Brazilian Journal of Biology®

ISSN 1519-6984 (Print)
ISSN 1678-4375 (Online)

Original Article

In vitro anti-leukemia, antioxidant, and anti-inflammatory properties of *Lantana camara*

Propriedades antileucêmicas, antioxidantes e anti-inflamatórias *in vitro* da *Lantana camara*

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Abstracts

It has been demonstrated that *Lantana camara* possesses several therapeutic properties that can be used to treat various human diseases, including dermatological and gastrointestinal conditions, tetanus, malaria, and tumours. In this investigation, every collected part of *L. camara* was extracted with absolute methanol to examine its antioxidant capacity using the DPPH assay and its anti-leukemia activity on two AML cell lines, MOLM-13 and MV4-11. In addition, anti-inflammatory effectiveness was evaluated. The results show that extracts from various sections of *L. camara* have a significant ability to neutralize free radicals, as indicated by their EC50 values. Most of the extracts had values less than 100 µg/ml, with the flower extract having an even lower value of less than 50 µg/ml. Experiments on two AML cell lines showed that the anti-leukemia effects of the extracts were remarkable, with the most potent impact belonging to the root extract (IC50 was 9.78 ± 0.61 and 12.48 ± 1.69 for MOLM-13 and MV4-11 cell lines). The antitumor effect of the extracts was determined to be time- and dose-dependent and did not correlate with antioxidant capacity. Furthermore, when BJ cells were exposed to *L. camara* root and leaf extracts, their migratory potential was dramatically reduced compared to untreated cells. The extracts demonstrated potential anti-inflammatory capabilities by lowering NO production in LPS-induced BJ cells.

Keywords: *Lantana camara*, antioxidant, anti-cancer, AML, anti-inflammatory.

Resumo

Foi demonstrado que *Lantana camara* possui diversas propriedades terapêuticas que podem ser utilizadas para tratar uma variedade de doenças humanas, incluindo condições dermatológicas e gastrointestinais, tétano, malária e tumores. Nesta investigação, cada parte coletada de *L. camara* foi extraída com metanol absoluto para examinar sua capacidade antioxidante utilizando o ensaio DPPH e sua atividade antileucêmica em duas linhagens celulares de LMA, MOLM-13 e MV4-11. Além disso, foi avaliada a eficácia anti-inflamatória. Os resultados mostram que os extratos de várias partes de *L. camara* têm uma capacidade significativa de neutralizar os radicais livres, como demonstrado pelos seus valores de EC50. A maioria dos extratos apresentava valores inferiores a 100 g/ml, com o extrato de flores apresentando um valor ainda mais baixo, inferior a 50 µg/ml. Experimentos em duas linhagens celulares de LMA mostraram que os efeitos antileucêmicos dos extratos foram notáveis, com o efeito mais forte pertencente ao extrato de raiz (IC50 foi 9,78 ± 0,61 e 12,48 ± 1,69 para linhas celulares MOLM-13 e MV4-11). O efeito antitumoral dos extratos foi determinado de maneira dependente do tempo e da dose e não se correlacionou com a capacidade antioxidante. Além disso, quando as células BJ foram expostas aos extratos de raiz e folhas de *L. camara*, o seu potencial migratório foi drasticamente reduzido em comparação com as células não tratadas. Os extratos acima mencionados demonstraram potenciais capacidades anti-inflamatórias ao reduzir a produção de NO em células BJ induzidas por LPS.

Palavras-chave: *Lantana camara*, antioxidante, anticancerígeno, AML, anti-inflamatório.

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Received: October 26, 2023 – Accepted: March 31, 2024

1. Introduction

Herbs used to play a crucial role in human disease treatment that was found to have existed 60,000 years ago in the eastern (Nontokozo and Mthokozisi, 2018). Many pharmaceutical products derived from plants have been applied in modern medicine (Yuan et al., 2016). *Lantana camara* is a member of *Lantana* L genus, which is mainly distributed in tropical and subtropical America, with a few in tropical Asia and Africa (Sousa and Costa, 2012). *L. camara* is widely recognized as a ubiquitous and deleterious weed species, known for its ability to induce hepatotoxicity in animals that engage in grazing activities (Al-Hakeim et al., 2021; Machado et al., 2023). Lantadene A extracted from its leaf is likely responsible for its toxicity to animals. It can also harm humans (Forrester and Petty, 2020). However, it is unclear what may produce toxic effects in humans. The onset of symptoms in humans may occur 2.5–6 hours after ingestion. The reported symptoms more commonly include gastrointestinal irritation (vomiting, abdominal pain or cramping, nausea, diarrhoea, throat or mouth irritation) and less frequently agitation, tachycardia, drowsiness, lethargy, respiratory distress, mydriasis, ataxia, weakness, and cyanosis (Wolfson and Solomons, 1964).

Contrarily, it has been shown that *L. camara* exhibits several therapeutic qualities that can be utilized to treat diverse human maladies, including dermatological and gastrointestinal disorders, tetanus, malaria, and tumours (Ghisalberti, 2000). This plant found and isolated various phytochemicals, including terpenoids, steroids, flavonoids, oligosaccharides, glycosides and naphthoquinones (Sousa and Costa, 2012). Many papers have been reported that this plant showed strong antioxidant capacity (Benites et al., 2009; Bhakta-Guha and Ganjewala, 2009); the antibacterial effects on *B.subtilis*, *B.cereus*, *S.typhi*, *P.aeruginos*, *S.aureus* (Barre et al., 1997; McGaw et al., 2005; Rasyid et al., 2020; Saleh et al., 1999); anti-inflammation (Wu et al., 2020) and cytotoxic effects on human cancers such as hepatocellular carcinoma, cervical cancer, oral cancer, lung cancer, brain cancer, prostate cancer (Badgujar et al., 2017; Bisi-Johnson et al., 2011; Meenakshi Sharma, 2020). With the increasing of cancer cases, the anti-cancer activity of plant extracts is a promising research orientation (Solowey et al., 2014).

Leukaemia is in the world's top 15 most common cancers, accounting for approximately 2.5% of all cancers, with 474.519 new cases and approximately 3.1% with 311.594 dead cases in 2020 (Sung et al., 2021). Recently, there was evidence confirmed that the compounds isolated from *L. camara,* such as lantadenes and derivation, had an effect on leukaemia cell line HL-60 with the IC50 range from 19 to 100 µg/ml and also induced apoptosis through regulating *Bcl-2* and *Bax* expression as well as cell cycle arrest in the G0/G1 phase (Sharma et al., 2008; Sharma et al., 2007). The activation of apoptosis on cancer cells was also proved to influence several phytochemicals from *L. camara,* including 15 pentacyclic triterpenoids (Litaudon et al., 2009). In this study, every collected part of *L. camara* was extracted with absolute methanol to investigate the antioxidant ability via DPPH assay and anti-leukaemia activity on two acute myeloid leukaemia (AML) cell lines, MOLM-13 and MV4-11. Moreover, anti-inflammatory efficacy was evaluated.

2. Materials and Methods

2.1. Plant materials and sample preparation

Lantana Camara was harvested in suburban districts in Ho Chi Minh City, Vietnam (Ly et al., 2020). The plants were washed, drained and dispensed into five parts: roots, stems, leaves, flowers and fruits. The samples were oven-dried and ground into fine powder. The extracts were obtained using the maceration method with a pure solvent of methanol.

2.2. Phytochemical analysis

The chemical composition of the extract was screened by featured chemical reactions, including Mayer and Wagner reagents for alkaloid testing (Jha et al., 2012); Keller-Kiliani reaction for cardiac glycoside detection; Fehling's solution for reducing sugar detection (Ayoola et al., 2008); reducing $FeCl_3$ reaction for dawning polyphenols presence (Macwilliam and Wenn, 1972); saponin foam formation (Edeoga et al., 2005); tannin-gelatin reaction (Baughman, 1927); and proanthocyanidins in acidic pH solution (Liu, 2012).

2.3. Free radicals scavenging activity

The modified α, α-diphenyl-β-picrylhydrazyl (DPPH) free radical scavenging method described by Hatano et al. (1988) was used for detecting the antioxidant of the extracts (Bui et al., 2019; Hatano et al., 1988). The assays were carried out by using the protocol described in detail elsewhere (Bui et al., 2019). The nonlinear regression equations were developed to determine the EC50 value.

