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SHORT COMMUNICATION



## Cytotoxicity of isoflavones from *Millettia dura*

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### ABSTRACT

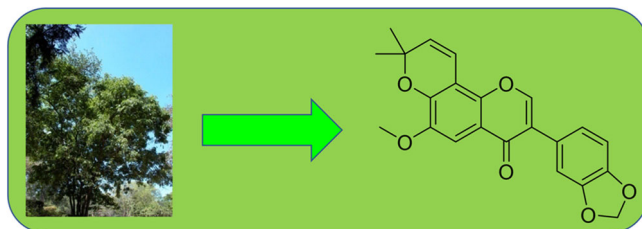
The first phytochemical investigation of the flowers of *Millettia dura* resulted in the isolation of seven isoflavones, a flavonol and a chalcone. Eleven isoflavones and a flavonol isolated from various plant parts from this plant were tested for cytotoxicity against a panel of cell lines, and six of these showed good activity with IC<sub>50</sub> values of 6–14 μM. Durmillone was the most active with IC<sub>50</sub> values of 6.6 μM against A549 adenocarcinomic human alveolar basal epithelial cancer cell line with low cytotoxicity against the non-cancerous cell lines BEAS-2B (IC<sub>50</sub> = 58.4 μM), LO2 hepatocytes (IC<sub>50</sub> 78.7 μM) and CCD19Lu fibroblasts (IC<sub>50</sub> >100 μM).

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*Millettia dura*; Leguminosae; isoflavone; cytotoxicity



## 1. Introduction

Cancer is a manifestation of the cells that grow out-of-control and invade healthy tissues. Different cancer types present different causal effects, manifestations and prognoses (WHO 2018). Inherited genetic defects, infections, for example, by Hepatitis A, HPV, HBV & HCV, EB-V, HTLV-1 and HIV (WHO 2018), environmental factors and poor lifestyle can damage DNA increasing cancer risks (Iqbal et al. 2017). Body cells are able to detect DNA damage and various repair mechanisms are then initiated. As a last resort, cells exhibiting too severe DNA damage undergo apoptosis. However, in some cases, DNA damage is

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not detected or not repaired quickly enough and can then be a cause of cancer (Haque et al. 2016). Cancer is a threat to global public health (WHO 2018), taking the lead cause of death in developed countries and the second contributor to fatality in Africa (Akhir et al. 2011). In 2018, the global cancer burden shot to 18.1 million new cases with 9.6 million deaths, and it is estimated that approximately 29.5 million new cases and 16.4 million cancer-related deaths will occur by 2040 (WHO 2018).

In the search for new anticancer drugs, isoflavonoids are attracting interest of researchers and have been tested for the treatment of ovarian, breast, cervical, pancreatic, and prostate cancer (Haque et al. 2016). *Millettia* species are good sources of isoflavonoids (Yenesew et al. 1996; Tu et al. 2019); herein, we report the first phytochemical investigation of the flowers, the cytotoxicity of 11 isoflavones and a flavonol isolated from *M. dura* against a panel of cell lines.

## 2. Results and discussion

Phytochemical investigation of the flowers of *Millettia dura* resulted in the identification of six known isoflavones: calopogonium isoflavone A (1) (Yenesew et al. 1996), jamaicin (2) (Yenesew et al. 1997), durmillone (3) (Yenesew et al. 1997), durallone (4) (Yenesew et al. 1996), ichthynone (5) (Ren et al. 2016), formononetin (6) (Yenesew et al. 1997) and 6-methoxycalopogoniumisoflavone A (7) (Yenesew et al. 1997) and the flavonol kaempferol (8) (Markham 1982) and the chalcone 4,2'-dihydroxy-4'-methoxychalcone (9) (Markham 1982). The structures are given in Supporting Information (Figure S1).

Eleven isoflavones and a flavonol isolated from *M. dura* (Yenesew et al., 1996, 1997) along with Paclitaxel (standard) were evaluated for cytotoxicity against two cancer cell-lines; A549 (adenocarcinomic human alveolar basal epithelial cells) and HepG2 (human liver cancer cell line), and three normal cell-lines; BEAS-2B (lung/bronchus cell line, epithelial virus transformed), LO2 (normal human hepatocytes) and CCD (19Lu normal human lung fibroblasts). The results are shown in Table 1.

