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Potential of *Myrmecodia* Species as an Anticancer Agent: A Review Article

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Abstract

Myrmecodia (Rubiaceae) is a genus of epiphytes (ant's nest plant) originating from Southeast Asia and the islands of southern Queensland Australia. Folkloric claims the efficacy of this plant in treating many chronic diseases such as cancer, arthritis, coronary heart diseases, and many inflammation-related diseases. The pharmacological and therapeutic application of only 356 plants has been published. Six (6) studies were done on the evaluation of *Myrmecodia platytyrea* in cancer cells study; 1. Cytotoxicity Effect of *Myrmecodia platytyrea* on Vero and HepG2 Cells Line and Toxicity Study of The Extract on Mice; 2. Cytotoxicity Effect of *Myrmecodia platytyrea* on Hela, HT-29 and MCF-7 Cells Line; 3. Cytotoxicity Study of *Myrmecodia pendans* on Fibroblast; 4. Toxicity Study of *Myrmecodia platytyrea* in Male and Female Albino Mice; 5. Potential of *Myrmecodia pendans* as Anti-Cancer on Tongue Cancer Cells; 6. Cytotoxicity Study of *Myrmecodia tuberosa* on Oral Carcinoma Cell line. In conclusion, *Myrmecodia* may have a role in cancer management as a metastasis inhibitor although much more work is needed in this area. It can be concluded that these are important findings that may augment the effectiveness of chemotherapeutic agents and increase the survival of cancer patients.

Keywords: Myrmecodia, Rubiaceae Ant's Nest Plant, Cancer

1.0 Introduction

Herbs and spices have been shown to have medicinal properties and many have demonstrated a strong pharmacological activity (Srinivasan, 2005). In controlled clinical trials of herbal medicines, 67% were reported to have a statistically significant positive result (Pittler et al., 2000). In 2010, about 12% of scientific evidence from 1000 plants available in the market has not been published. The pharmacological and therapeutic application of only 356 plants has been published (Cravotto *et al*., 2010). There is no doubt that medicinal plants could effectively improve health since they have been used in folk medicine to treat various diseases since time immemorial. Drugs derived from the natural origin are considered ideal candidates for anticancer drug development since most anticancer leads are derived from plants.

Myrmecodia (scientific name of ant's nest) is a plant that has a structure like an anthill and ants (Lok and Tan, 2009). *Myrmecodia* plants grow on tree branches and trunks. Naturally, sugar *Myrmecod*ia often grows hanging down on the bare branches of a large number of substrates, and thus depends on the symbiosis nutriment. Plants store food and water in swollen caudex greyish brown and thorns grow over time. Thick, unbranched stems covered in clypeoli and alveoli also develop thick bush and filled with dried bracts. Caudex will grow to 20 centimeters in diameter and the shaft can reach 30 centimeters. The flowers are white (15 or 16 mm in length), and the plant can only be reproduced by seed. Table 1 showed the list of *Myrmocodia* species.

Table 1: **List of** *Myrmecodia* **Species**

List of *Myrmecodia* **species**
Myrmecodia beccarii
Myrmecodia tuberosa
Myrmecodia platytyrea
Myrmecodia brassii
Myrmecodia alata

Myrmecodia melanacantha
Myrmecodia longissima
Myrmecodia schlechteri
Myrmecodia pendans
Myrmecodia kutubuensis
Myrmecodia archboldiana
Myrmecodia platyrea
Myrmecodia jobienses
Myrmecodia lamii

Cancer is a neoplastic disease that is characterized by uncontrolled cell growth leading to the formation of a tumor mass. The tumor mass can either be benign (non-cancerous) or malignant (cancerous). Benign tumors are static and do not metastasize to other parts of the body. On the other hand, malignant cancer cells can metastasize via circulatory and lymphatic systems to set up tumors at new sites of the body eventually causing death. Cancer can develop in any organ or tissue such as lung, breast, colon, prostate, stomach, oral, liver, skin, etc. Cancer is ranked by World Health Organization (WHO) as the top ten leading cause of human fatalities. It is predicted that there will be 22 million new cancer cases every year in the next two decades (WHO, 2014). There are more than 100 types of cancer, the tumor is primarily characterized by the site at which it occurs, such as liver, oral, colorectal, lung, breast, ovarian etc (Bartlet *et al*., 2015). An estimated 12.7 million cancer cases and 7.6 million cancer deaths were reported in 2008 worldwide (Jemal *et al*., 2011). It is predicted that there will be 22 million new cancer cases diagnosed annually in the next two decades (WHO, 2014). Approximately 43% of cancer deaths are due to tobacco use, a Westernized diet, alcohol consumption, an inactive lifestyle, and infections (Lopez *et al*., 2006). Lung and breast cancer were the most frequently diagnosed cancers and the major cause of death in males and females in 2008 worldwide (Jemal *et al*., 2011). In Malaysia, 21,773 cancer cases were reported in the year 2006 which comprised 9,974 males and 11, 799 females (National Cancer Registry, 2008) with cancer of the breast, colorectal, lung, and cervix as the most common cancers diagnosed. The therapeutic options in treating cancer patients are highly dependent on the type, stage, and locality of the tumor, the patient's age, health status, and

attitude towards life. The goal of cancer treatment is to entirely eradicate cancer cells without affecting healthy cells.