2.4. Cell lines and cell culturing

Two AML-derived cell lines were used for studying: MOLM-13 cell harbouring the *FLT3-ITD* in heterozygous and MV4-11 cell harbouring the *FLT3-ITD* in homozygous stably expressing FLT3 mutant protein (Beverly et al., 1987; Matsuo et al., 1997; Quentmeier et al., 2003).

The cells were cultured in Roswell Park Memorial Institute 1640 medium (Sigma-Aldrich) supplemented with 10% fetal bovine serum (Thermofisher Scientific), 100 IU/ml penicillin and 0.1 mg/ml streptomycin (Sigma-Aldrich) in a humidified incubator containing 5% CO_2 at 37°C. The sub-culture was conducted every three days with approximately 80% flask coverage.

2.5. Trypan blue exclusion assay

Trypan blue was utilized to ascertain the number of viable cells (Strober, 2015). The cell suspension was mixed with 0.4% trypan blue at a ratio of 1:1, and a hemocytometer was used to manually count the cells (Ly et al., 2013).

2.6. Cytotoxic assay

Cytotoxicity effects of the extracts on two AML cell lines were carried out by adding the extracts at the concentration of 0 to 100 µg/ml into the cell biomass at the density of $2x10^5$ cells/ml for 72 hours. A phase-contrast microscope was used for cell morphological change observation. The MV4-11 cell response to the root extract at 20 µg/ml

was also continuously monitored for six days after trial and at the different cell initial densities.

2.7. MTT assay

Fibroblasts (ATCC® CRL-2522TM BJ cells) were seeded in 96-well plates with a $1x10^5$ cells/mL density. After 24 hours of incubation, *L. camara* extracts were added into wells at different concentrations. The cells were exposed to the treatment approximately before indicating cell viability. The cells were separated from the medium before doubly washing with DPBS (Stemcell, Singapore). A volume of 100 µL basal RPMI medium supplemented with 10% 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide solution (MTT, Sigma-Aldrich, USA) was added into wells (Florento et al., 2012). After a 3-hour of incubation, the medium was replaced by 100 µL of DMSO (Dimethyl sulfoxide, Sigma-Aldrich, USA); the plates were gently shaken for 2 minutes before 490 nm absorbance determination. The cell viability (%) was computed as the percentage of the absorbance of the test/ the absorbance of the negative control performed with DMSO.

2.8. Migration assay

The migration assay was performed on BJ cells. First, BJ cells were examined for cytotoxicity against *L. camara* root and leaf extracts using the MTT assay. The concentration of these extracts at 50 µg/ml that was non-toxic to BJ cells was subsequently determined. Second, BJ cells were seeded at a density of 35,000 per well and incubated until confluence was reached. A 200 µl pipette tip was used in each well to produce a scratch (Addis et al., 2020). The media was removed, and the cells were then cleansed with phosphate-buffered saline before adding the medium that had been conditioned with extracts from both roots and leaves.

Optical microscopy was employed to analyze five distinct regions along the scratches of each well at two-time points: immediately after the damage was induced (0 hours) and after a 24-hour interval. The distance between the edges of the scratch was measured using the software Image J. The results were then reported as a percentage, representing the closure of the region with the control group of untreated cells.

2.9. Determination of NO production

BJ cells at a density of 1×10^5 cells/ml were cultured in a 24-well plate for 24 hours. Subsequently, the cells were subjected to pre-incubation with extracts derived from the roots and leaves of *L. camara* (50µg/ml) at a temperature of 37 °C for 1 hour. The cells were incubated at a consistent temperature for 24 hours in the presence of 1 µg/ml of lipopolysaccharide (LPS). After incubation, nitrite concentration in the culture media was assessed to gauge nitric oxide (NO) synthesis. In this experiment, a total volume of 100 µl of the cell culture medium was combined with an equal volume of Griess reagent (0.1% naphthylethylenediamine dihydrochloride and 1% sulfanilamide in 2.5% phosphoric acid). The resulting mixture was then subjected to incubation at room temperature for 10 minutes. Subsequently, the optical density at a wavelength of 540 nm was determined using a microplate reader. Control groups consisted of cells that were treated with LPS and cells that did not get treatment with *L. camara* extracts. A blank sample consisting of fresh culture media was employed in each experiment.

2.10. Data analysis

The experiments were performed in triplicate. Data were calculated using GraphPad Prism software version 9.0.0. Significant differences were determined by p-value with p-value less than 0.033 (*); 0.002 (**); 0.0002 (***); 0.0001 (****). Data were presented as mean ± standard error of the mean.

3. Results and Discussion

3.1. The diversity of phytochemicals in L. camara

The phytochemical analysis of L. camara extracts suggested the presence of many secondary metabolites, including alkaloid, coumarin, flavonoid, anthocyanin, cardiac glycoside, tannin, reduced sugar, and polyuronid compounds (Table 1).

The crude plant extracts that were used for investigation were prepared by conducting the maceration method. This method was known for high efficiency and suitable for the extraction of active ingredients in medicinal plants (Handa et al., 2008). The amount of 30 - 40 grams of dried powder of different herbal parts was extracted, and the yield was measured. The highest yield of crude extraction is leaf powder with an efficiency of 19.70% (and 19.51%, 13.48%, 8.02% and 5.52% for flower, fruit, root and stem powder, respectively). The extraction yield in this study was more effective than that reported in the previous paper, which showed that the efficiency of *L. camara* leaf extraction with water was 6.10% (Kalita et al., 2011).

3.2. Cytotoxic effect

To test the anti-proliferation effects, MOLM-13 and MV4-11 cells were exposed to the extracts at different concentrations for 72 hours. In the higher concentration of extracts, the cell viability was more attenuated (Figures 1 and 2, left panels). The morphology changes

Table 1. Secondary metabolites groups existing in *L. camara*.

Chemical groups	The presence in the extract*
Alkaloids	+
Cardiac glycoside	+
Phenolic compounds	+
Anthocyanosid	-
Proanthocyanidin	+
Tanins	+
Saponin	+
Reducing sugar	+
Organic acids	+

* (-): Absence (+): Presence.

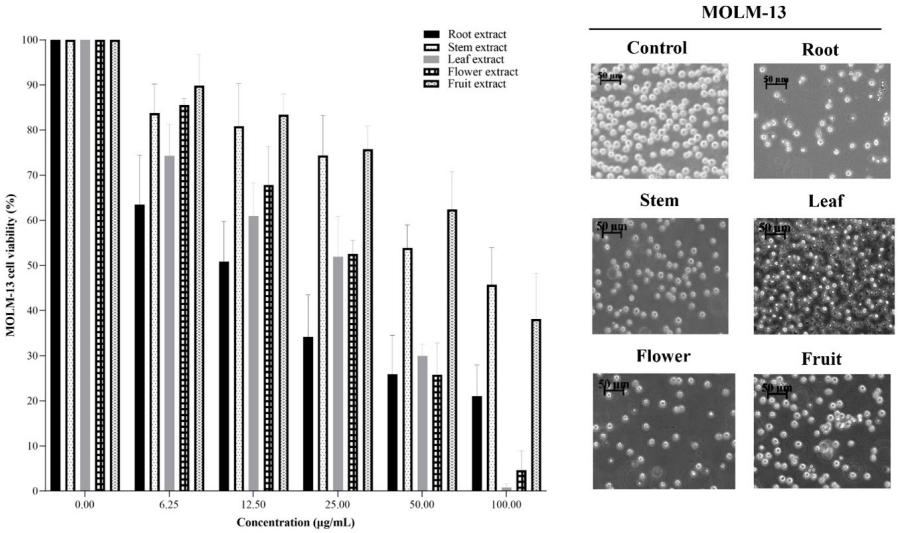


Figure 1. The anti-leukaemia capacity of the *L. camara* extracts on MOLM-13 cells. A concentration of 1 x 10^5 cells/ml of MOLM-13 was subjected to co-cultivation with varying concentrations (ranging from 6.25 µg/ml to 100 µg/ml) of *L. camara* extracts for 72 hours.