**Table 1.** Cytotoxicity (IC<sub>50</sub> in  $\mu$ M) of some isoflavones isolated from *Millettia dura*.

Compound	Normal cell-line			Cancer cell-line	
	BEAS-2B(N)	LO2 Liver (N)	CCD19Lu (N)	A549 (C)	HepG2 (C)
Calopogonium isoflavone A (1)	>100	6.3 $\pm$ 0.8	>100	>100	24.2 $\pm$ 2.9
Jamaicin (2)	>100	68.7 $\pm$ 10.6	>100	11.4 $\pm$ 5.0	44.3 $\pm$ 3.1
Durmillone (3)	58.4 $\pm$ 2.8	78.4 $\pm$ 2.8	>100	6.6 $\pm$ 1.2	>100
Durallone (4)	>100	>100	>100	>100	>100
Ichthynone (5)	>100	>100	NT	>100	>100
Kaempferol (8)	57.1 $\pm$ 6.4	>100	NT	>100	>100
Isoerythrin-A-4'-prenyl ether (10)	21.2 $\pm$ 3.8	55.8 $\pm$ 3.1	NT	14.3 $\pm$ 1.2	37.7 $\pm$ 3.8
Maximaisoflavone-J (11)	55.8 $\pm$ 7.9	38.6 $\pm$ 2.2	NT	48.5 $\pm$ 9.0	>100
Maximaisoflavone-G (12)	100	67.5 $\pm$ 1.5	NT	84.5 $\pm$ 7.3	>100
7,2'-Dimethoxy-3',4'-methyleneedioxisoflavone (13)	>100	>100	>100	>100	88.4 $\pm$ 4.1
Maximaisoflavone D (14)	47.9 $\pm$ 3.8	29.5 $\pm$ 3.2	49.6	>100	10.4 $\pm$ 1.1
Isojamaicin (15)	>100	75.5 $\pm$ 2.8	>100	>100	34.5 $\pm$ 3.9
Paclitaxel (standard)	<0.1	<0.1	<0.1	0.0033	0.19

Key: (N)-Normal cell-line, (C)-Cancer cell-line, NT-Not Tested. Normal cell-lines: BEAS-2B (lung/bronchus cell line, epithelial virus transformed), LO2 (normal human hepatocytes) and CCD (19Lu normal human lung fibroblasts). Cancer cell-lines: A549 (adenocarcinomic human alveolar basal epithelial cells) and HepG2 (human liver cancer cell line). The structures of the tested compounds are given in Supporting Information (Figure S1).

Durmillone (**3**) is the most active compound showing selective cytotoxicity against A549 cancer cell line ( $IC_{50}$   $6.6 \pm 1.2 \mu\text{M}$ ) with low cytotoxicity towards the normal cell lines BEAS-2B ( $IC_{50}$   $58.4 \pm 2.8 \mu\text{M}$ ), CC919Lu ( $IC_{50} > 100 \mu\text{M}$ ) and LO2 ( $IC_{50}$   $78.4 \pm 2.8 \mu\text{M}$ ). The anticancer activity of durmillone against leukaemia CCRFCM Cells have been reported (Adem et al. 2019). Jamaicain (**2**) ( $IC_{50}$   $11.4 \pm 5.0 \mu\text{M}$ ) and isoerythrin-A-4'-prenyl ether (**10**) ( $IC_{50}$  of  $14.3 \pm 1.2 \mu\text{M}$ ) also showed good activity against A549 cell-line with lower cytotoxicity against normal cell-lines (Table 1). Isojamaicin (**15**), which differs from jamaicin by the position of methoxy group in ring B, was inactive against A549 cells but showed moderate activity ( $IC_{50}$   $34.5 \pm 3.9 \mu\text{M}$ ) against HepG2 cells as jamaicin ( $IC_{50}$   $44.3 \pm 3.1 \mu\text{M}$ ). Apart from maximosoflavone D (**14**),  $IC_{50}$  of  $10.4 \pm 1.1 \mu\text{M}$  against HepG2 cancer cell-line, all the active compounds possess a 2, 2-dimethylchromene group in ring A at C-7/C-8. This extra  $C_5$  unit, which is formed through cyclisation of isoprenoid moiety at C-8, increases lipophilicity and membrane permeability as suggested by Sasaki et al. (2011). The isomeric compounds jamaicin (**2**) and isojamaicin (**15**) were also tested against DLD-1WT colorectal adenocarcinoma cells and DLD-1 DKO Bax-Bak double knockout, apoptosis-resistant colorectal adenocarcinoma cells. Bax and Bak are multidomain pro-apoptotic members of the Bcl-2 family of proteins that regulate mitochondria-mediated apoptosis by direct modulation of mitochondrial membrane permeability (Mizuta et al. 2007). Recent studies demonstrated variety of natural small-molecules could induce autophagic cell death in apoptosis-resistant cancer cells (Law et al. 2017). Jamaicain showed moderate activity against the DLD-1WT cells ( $IC_{50} = 20.9 \pm 0.9 \mu\text{M}$ ) without toxicity against the DLD-1 DKO cells ( $IC_{50} > 100 \mu\text{M}$ ). Interestingly the isomeric isoflavone isojamaicin was cytotoxic against both cancer cell lines ( $IC_{50} = 14.5 \pm 3.4 \mu\text{M}$  and  $IC_{50} = 13.5 \pm 0.6 \mu\text{M}$ , respectively) and this results showed the need for further study of isojamaicin in drug resistant cancer therapy. The only flavonol tested, kaempferol (**8**), was cytotoxic to the normal cell line BEAS-2B with  $IC_{50}$  value of  $57.1 \pm 6.4 \mu\text{M}$  but did not show activity to the other cell lines ( $IC_{50} > 100 \mu\text{M}$ ).

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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