|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 102|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 103|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 104|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 105|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 106|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 107|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 108|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 109|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 110|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 111|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 112|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 113|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 114|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 115|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 116|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 117|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 118|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 119|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |
| 120|                      |     |                           |     |                           |     |                           |     |                           |     |                           |     |

The upper numbers represent those ones used in the present study. The lower numbers (underlined) can be used to get detailed information about a drug from available databases.
Figure S1

A. The influence of natural compounds (5 µM) on viable cell numbers in melanoma (DMBC11 and DMBC12) and leukemia (K562) cell cultures assessed by APA assay. Data are the mean ± SD of two independent experiments performed in triplicates.
B. The influence of natural compounds (5 µM) on viable cell numbers in melanoma (DMBC11 and DMBC12) and leukemia (K562) cell cultures assessed by flow cytometry using an automated cell viability analyzer (volumetric assay). Data are the mean ± SD of two independent experiments performed in triplicates.
Figure S2

Effects of natural compounds (5 µM) on viability of melanoma cells (DMBC11 and DMBC12) and leukemia cells (K562). Changes in cell viability were assessed by PI staining and flow cytometry and they are expressed as % of vehicle control. Data are the mean ± SD of two independent experiments performed in triplicates.
Figure S3A
The influence of natural compounds on cell distribution in cell cycle and cell death shown as accumulation in subG1. (A) Representative histograms of DMBC12 cells treated with natural compounds at a single concentration of 5 µM for 30 h are shown.
Figure S3B
Effects of lower concentrations for the most cytotoxic compounds or of longer exposure for compounds that were ineffective at 30 h.
The influence of natural compounds used at a single concentration of 5 μM on the clonogenic growth of melanoma cells. Cells were incubated in drug-containing medium for 4 h and then they were grown on agar for 14 days in drug-free medium. Cell colonies were stained and counted. Anti-clonogenic activity was expressed as percentage of control treated with vehicle (0.05% DMSO). At least two independent experiments were performed in duplicates.
| Table S2. Viability assessed in six different melanoma cell lines after 45 h of treatment with selected drugs at indicated concentration |
|---------------------------------------------------------------|
| **viability at 1 µM** |  | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|----------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| **DMBC**             |  |  |  |  |  |  |  |  |  |  |  |  |
| 2                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 3                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 4                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 5                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 6                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 7                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 8                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 9                   |  |  |  |  |  |  |  |  |  |  |  |  |
| 10                  |  |  |  |  |  |  |  |  |  |  |  |  |
| 11                  |  |  |  |  |  |  |  |  |  |  |  |  |
| 12                  |  |  |  |  |  |  |  |  |  |  |  |  |
| **viability at 0.1 µM** |  |  | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|----------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **DMBC**             |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 2                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 3                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 4                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 5                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 6                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 7                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 8                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 9                   |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 10                  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 11                  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 12                  |  |  |  |  |  |  |  |  |  |  |  |  |  |
Viability was measured by flow cytometry after PI staining in six different melanoma cell lines DMBC2, DMBC8, DMBC9, DMBC10, DMBC11 and DMBC12. Data expressed as % of control are means ± SD of two independent experiments conducted in triplicates.
Figure S5.
Dose-response curves prepared for compounds exerting anti-clonogenic and/or cytotoxic potentials. Blue curves, anti-clonogenic activity; black curves, cytotoxic activity; DMBC11 (filled square) and DMBC12 (open square) cell lines.
Table S3. Activity profiles of natural compounds selected in this study prepared based on a literature search. Only the main biological activities of compounds are included.