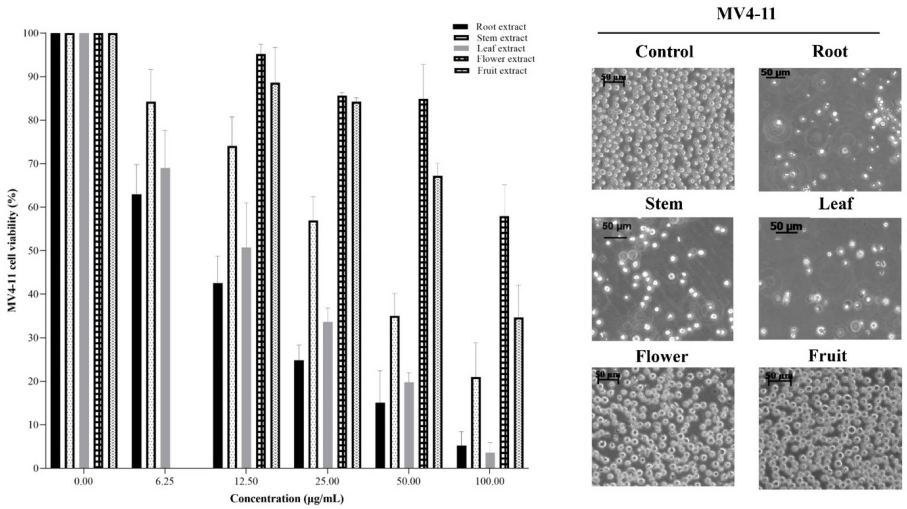


Figure 2. The anti-leukaemia capacity of the *L. camara* extracts on MV4-11 cells. A concentration of 1 x 10^5 cells/ml of MOLM-13 was subjected to co-cultivation with varying concentrations (ranging from 6.25 µg/ml to 100 µg/ml) of *L. camara* extracts for 72 hours.

were monitored in parallel with the cytotoxicity experiment. Cells were observed after 72 h exposure to the treatment at different concentrations of *L. camara* extracts. The gradual death of leukaemia cells was noticed in the increasing concentration of extracts from all five plant parts (Figures 1 and 2, right panels). The results showed that the experiments treated with the root, stem and leaf extracts had significant differences in the density of living cells compared to others. Cell debris was found in the 100 µg/ml concentrations - wells for the root, stem and leaf extracts. The growth-inhibiting effects of *L. camara* extracts on these cells were found to be dose-dependent. The inhibitory impact of the extracts on MV4-11 seemed to be less sensitive than that on MOLM-13, especially flower extract. The IC50 values calculated on MOLM-13 were 9.78 ± 0.61, 12.99 ± 0.99, 30.56 ± 1.89, 68.86 ± 3.47 and 123.00 ± 9.50 (µg/ml) for root, leaf, stem, flower and fruit extracts. The IC50 values calculated on MV4-11 were 12.48 ± 1.69, 20.02 ± 2.00, 46.62 ± 2.69, 76.10 ± 11.32, and 141.30 ± 14.00 (µg/ml) for root, leaf, flower, stem and fruit extracts (Figure 3A). Except for the fruit extract, the IC50 for all other extracts on both cell lines was less than 100 ug/ml, indicating potent cytotoxicity for a crude extract.

The effect of *L. camara* root extract was also tested on THP-1 cells (cells with FLT3-WildType), and the results shown in Figure 3B with IC50 is 48.92 ± 4.1 µg/ml indicated that this cell was also sensitive to *L. camara* root extract like MOLM-13 and MV4-11.

The anti-leukaemia effect of the root extract was further investigated in different initial cell densities and expanding

exposed time. The density of 10^4 to $5x10^5$ cells/ml of MV4-11 and MOLM-13 were used for cell density optimization. The results indicated no statistical difference among the tested density groups (Figure 4A). The growth inhibition of MV4-11 and MOLM-13 cells by *L. camara* root extracts was illustrated in a time-dependent manner (Figure 4B). After the time point of 72 hours of treatment, the cell viability promptly collapsed.

3.3. Antioxidant effect

The ability of free electrons or hydrogen atoms to donate establishes a reducing capacity for secondary compounds that leads to the antioxidant activity of plant extracts (Santos Sánchez et al., 2019). The DPPH method, which uses a stable free radical, was first described by Marsden S.Blois in 1958 and is widely used for detecting free radical scavengers and hydrogen atom dedicator agents (Blois, 1958). The extracts from different parts of *L. camara* were evaluated for the antioxidant effect by performing the DPPH assays.

The floral extract demonstrated the most significant influence when trapped ginned over 80% of DPPH radical at the dose of 62.5 µg/ml (Figure 5). The root and leaf extracts exhibited comparable DPPH scavenging tendencies. The extract from the stem exhibited the least significant effect, with a DPPH trapping rate of 80% at a concentration of 500 µg/ml. The EC50, representing the half-maximal effective concentration, was determined using nonlinear regression analysis. In the context of dose-response studies, the EC50 value denotes the concentration of the extract that elicits a reaction that is half of the maximum achievable response (Jiang and Kopp-Schneider, 2014). As depicted in Figure 5, the EC50 values of the extracts were found to be below 100 µg/ml, except for the stem extract. The flower extract had the lowest EC50 value of 29.55 ± 4.91 µg/ml, followed by the leaf extract with a value of 53.88 ± 6.40 µg/ml. The root extract had a slightly higher EC50 value of 59.10 ± 6.70 µg/ml, while the fruit extract showed a further increase to 92.33 ± 8.15 µg/ml. The stem extract had the highest EC50 value of 171.90 ± 20.00 µg/ml.

3.4. The correlation between the anti-proliferative and the antioxidant effect

The antioxidant activity is believed to be directly or indirectly preventing cancer development (George and Abrahamse, 2020; Ullah et al., 2013). The Pearson correlation coefficient was analyzed to confirm whether there was any relationship between the antioxidant and anti-cancer effects of the extracts. The correlation between the two biological activities was expressed through Pearson's r, which ranges from −1 (a perfect negative correlation) to +1 (a perfect positive correlation) (Mukaka, 2012; Taylor, 1990). Pearson's r value was hierarchical into five groups in consist of negligible correlation (-.1 to +.1),

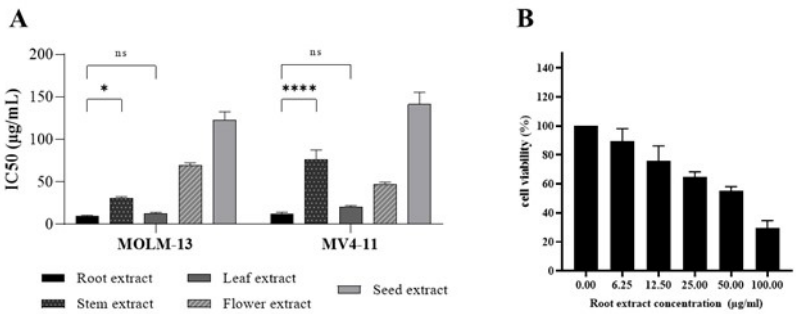


Figure 3. (A) The half maximal inhibitory concentration of the *L. camara* extracts**.** The comparison of IC50 values of root, leaf, fruit, stem and flower extracts on MOLM-13 and MV4-11 cells. (B) the anti-leukaemia capacity of the *L. camara* root extracts on THP-1 cells. A concentration of 1 x 10^5 cells/ml of THP-1 was subjected to co-cultivation with varying concentrations (ranging from 6.25 µg/ml to 100 µg/ml) of *L. camara* root extracts for 72 hours. *P<0.05 and ****P<0.0001, ns: not significant.

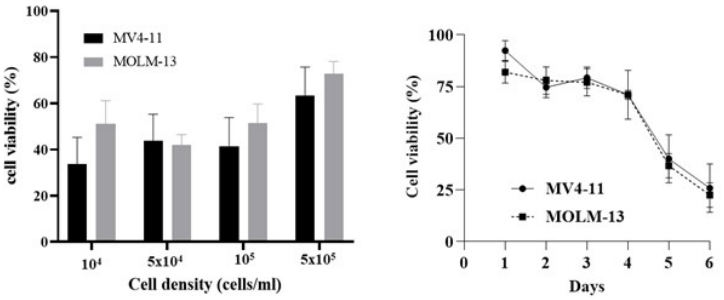


Figure 4. The inhibitory effect of root extract on MV4-11 and MOLM-13 cells in different initial cell densities (A) and exposure time (B). The cells were cultivated at varying densities ranging from 10^4 to $5x10^5$ cells/ml. The cells were then treated with the root extract of *L. camara* for 72 hours. Following the treatment, the number of viable cells was determined using the trypan blue test.

low positive (negative) correlation (.1 to .39 or -.1 to -.39), moderate positive (negative) correlation (.40 to .69 or −.40 to −.69), high positive (negative) correlation (.70 to .89 or −.70 to −.89) and very high positive (negative) correlation (.90 to 1.00 or −.90 to −1.00) (Mukaka, 2012; Schober et al., 2018). As shown in Figure 6, The anti-proliferative impact on both MOLM-13 and MV4-11 cells and the antioxidant activity were found to be non-correlated, r (3) = .0023, p = .997 and r(3) = .0.45, p = .447.

3.5. Inhibition of migration assay

MTT assay was used to determine the concentration of root and leaf extracts that are not toxic to the BJ cells, and the results in Figure 7, panel A show that IC50 of these extracts on BJ cells were above 200µg/ml so that for migration scratch assay, the concentration of extract at 50 µg/ml was chosen. Our data demonstrates that treatment with root and leaf extracts of *L. camara* significantly inhibited the migration of BJ cells compared to untreated cells Figure 7, panels B and C.

3.6. The effects of L. camara root and leaf extract on LPS-induced NO production

The generation of NO in various tissues is a dependable indicator of inflammation in numerous disorders. To investigate the anti-inflammatory properties of the root and leaf extract of *L. camara*, the BJ cells were utilized because of their capacity to produce NO when stimulated by LPS (Wang et al., 1996). The cells underwent pre-incubation with two concentrations (25 and 50 µg/ml) of each root and leaf extract derived from *L. camara* for 1 hour. Following this, the cells were subjected to stimulation using a concentration of 1 µg/ml of LPS for 24 hours. Our investigation utilized two control groups. The initial control group did not undergo any exposure to lipopolysaccharide (LPS) or Lantana camara extracts. The second control group was subjected to incubation exclusively with LPS, without any preceding treatment involving *L. camara* (hence referred to as LPS-treated cells). After examining the nitrite levels in the media, it was observed that the root and leaf extract of L. camara

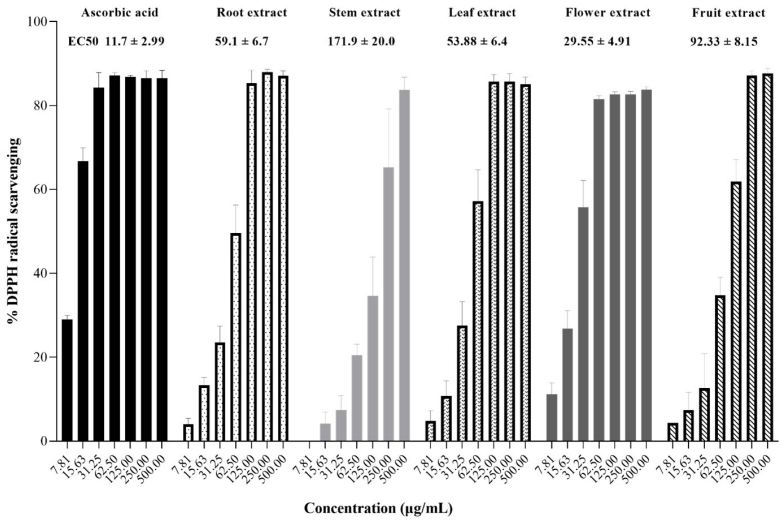
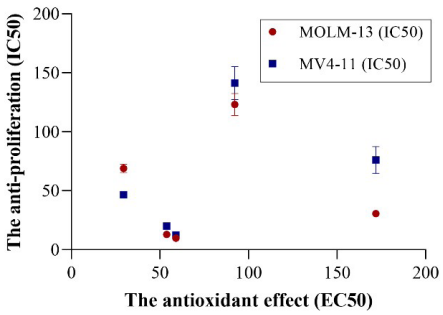


Figure 5. The DPPH radical scavenging capacity of the extracts. Determination of the antioxidant activity of the root, stem, leaf, flower, and fruit extracts of *L. camara* using the DPPH method at various concentrations, expressed as a percentage. The mean of an analysis performed in triplicate (n=3). Ascorbic acid was used as a control substance.



	MOLM-13	MV4-11
Degress of freedom (DOF) *Degrees of freedom for r is N-2*	3	
Pearson r	-.002296	.4498
P-value	.997	.447

Figure 6. The correlation between the anti-proliferative and the antioxidant effect of *L. camara* extracts. The scatter diagrams with different values of correlation coefficient (A) and pearson correlation coefficient (B)

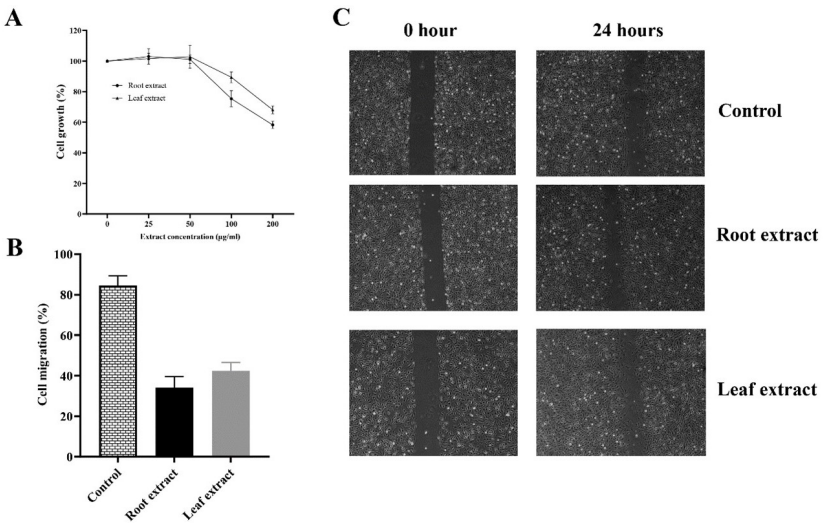


Figure 7. Migration of control cells after scratch. Migration of BJ cells after scratch and treatment with 50 µg/ml of root and leaf extracts. Images are acquired by optical microscope and are examples of different independent experiments.

demonstrated a noteworthy decrease in NO generation (Figure 8) compared to the LPS-induced cells that did not receive any treatment. The findings suggest that the extracts obtained from the roots and leaves of *L. camara* exhibit promising anti-inflammatory effects, as evidenced by the observed inhibition of NO production.

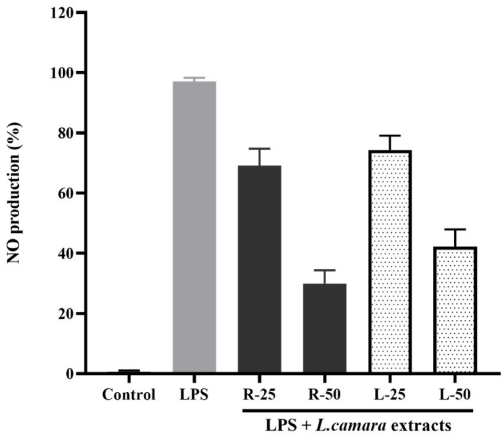


Figure 8. Root and leaf extracts of *L. camara* inhibit LPS-induced NO production in BJ cells. The concentration of NO was measured in the medium of BJ cells stimulated for 24 hours with LPS in the presence or absence of extracts. According to their quality standard, data are expressed as mean standard deviation (n=3).

4. Discussion

The results of phytochemical screening are consistent with previous studies that identified Lanatoside A, a cardiac glycoside, in *L. camara*. It has been noted that alkaloids are also present in the leaves of *L. camara*, although in relatively small quantities (Al-Hakeim et al., 2021). Furthermore, it has been documented that the leaves of this plant possess several substances, including phenolics, tannins, glycosides, and saponins (Bhakta-Guha and Ganjewala, 2009; Swamy et al., 2015). Several phytochemical constituents were found in the leaf and flower extracts of *L. camara,* and some of them harbouring strong bioactive such as polyphenol, flavonoid, cardiac glycoside, alkaloid and other secondary metabolisms (Mansoori et al., 2020; Naz and Bano, 2013). The critical active ingredients were determined at high concentrations in the leaf extract of *L. camara* including polyphenol at 40.859 ± 0.017 mg/g (gallic acid equivalents), flavonoid at 53.112 ± 0.199 mg/g (rutin equivalents), tannin at 0,860 ± 0,038 and alkaloid at the rate of 1.80 ± 0,73 (Mansoori et al., 2020; Naz and Bano, 2013). The above results demonstrate that *L. camara* plants raised in Vietnam have similar chemical components to those grown elsewhere.