| Compound and its source | Main biological activities |
|-------------------------|-----------------------------|
| **Nanaomycin A**  
*Streptomyces rosa* | selective inhibitor of DNMT3B (DNA methyltransferase 3B) that reactivates the expression of silenced tumor suppressor gene RASSF1A in human cancer cells [1]; |
| **Illudin M**  
*Omphalotus illudens* | alkylation agent of DNA, RNA and proteins [2]; |
| **Geldanamycin**  
*Streptomyces hygroscopicus* | inhibitor of Hsp90 (heat shock protein 90) [3]; |
| **Bryostatin 1**  
*Bugula neritina* | highly potent activator of PKC (protein kinase C) [4]; ligand for TLR4 (Toll-like receptor 4) triggering NF-κB (nuclear factor-kappa B) activity and the expression of interleukins (IL-5, IL-6, IL-10) and chemokines: RANTES (regulated on activation normal T cell expressed and secreted) and MIP1-α (macrophage inflammatory protein 1α) [5]; activator of STAT1 (signal transducer and activator of transcription 1) activity through an IFNγ (interferon gamma) autocrine loop [6]; enhancer of CD4+ T cell-mediated recognition of melanoma cells, inducer of the expression of costimulatory molecules (CD80 and CD86) in melanoma cells prolonging immune response, inducer of melanoma cell differentiation [7]; |
| **Siomycin A**  
*Streptomyces sioyaensis* | inhibitor of the oncogenic transcription factor FoxM1 (forkhead box M1) and selective inducer of apoptosis in transformed cells [8,9]; proteasome inhibitor stabilizing the expression of p21, Mcl-1, p53 and Hdm-2 [10]; inhibitor of MELK (maternal embryonic leucine zipper kinase) [11]; |
| **Fumitremorgin C**  
*Aspergillus elongatus, Aspergillus fumigatus* | inhibitor of ABCG2/BCRP (breast cancer resistance protein) [12]; inhibitor of the AKT pathway [13]; |
| **Fumagillin**  
*Aspergillus fumigatus* | inhibitor of MetAP-2 (methionine aminopeptidase-2) [14]; anti-angiogenic agent reducing the expression of cyclin E2, ALCAM (activated leukocyte cell adhesion molecule) and ICAM-1 (intercellular adhesion molecule-1) [15]; inhibitor of FGFR1 (fibroblast growth factor receptor 1) [16]; |
| **Michellamine B**  
*Ancistrocladus korupensis* | inhibitor of HIV (human immunodeficiency virus) reverse transcriptase and human DNA polymerases α and β [17]; inhibitor of PKC [18]; mitochondria-protective agent against adenosine diphosphate- and Fe2+-induced lipid peroxidation [19]; |
| Compound                  | Description                                                                                                                                                                                                 |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Pentoxifylline**       | competitive non-specific phosphodiesterase inhibitor [20]; activator of PKA (protein kinase A), inhibitor of TNF-α (tumor necrosis factor alpha) production [21,22]; inducer of lipid peroxidation increasing the activity of glutathione-S-transferase and leading to glutathione depletion [23]; inhibitor of MMP-2 and MMP-9 (metalloproteinase-2 and -9) secretion [24]; inducer of apoptosis related to up-regulation of DR4 and DR5 (death receptor-4 and -5) expression on cell surface, and down-regulation of the expression of anti-apoptotic proteins [25]; |
| **Croton Factor F1**     | unidentified                                                                                                                                                                                               |
| **Helenin**              | unidentified                                                                                                                                                                                               |
| **Nordracorubin**        | unidentified                                                                                                                                                                                               |
| **Confertifoline**       | antimicrobial agent [26];                                                                                                                                                                                    |
| **Wortmannin**           | inhibitor of MAPK (mitogen-activated protein kinase) [27]; inhibitor of PI3K (phosphoinositide-3-kinase) [28];                                                                                                   |
| **4-Ipomeanol**          | unidentified                                                                                                                                                                                               |
| **Crassin**              | inhibitor of allogeneic leukocyte reaction as well as antigen-specific activation of CD4+ T cells by bone marrow-derived dendritic cells [29];                                                              |
| **Castanospermine**      | inhibitor of selected glucosidase enzymes [30];                                                                                                                                                            |
| **Lonchocarpic Acid**    | unidentified                                                                                                                                                                                               |
| **Pleurotin**            | inhibitor of HIF-1α (hypoxia-induced factor-1alpha) and VEGF (vascular endothelial growth factor) expression [31];                                                                                          |
| **Maytansine**           | inhibitor of the microtubule assembly by binding to tubulin at or near the rhizoxin-binding site [32];                                                                                                       |
| **Streptonigrin**        | inhibitor of DNA/RNA synthesis and topoisomerase II [33]; inhibitor of β-catenin/TCF signaling [34];                                                                                                         |
| **Toyocamycin**          | inhibitor of RNA synthesis and splicing, ribosome maturation and function [35,36,37];                                                                                                                     |