Thus far, *L. camara* was proved to have anti-cancer effects on several human cancer cell types such as hepatoma cell line - Huh7 (IC50 = 169.0; 44.1; 150.0 µg/mL for methanol, ethyl acetate and n-butanol fractions of flowers and fruits; IC50 = 161.0 µg/ml for methanol fraction of leaves); cervical cancer cell line - Hela (LD50 = 222 ± 3.35 µg/ml for entire plant methanol extract); oral cancer cell line - KP (LD50 = 188.69 ± 1.4 µg/ml for whole plant methanol extract); lung cancer cell line - A549 (IC50 = 42.39 ± 3.08 µg/ml for flowers hexane extract); brain cancer cell line - A-172 (IC50 = 8.30 ± 1.48 µg/ml for flowers hexane extract); prostate cancer cell line - PC3 (IC50 = 66.40 ± 2.68 µg/ml for flowers hexane extract) (Badgujar et al., 2017; Bisi-Johnson et al., 2011; Meenakshi Sharma, 2020). Moreover, the alkaloids isolated from *L. camara* had a forceful influence on the growth of human cancer cell lines, including MCF-7, HeLa and HCT-116, with the IC50 lower than ten µg/ml (Al-Hakeim et al., 2021).

The anti-leukaemia capacity of most of the extracts from *L. camara* was clarified as good activity, and the root extract was the most effective (Figures 1, 2 and 3B). By conducting the nonlinear regression, the IC50 of the extracts from parts of *L. camara* was determined and described in Figure 3A. The effect of the root extract on MOLM-13 (IC50 = 9.78 ± 0.61 µg/ml) was classified as a good activity or very strong cytotoxicity.

Predicting the cytotoxicity of *L.camara*, we believe it may be related to cancer-causing molecules in the cell lines we use. In the AML cell lines used for this study, there are abnormalities in the FLT3 gene, including FLT3-ITD (MOLM-13 and MV4-11) and FLT3-WT (THP-1). In MOLM-13 cells, two mutations within *FLT3* exon 14 were detected: ITD of 21 bps corresponding to codons Phe594-Asp600 and a novel missense nucleotide substitution at the codon 599 (Tyr599Phe) (Furukawa et al., 2007; Taketani et al., 2004). Two mutations were located on the same allele (Furukawa et al., 2007). In MV4-11 cells, there are included ITDs of 30 bps within *FLT3* exon 14 corresponding to codons Tyr591-Asp600, and a Tyr591His mutation (Furukawa et al., 2007; Taketani et al., 2004). The cell line THP-1 came from the peripheral blood of a one-year-old infant male with monocytic AML (Tsuchiya et al., 2002). They do not contain any known FLT3 mutations but have high endogenous FLT3-WT expression. The oncogene FLT3-ITD and overexpressed FLT3-WT play a vital role in the generation of AML, and FLT3-ITD is found to be present in about 20% of AML cases (Lagunas-Rangel and Chávez-Valencia, 2017; Quentmeier et al., 2003). Our previous paper has shown that *L. camara* crude extract inhibited the phosphorylation signal caused by the interaction between isolated GST-FLT3S and FLT3-WT using an *in-vitro* kinase assay model (Hoang and Bui, 2020). Furthermore, compounds isolated from *L. camara* were proved to participate in many cell signalling pathways, such as NF-kB downregulation of lantadene A (Grace-Lynn et al., 2012); interrupted MAPK, Wnt, JAK-STAT, and PI3K/AKT/mTOR signalling by lanatoside C (Reddy et al., 2019). Therefore, it is likely that *L.camara* extract affected FLT3 and its underlying signal transduction pathway, thereby affecting the proliferation of FLT3-related cell lines. However, further experiments are needed to clarify whether this effect is specific to FLT3 or involves other protein tyrosine kinases.

Secondary metabolites that can function as antioxidants include alkaloids, flavonoids, and phenolic chemicals (Table 1), which may contribute to *L. camara*'s antioxidant effect. A study conducted by Badakhshan et al. demonstrated that *L. camara* exhibited a significant and potent reduction in DPPH. The recorded EC50 values for several plant parts, including the root, stem, leaf, flower, and fruit, were all found to be less than 100 µg/ml (Mahdi-Pour et al., 2012). The results were consistent with previous studies, which indicated that flower and leaf extract gave the best radical scavenging activity compared to other plant parts (Basar et al., 2020; Dehshiri et al., 2013). The difference in antioxidant capacity comes from the unequal distribution of phytochemicals in different parts of the plant, which has already been proved through quantitative experiments (Basar et al., 2020; Ketaren et al., 2015; Panawala et al., 2016). Multiple studies have shown that natural extracts possess anti-oxidative properties, including free radical scavenging, lipid peroxidation inhibition, and metal chelating activities. These properties have been shown to augment the anti-cancer effects of various chemical anti-cancer medications (Prasad et al., 2009). Significant correlations between antioxidant and anti-proliferative actions have been identified in HeLa, HT-29, and MCF7 cell line models (Olsson et al., 2004). Additionally, this research demonstrates a correlation between antioxidant activity and anti-cancer properties as shown in Figure 6.

The anti-inflammatory properties of *L. camara* extracts have primarily been demonstrated *in vivo*, with limited evidence *in vitro* models. The i*n vivo* evidence showed that *L. camara* extract inhibited the cyclooxygenase-2 (COX-2) enzyme activity in male white rats ($P < 0.05$) (Ifora et al., 2020). COX-2 is an enzyme secreted at the location of tissue damage to generate prostaglandin E2 (PGE2), a hormone-like compound that induces pain and inflammation. The promotion of tumour growth can be facilitated by prostaglandin generated from COX-2 by its binding to receptors and subsequent activation of signalling pathways that regulate cellular proliferation (Sheng et al., 2001). Swiss Albino mice treated with the aqueous *L. camara* crude extracts also exhibited a highly significant oedema diminishing effect, which may be due to the inhibition of COX activity (Millycent et al., 2017). Compounds including Lantrieuphpene B, Lantrieuphpene C, and 19α-hydroxyoleanonic acid isolated from *L. camara* were more active for the inhibition of NO production using a zebrafish model (Wu et al., 2020). *In vitro* evidence shows that the compound (3b,22bDi(2-(2-(2,6-dichlorophenylamino)phenyl)acetoyloxy)-olean12-en-28-oic acid) from *L. camara* leaves can suppress the TNF-α-induced activation of NF-kB by inhibiting IKK activation and IkBα degradation. This compound also inhibited the NF-kB-regulated protein expression of COX-2, which regulates inflammation and cyclin D1, which governs proliferation (Kumar et al., 2014). The findings of this research have provided more *in vitro* evidence about the anti-inflammatory properties of *L. camara*, particularly concerning the root and leaf extracts, which have demonstrated inhibitory effects on NO generation and cell migration (refer to Figures 7 and 8).

5. Conclusion

The extracts from different parts of *L. camara* demonstrated a notable capacity to scavenge free radicals, as seen by their EC50 values, which were consistently below 100 µg/ml for most of the extracts and below 50 µg/ml for the flower extract. The extracts were assessed for their anti-proliferative potential on two AML cell lines, and the root extract, in particular, showed significant cytotoxicity. Furthermore, the migration of BJ cells was significantly decreased by the root and leaf extracts of *L. camara* compared to untreated cells. These extracts also show potential anti-inflammatory properties, as indicated by the observed suppression of NO generation.

Acknowledgements

This study was funded by the Vietnam National Foundation for Science and Technology Development (grant no. 106.02 2019.50).

References

ADDIS, R., CRUCIANI, S., SANTANIELLO, S., BELLU, E., SARAIS, G., VENTURA, C., MAIOLI, M. and PINTORE, G., 2020. Fibroblast proliferation and migration in wound healing by phytochemicals: evidence for a novel synergic outcome. *International Journal of Medical Sciences*, vol. 17, no. 8, pp. 1030-1042. http://doi.org/10.7150/ijms.43986. PMid:32410832.

AL-HAKEIM, H.K., AL-ZABIBAH, R.S., ALZIHARI, H.F., ALMENSOORI, A.K., AL-ZUBAIDI, H.A. and HASSAN, L.E.A.H., 2021. Anticancer and antiangiogenic activities of alkaloids isolated from lantana camara by adsorption on the magnetic nanoparticles. *Karbala International Journal of Modern Science*, vol. 7, no. 1, pp. 90-99. http://doi.org/10.33640/2405-609X.2577.

AYOOLA, G., COKER, H., ADESEGUN, S., ADEPOJU-BELLO, A., OBAWEYA, K., EZENNIA, E., ATANGBAYILA, T. and SALAKO, K., 2008. Phytochemical screening and antioxidant activities of some selected medicinal plants used for malaria therapy in southwestern nigeria. *Tropical Journal of Pharmaceutical Research*, vol. 7, no. 3, pp. 1019-1024. http://doi.org/10.4314/tjpr.v7i3.14686.

BADGUJAR, N., MISTRY, K., CHUDASAMA, P. and PATEL, J., 2017. In vitro antioxidant and cytotoxic effects of methanol extracts of vitex negundo, lantana camara, bauhinia variegata and barringtonia racemosa on human cancer cell lines. *Indian Journal of Pharmaceutical Sciences*, vol. 79, no. 3, pp. 431-437. http://doi.org/10.4172/pharmaceutical-sciences.1000246.

BARRE, J.T., BOWDEN, B.F., COLL, J.C., DE JESUS, J., DE LA FUENTE, V.E., JANAIRO, G.C. and RAGASA, C.Y., 1997. A bioactive triterpene from Lantana camara. *Phytochemistry*, vol. 45, no. 2, pp. 321-324. http://doi.org/10.1016/S0031-9422(96)00805-9.

BASAR, N., KUTHI, N. and RUFAI, Y., 2020. Phytochemical screening, isolation of coumarins and examining bioactivity of prangos platychlaena boiss. Plant in iraq. *Applied Ecology and Environmental Research*, vol. 18, no. 2, pp. 2425-2443. http://doi.org/10.15666/aeer/1802_24252443.

BAUGHMAN, I.P., 1927. The study of the tannin-gelatin reaction. *Journal of Physical Chemistry*, vol. 31, no. 3, pp. 448-458. http://doi.org/10.1021/j150273a011.

BENITES, J., MOITEIRO, C., MIGUEL, G., ROJO, L., LÓPEZ, J., VENÂNCIO, F., RAMALHO, L., FEIO, S., DANDLEN, S., CASANOVA, H. and TORRES MARQUINA, I., 2009. Composition and biological activity of the essential oil of Peruvian Lantana camara. *Journal of the Chilean Chemical Society*, vol. 54, no. 4, pp. 379-384. http://doi.org/10.4067/S0717-97072009000400012.

BEVERLY, L., MAURO, V., DANIELA, S., DANIELE, C., FULVIO, M., INGRID, G., CONSTANCE, G., BEVERLY, E., JANET, F., PETER, N. and GIOVANNI, R., 1987. Growth factor requirements of childhood acute leukemia: establishment of GM-CSF-dependent cell lines. *Blood*, vol. 70, no. 1, pp. 192-199. http://doi.org/10.1182/blood.V70.1.192.192. PMid:3496132.

BHAKTA-GUHA, D. and GANJEWALA, D., 2009. Effect of leaf positions on total phenolics, flavonoids and proanthocyanidins content and antioxidant activities in Lantana Camara (L). *Journal of Scientific Research*, vol. 1, no. 2, pp. 363-369. http://doi.org/10.3329/jsr.v1i2.1873.

BISI-JOHNSON, M.A., OBI, C.L., HATTORI, T., OSHIMA, Y., LI, S., KAMBIZI, L., ELOFF, J.N. and VASAIKAR, S.D., 2011. Evaluation of the antibacterial and anticancer activities of some South African medicinal plants. *BMC Complementary and Alternative Medicine*, vol. 11, pp. 14. http://doi.org/10.1186/1472-6882-11-14.

BLOIS, M.S., 1958. Antioxidant determinations by the use of a stable free radical. *Nature*, vol. 181, no. 4617, pp. 1199-1200. http://doi.org/10.1038/1811199a0.

BUI, L., NGUYEN, Q., DAO, L., NGUYEN, H., LAM, M. and HOANG, C., 2019. Evaluation of antimicrobial, antioxidant and cytotoxic activities of dialium cochinchinensis seed extract. *Indian Journal of Pharmaceutical Sciences*, vol. 81, no. 5, pp. 975-980. http://doi.org/10.36468/pharmaceutical-sciences.594.

DEHSHIRI, M.M., AGHAMOLLAEI, H., ZARINI, M., NABAVI, S.M., MIRZAEI, M., LOIZZO, M.R. and NABAVI, S.F., 2013. Antioxidant activity of different parts of Tetrataenium lasiopetalum. *Pharmaceutical Biology*, vol. 51, no. 8, pp. 1081-1085. http://doi.org/10.3109/13880209.2013.775594.

EDEOGA, H., OKWU, D.E. and MBAEBIE, B.O., 2005. Phytochemical constituents of some Nigerian Medicinal Plants. *African Journal of Biotechnology*, vol. 4, no. 7, pp. 685-688. http://doi.org/10.5897/AJB2005.000-3127.

FLORENTO, L., MATIAS, R., TUAÑO, E., SANTIAGO, K., DELA CRUZ, F. and TUAZON, A., 2012. Comparison of cytotoxic activity of anticancer drugs against various human tumor cell lines using in vitro cell-based approach. *International Journal of Biomedical Science; IJBS*, vol. 8, no. 1, pp. 76-80. http://doi.org/10.59566/IJBS.2012.8076. PMid:23675259.

FORRESTER, M.B. and PETTY, L., 2020. Pediatric Lantana camara ingestions reported to Texas poison centers. *The American Journal of Emergency Medicine*, vol. 38, no. 11, pp. 2456-2457. http://doi.org/10.1016/j.ajem.2020.02.012. PMid:32063425.

FURUKAWA, Y., VU, H., AKUTSU, M., ODGEREL, T., IZUMI, T., TSUNODA, S., MATSUO, Y., KIRITO, K., SATO, Y., MANO, H. and KANO, Y., 2007. Divergent cytotoxic effects of PKC412 in combination with conventional antileukemic agents in FLT3 mutation-positive versus -negative leukemia cell lines. *Leukemia*, vol. 21, no. 5, pp. 1005-1014. http://doi.org/10.1038/sj.leu.2404593. PMid:17330105.

GEORGE, S. and ABRAHAMSE, H., 2020. Redox potential of antioxidants in cancer progression and prevention. *Antioxidants*, vol. 9, no. 11, pp. 1-21. http://doi.org/10.3390/antiox9111156. PMid:33233630.

GHISALBERTI, E.L., 2000. Lantana camara L. (Verbenaceae). *Fitoterapia*, vol. 71, no. 5, pp. 467-486. http://doi.org/10.1016/S0367-326X(00)00202-1. PMid:11449493.

GRACE-LYNN, C., DARAH, I., CHEN, Y., LATHA, L.Y., JOTHY, S.L. and SASIDHARAN, S., 2012. In vitro antioxidant activity potential of lantadene a, a pentacyclic triterpenoid of lantana plants. *Molecules (Basel, Switzerland)*, vol. 17, no. 9, pp. 11185-11198. http://doi.org/10.3390/molecules170911185.

HANDA, S.S., KHANUJA, S.P.S., LONGO, G. and RAKESH, D.D., 2008. *Extraction technologies for medicinal and aromatic plants*. Trieste: International Centre for Science and High Technology.

HATANO, T., KAGAWA, H., YASUHARA, T. and OKUDA, T., 1988. Two new flavonoids and other constituents in licorice root: their relative astringency and radical scavenging effects. *Chemical & Pharmaceutical Bulletin*, vol. 36, no. 6, pp. 2090-2097. http://doi.org/10.1248/cpb.36.2090. PMid:3240445.

HOANG, T.C. and BUI, T.K.L., 2020. Screening for the potent FMS-like tyrosine kinase 3 (FLT3) inhibitors from Vietnamese traditional herbal medicines. *International Journal of Pharmaceutical*

Research, vol. 13, no. 2, pp. 2890-2900. http://doi.org/10.31838/ijpr/2021.13.02.353.