| **Colchicine**           | inhibitor of microtubule polymerization by binding to tubulin [38]; inducer of apoptosis accompanied by loss of mitochondrial membrane potential, activator of caspase-3 and -9, and inhibitor of Bcl-2 (B-cell leukemia/lymphoma 2) expression [39]; |
| **Echinomycin A**        | DNA intercalator targeting HIF-1α [40]; suppressor of NOTCH1, MYC, AKT, mTOR signaling [41];                                                                                                               |
| Name                  | Species                                | Description                                                                                                                                                                                                 |
|-----------------------|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cucurbitacin E        | *Cucurbitaceae*                        | suppressor of NF-κB activity [42]; inducer of caspase-3-mediated apoptosis [43]; inhibitor of VEGFR2 (vascular endothelial growth factor receptor 2)-mediated Jak-STAT3 and MAPK signaling pathways [44]; |
| Didemnin B            | *Trididemnum solidum*                  | inhibitor of DNA and protein synthesis [45];                                                                                                                                                                |
| Tubulosine            | *Pogonopus tubulosus*                  | inhibitor of peptide chain elongation during protein synthesis [46];                                                                                                                                         |
| Tetrocarcin A         | *Micromonospora*                       | inhibitor of the anti-apoptotic function of Bcl-2 [47]; activator of intrinsic pathway of apoptosis, inducer of Hsp70 and Hsp110 expression [48];        |
| Vincristine           | *Catharanthus roseus*                  | inhibitor of microtubule assembly by binding to tubulin dimmers [49];                                                                                                                                       |
| Bactobolin            | *Pseudoisononas*                       | unidentified                                                                                                                                                                                                |
| Helenalin             | *Arnica montana,*                      | inhibitor of NF-κB [50]; selective inhibitor of telomerase [51];                                                                                                                                              |
| Cytochalasin H        | *Arnica chamissonis foliosa*           | inhibitor of cytoskeletal reorganization [52];                                                                                                                                                             |
| Daunorubicin (43)     | *Streptomyces peucetius*               | inhibitor of topoisomerase II [53];                                                                                                                                                                          |
| Hispanolone           | unidentified                            |                                                                                                                                                                                                              |
| Geldanamycin analog   | *Streptomyces hygroscopicus*           | inhibitor of Hsp90 [54]; inducer of MITF (microphthalmia-associated transcription factor) expression [55]; inhibitor of cytochrome P450 enzymes: CYP3A4/5 and CYP2C19 [56]; |
| Rhizoxin              | *Rhizopus microsporus*                 | inhibitor of cell division through binding to β-tubulin and disrupting microtubule formation [57];                                                                                                             |
| Baccatin III          | *Taxus brevifolia*                     | inhibitor of spindle function, inducer of caspase-10-dependent apoptosis [58];                                                                                                                           |
| Imidazoquinoline      | *Fusarium solani*                      | inducer of TLR7-mediated immune cell activation [59];                                                                                                                                                      |
| Rotenone              | *Lonchocarpus nicou*                   | inhibitor of the transfer of electrons from iron-sulfur centers in complex I to ubiquinone in electron transport chain [60];                                                                           |
| Chaetochromin         | *Chaetomium spp.*                      | inhibitor of DNA, RNA and protein synthesis [61];                                                                                                                                                           |
| Fastigilin B          | *Baileya multiradiata*                 | unidentified                                                                                                                                                                                                |
| Physalin B            | *Physalis alkekengi,*                  | inhibitor of the ubiquitin-proteasome pathway [62]; inducer of apoptosis via JNK (c-Jun N-terminal kinase) and/or ERK (extracellular signal-regulated kinase) activation, decreases androgen receptor expression [63]; inducer of mitochondria-mediated apoptosis pathway [64]; |
| Parthenin             | *Parthenium hysterophorus*             | modulator of oxidative phosphorylation [65];                                                                                                                                                                |
| Teniposide            | *Taxus brevifolia*                     | inhibitor of DNA synthesis that forms a complex with topoisomerase II and DNA [66];                                                                                                                       |
Valinomycin
Streptomyces tsusimaensis
Streptomyces fulvissimus

natural ionophore with potassium-specific transporter activity [67].

References to Table S3

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