IFORA, I., FITRA, F. and SUCI, A.M., 2020. Aktivitas anti-inflamasi dan daya hambat siklooksigenase-2 ekstrak etanol daun tembelekan (Lantana camara L.). *Jurnal Farmasi Higea*, vol. 12, no. 1, pp. 32-39.

JHA, D.K., PANDA, L., LAVANYA, P., RAMAIAH, S. and ANBARASU, A., 2012. Detection and confirmation of alkaloids in leaves of Justicia adhatoda and bioinformatics approach to elicit its anti-tuberculosis activity. *Applied Biochemistry and Biotechnology*, vol. 168, no. 5, pp. 980-990. http://doi.org/10.1007/s12010-012-9834-1.

JIANG, X. and KOPP-SCHNEIDER, A., 2014. Summarizing EC50 estimates from multiple dose-response experiments: A comparison of a meta-analysis strategy to a mixed-effects model approach. *Biometrical Journal. Biometrische Zeitschrift*, vol. 56, no. 3, pp. 493-512. http://doi.org/10.1002/bimj.201300123. PMid:24478144.

KALITA, S., KUMAR, G., LOGANATHAN, K. and RAO, B., 2011. Phytochemical composition and in vitro hemolytic activity of Lantana camara l. (verbenaceae) leaves. *Pharmacologyonline*, vol. 1, pp. 59-67.

KETAREN, B., AHMAD, S., FARHANA, S., MOHAMMAD, M., TAJIDIN, E. and ANWAR, M., 2015. Changes in phytochemical contents in different parts of Clinacanthus nutans (Burm. f.) lindau due to storage duration. *Bragantia*, vol. 74, no. 4, pp. 445-452. http://doi.org/10.1590/1678-4499.0469.

KUMAR, S., LEE, H. and SHARMA, M., 2014. The synthesis of non-steroidal anti-inflammatory drug (NSAID)–lantadene prodrugs as novel lung adenocarcinoma inhibitors via the inhibition of cyclooxygenase-2 (COX-2), cyclin D1 and TNF-α-induced NF-κB activation. *RSC Advances*, vol. 4, no. 37, pp. 19283-19293. http://doi.org/10.1039/c4ra00280f.

LAGUNAS-RANGEL, F.A. and CHÁVEZ-VALENCIA, V., 2017. FLT3-ITD and its current role in acute myeloid leukaemia. *Medical Oncology (Northwood, London, England)*, vol. 34, no. 6, pp. 114. http://doi.org/10.1007/s12032-017-0970-x. PMid:28470536.

LITAUDON, M., JOLLY, C., LE CALLONEC, C., CUONG, D.D., RETAILLEAU, P., NOSJEAN, O., NGUYEN, V.H., PFEIFFER, B., BOUTIN, J.A. and GUÉRITTE, F., 2009. Cytotoxic pentacyclic triterpenoids from Combretum sundaicum and Lantana camara as inhibitors of Bcl-xL/BakBH3 domain peptide interaction. *Journal of Natural Products*, vol. 72, no. 7, pp. 1314-1320. http://doi.org/10.1021/np900192r. PMid:19572612.

LIU, S., 2012. Extraction and characterization of proanthocyanidins from grape seeds. *The Open Food Science Journal*, vol. 6, no. pp. 5-11. http://doi.org/10.2174/1874256401206010005.

LY, B.T.K., CHI, H.T., YAMAGISHI, M., KANO, Y., HARA, Y., NAKANO, K., SATO, Y. and WATANABE, T., 2013. Inhibition of FLT3 expression by green tea catechins in FLT3 mutated-AML cells. *PLoS One*, vol. 8, no. 6, pp. e66378. http://doi.org/10.1371/journal.pone.0066378. PMid:23840454.

LY, B.T.K., LY, D.M., LINH, P.H., SON, H.K., HÁ, N.L. and CHI, H.T.C., 2020. Screening of medicinal herbs for cytotoxic activity to leukemia cells. *Journal of the Balkan Union of Oncology*, vol. 25, no. 4, pp. 2241-6293.

MACHADO, M., OLIVEIRA, L.G.S., SCHILD, C.O., BOABAID, F., LUCAS, M., BURONI, F., CASTRO, M.B. and RIET-CORREA, F., 2023. *Lantana camara* poisoning in cattle that took refuge during a storm in a forest invaded by this plant. *Toxicon*, vol. 229, pp. 107124. http://doi.org/10.1016/j.toxicon.2023.107124.

MACWILLIAM, I.C. and WENN, R., 1972. Interpretation of colour tests for polyphenols and melanoidins. *Journal of The Institute of Brewing*, vol. 78, pp. 309. http://doi.org/10.1002/j.2050-0416.1972.tb03452.x.

MAHDI-POUR, B., JOTHY, S.L., LATHA, L.Y., CHEN, Y. and SASIDHARAN, S., 2012. Antioxidant activity of methanol extracts of different parts of Lantana camara. *Asian Pacific Journal of Tropical Biomedicine*, vol. 2, no. 12, pp. 960-965. http://doi.org/10.1016/S2221-1691(13)60007-6. PMid:23593576.

MANSOORI, A., SINGH, N., DUBEY, S.K., THAKUR, T.K., ALKAN, N., DAS, S.N. and KUMAR, A., 2020. Phytochemical characterization and assessment of crude extracts from lantana camara l. For antioxidant and antimicrobial activity. *Frontiers in Agronomy*, vol. 2, no. 16, pp. 1-14. http://doi.org/10.3389/fagro.2020.582268.

MATSUO, Y., MACLEOD, R.A., UPHOFF, C.C., DREXLER, H.G., NISHIZAKI, C., KATAYAMA, Y., KIMURA, G., FUJII, N., OMOTO, E., HARADA, M. and ORITA, K., 1997. Two acute monocytic leukemia (AML-M5a) cell lines (MOLM-13 and MOLM-14) with interclonal phenotypic heterogeneity showing MLL-AF9 fusion resulting from an occult chromosome insertion, ins(11;9)(q23;p22p23). *Leukemia*, vol. 11, no. 9, pp. 1469-1477. http://doi.org/10.1038/sj.leu.2400768. PMid:9305600.

MCGAW, L.J., ELOFF, J.N. and MEYER, J.J.M., 2005. Screening of 16 poisonous plants for antibacterial, anthelmintic and cytotoxic activity in vitro. *South African Journal of Botany*, vol. 71, no. 3, pp. 302-306. https://doi.org/10.1016/S0254-6299(15)30102-2.

MEENAKSHI SHARMA, S.S., 2020. Anticancer activity of Lantana Camara hexane extract against brain carcinoma. *International Journal of Chemical and Biological Sciences*, vol. 2, no. 2, pp. 1-3. http://doi.org/10.33545/26646765.2020.v2.i2a.19.

MILLYCENT, S., MWONJORIA, M., JUMA, K., NGUGI, M. and NJAGI, E., 2017. Evaluation of analgesic, anti-inflammatory and toxic effects of lantana camara l. *International Journal of Phytopharmacology*, vol. 8, no. 3, pp. 89-97.

MUKAKA, M.M., 2012. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. *Malawi Medical Journal: The Journal of Medical Association of Malawi*, vol. 24, no. 3, pp. 69-71. PMid: 23638278.

NAZ, R. and BANO, A., 2013. Phytochemical screening, antioxidants and antimicrobial potential of Lantana camara in different solvents. *Asian Pacific Journal of Tropical Disease*, vol. 3, no. 6, pp. 480-486. http://doi.org/10.1016/S2222-1808(13)60104-8.

NONTOKOZO, Z.M. and MTHOKOZISI, B.C.S., 2018. Herbal medicine. In: P.F. BUILDERS, ed. *Herbal medicine*. Rijeka: IntechOpen, Chap. 11. http://doi.org/10.5772/intechopen.72816.

OLSSON, M.E., GUSTAVSSON, K.E., ANDERSSON, S., NILSSON, A. and DUAN, R.D., 2004. Inhibition of cancer cell proliferation in vitro by fruit and berry extracts and correlations with antioxidant levels. *Journal of Agricultural and Food Chemistry*, vol. 52, no. 24, pp. 7264-7271. http://doi.org/10.1021/jf030479p. PMid:15563205.

PANAWALA, P., ABEYSINGHE, D. and DHARMADASA, R.M., 2016. Phytochemical distribution and bioactivity of different parts and leaf positions of Pimenta Dioica (L.) Merr (Myrtaceae). *World Journal of Agricultural Research*, vol. 4, no. 5, pp. 143-146. http://dx.doi.org/10.12691/wjar-4-5-3.

PRASAD, K.N., HAO, J., SHI, J., LIU, T., LI, J., WEI, X., QIU, S., XUE, S. and JIANG, Y., 2009. Antioxidant and anticancer activities of high pressure-assisted extract of longan (Dimocarpus longan Lour.) fruit pericarp. *Innovative Food Science & Emerging Technologies*, vol. 10, no. 4, pp. 413-419. http://doi.org/10.1016/j.ifset.2009.04.003.

QUENTMEIER, H., REINHARDT, J., ZABORSKI, M. and DREXLER, H.G., 2003. FLT3 mutations in acute myeloid leukemia cell lines.

Leukemia, vol. 17, no. 1, pp. 120-124. http://doi.org/10.1038/sj.leu.2402740. PMid:12529668.

RASYID, S.A., SUGIRENG, SURYA, R.A., SANATANG, ROSDARNI and NATALIA, W.O.R., 2020. The antibacterial activity of Tembelekan leaf (Lantana camara L.) and Kopasanda leaf (Chromolaena odorata L.) extracts against Staphylococcus aureus. *Infectious Disease Reports*, vol. 12, no. s1, pp. 8734. http://doi.org/10.4081/idr.2020.8734.

REDDY, D., KUMAVATH, R., GHOSH, P. and BARH, D., 2019. Lanatoside C induces G2/M cell cycle arrest and suppresses cancer cell growth by attenuating MAPK, WNT, JAK-STAT, and PI3K/AKT/MTOR signaling pathways. *Biomolecules*, vol. 9, no. 12, pp. 1-20. http://doi.org/10.3390/biom9120792. PMid:31783627.

SALEH, M., KAMEL, A., LI, X. and SWARAY, J., 1999. Antibacterial Triterpenoids Isolated from Lantana camara. *Pharmaceutical Biology*, vol. 37, no. 1, pp. 63-66. http://doi.org/10.1076/phbi.37.1.63.6317.

SANTOS SÁNCHEZ, N., SALAS-CORONADO, R., VILLANUEVA, C. and HERNÁNDEZ-CARLOS, B., 2019. Antioxidant compounds and their antioxidant mechanism. In: E. SHALABY, ed. *Antioxidants*. London: IntechOpen. http://doi.org/10.5772/intechopen.85270.

SCHOBER, P., BOER, C. and SCHWARTE, L.A., 2018. Correlation coefficients: appropriate use and interpretation. *Anesthesia and Analgesia*, vol. 126, no. 5, pp. 1763-1768. http://doi.org/10.1213/ANE.0000000000002864. PMid:29481436.

SHARMA, M., SHARMA, P.D. and BANSAL, M.P., 2008. Lantadenes and their esters as potential antitumor agents. *Journal of Natural Products*, vol. 71, no. 7, pp. 1222-1227. http://doi.org/10.1021/np800167x. PMid:18553923.

SHARMA, P.D., BANSAL, M.P., SINGH, J. and SHARMA, M., 2007. Lantadene A-induced apoptosis in human leukemia HL60 cells. *Indian Journal of Pharmacology*, vol. 39, no. 3, pp. 140-144. http://doi.org/10.4103/0253-7613.33433.

SHENG, H., SHAO, J., WASHINGTON, M.K. and DUBOIS, R.N., 2001. Prostaglandin E2 increases growth and motility of colorectal carcinoma cells. *The Journal of Biological Chemistry*, vol. 276, no. 21, pp. 18075-18081. http://doi.org/10.1074/jbc.M009689200. PMid:11278548.

SOLOWEY, E., LICHTENSTEIN, M., SALLON, S., PAAVILAINEN, H., SOLOWEY, E. and LORBERBOUM-GALSKI, H., 2014. Evaluating medicinal plants for anticancer activity. *The Scientific World Journal*, vol. 2014, pp. 721402. http://doi.org/10.1155/2014/721402.

SOUSA, E. and COSTA, J., 2012. Genus Lantana: chemical aspects and biological activities. *Revista Brasileira de Farmacognosia*, vol. 22, no. 5, pp. 1115-1180. http://dx.doi.org/10.1590/S0102-695X2012005000058.

STROBER, W., 2015. Trypan blue exclusion test of cell viability. *Current Protocols in Immunology*, vol. 111, no. 1, pp. A3.B.1-A3.B.3. http://doi.org/10.1002/0471142735.ima03bs111.

SUNG, H., FERLAY, J. and SIEGEL, R.L., 2021. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209-249. http://doi.org/10.3322/caac.21660.

SWAMY, M.K., SINNIAH, U.R. and AKHTAR, M.S., 2015. In vitro pharmacological activities and GC-MS analysis of different solvent extracts of lantana camara leaves collected from tropical region of Malaysia. *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, pp. 506413. http://doi.org/10.1155/2015/506413.

TAKETANI, T., TAKI, T., SUGITA, K., FURUICHI, Y., ISHII, E., HANADA, R., TSUCHIDA, M., SUGITA, K., IDA, K. and HAYASHI, Y., 2004. FLT3 mutations in the activation loop of tyrosine kinase domain are frequently found in infant ALL with MLL rearrangements and pediatric ALL with hyperdiploidy. *Blood*, vol. 103, no. 3, pp. 1085-1088. http://doi.org/10.1182/blood-2003-02-0418. PMid:14504097.

TAYLOR, R., 1990. Interpretation of the correlation coefficient: a basic review. *Journal of Diagnostic Medical Sonography : JDMS*, vol. 6, no. 1, pp. 35-39. http://doi.org/10.1177/875647939000600106.

TSUCHIYA, T., HAGIHARA, M., SHIMAKURA, Y., UEDA, Y., GANSUVD, B., MUNKHBAT, B., INOUE, H., TAZUME, K., KATO, S. and HOTTA, T., 2002. The generation of immunocompetent dendritic cells from CD34+ acute myeloid or lymphoid leukemia cells. *International Journal of Hematology*, vol. 75, no. 1, pp. 55-62. http://doi.org/10.1007/BF02981980. PMid:11843292.

ULLAH, M.F., AHMAD, A., KHAN, H.Y., ZUBAIR, H., SARKAR, F.H. and HADI, S.M., 2013. The prooxidant action of dietary antioxidants leading to cellular DNA breakage and anticancer effects: implications for chemotherapeutic action against cancer. *Cell Biochemistry and Biophysics*, vol. 67, no. 2, pp. 431-438. http://doi.org/10.1007/s12013-011-9303-4.

WANG, R., GHAHARY, A., SHEN, Y.J., SCOTT, P.G. and TREDGET, E.E., 1996. Human dermal fibroblasts produce nitric oxide and express both constitutive and inducible nitric oxide synthase isoforms. *Journal of Investigative Dermatology*, vol. 106, no. 3, pp. 419-427. http://doi.org/10.1111/1523-1747.ep12343428.

WOLFSON, S.L. and SOLOMONS, T.W., 1964. Poisoning by fruit of lantana camara: an acute syndrome observed in children following ingestion of the green fruit. *American Journal of Diseases of Children*, vol. 107, no. 2, pp. 173-176. http://doi.org/10.1001/archpedi.1964.02080060175011. PMid:14091823.

WU, P., SONG, Z., WANG, X., LI, Y., LI, Y., CUI, J., TUERHONG, M., JIN, D.-Q., ABUDUKEREMU, M., LEE, D., XU, J. and GUO, Y., 2020. Bioactive triterpenoids from Lantana camara showing anti-inflammatory activities in vitro and in vivo. *Bioorganic Chemistry*, vol. 101, pp. 104004. https://doi.org/10.1016/j.bioorg.2020.104004.

YUAN, H., MA, Q., YE, L. and PIAO, G., 2016. The traditional medicine and modern medicine from natural products. *Molecules (Basel, Switzerland)*, vol. 21, no. 5, pp. 559. http://doi.org/10.3390/molecules21050559. PMid:27136524.