The ability of cells to survive the toxic insult was the basis of most of the cytotoxicity assays. It depends on both the number of cells that are the viable and mitochondrial activity of cells. The 3- (4, 5-dimethylthiazol-2-yl) -2, 5-diphenyltetrazolium bromide (MTT) assay assumes that dead cells or their products do not reduce tetrazolium. Tetrazolium salt is reduced only by metabolically active cells. Therefore, MTT can be reduced to formazan blue by the mitochondrial enzyme succinate dehydrogenase. The amount of formazan produced is directly proportional to the number of active cells (Asoka and Thangavel, 2014).

2.0 Cytotocixity Effect of *Myrmecodia platytyrea* on Vero and HepG2 Cells Line and Toxicity Study of The Extract on Mice.

The methanolic extract of *Myrmecodia platytyrea* (*M. platyrea*) showed IC_{50} values of 0.76 ± 0.07 and 0.07 ± 0.03 mg/mL on Vero and HepG2 cells, respectively (Table 2). The results indicated that the extract is toxic to human hepatoma without affecting the normal monkey kidney (Vero) and cells (CSSR, 2010). The study of the aqueous extract of *Myrmecodia pendans* was where the data demonstrated potent anticancer activity against HeLa and MCM-B2 cells (Soeksmanto *et al*., 2010). Meanwhile, in vivo study showed that the dose of 2 and 5 g/kg of methanolic extract of *M. platytyrea* demonstrated no sign of toxicity in mice (OECD, 2010). The high IC_{50} value of the methanolic extract of *M. platytyrea* on Vero cells and no toxic effect on the mice suggested that this plant is safe for consumption. In contrast, this extract showed great antiproliferative activity on HepG2 cells indicating potential anticancer properties (CSSR, 2010).

Table 2: Cytotoxic Effect of Methanolic Extract of *Myrmecodia Platytyrea*. Adopted From CSSR, 2010.

IC_{50} (mg/ml)	
Vero	Hepg2
0.76±0.07	0.07±0.03

3.0 Cytotocixity Effect of *Myrmecodia platytyrea* on Hela, HT-29 and MCF-7 Cells Line

The *M. platyrea* ethanolic tuber extract exhibited the strongest cytotoxicity against HT-29 (figure 1) and Hela cell lines (figure 2) with the IC_{50} value of 16 µg/mL and 14 µg/mL respectively. Meanwhile, the ethanolic bark extract exhibited the strongest cytotoxicity against MCF-7 with IC_{50} value of 6.0 µg/mL (figure 3) (Saidi *et al*., 2014).

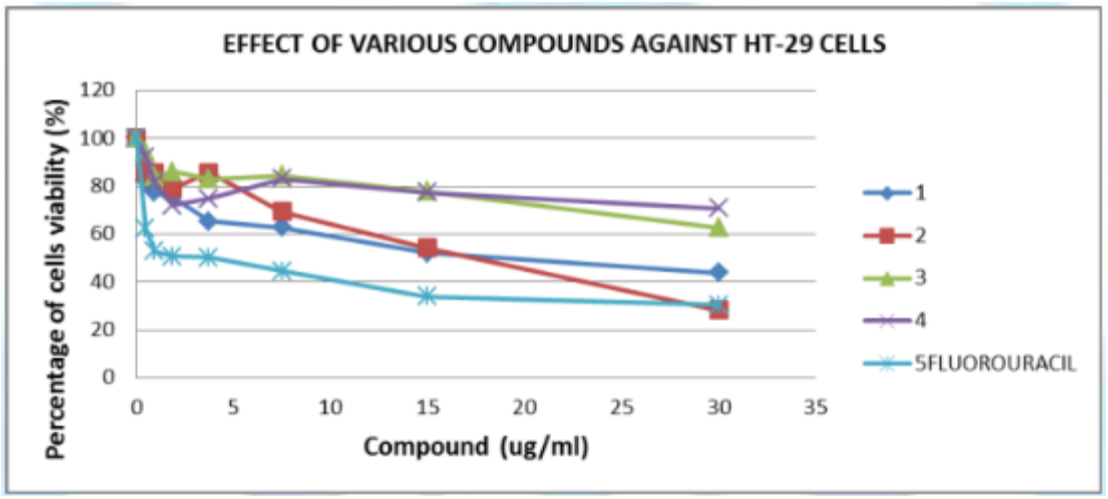

Figure 1: Effect of various extracts against HT-29 cells. Adopted from Saidi *et al*., 2014.

* [1]: Ethyl Acetate Tuber; [2]: Ethanol Tuber; [3]:Ethanol Leaves; [4]: Ethanol Bark

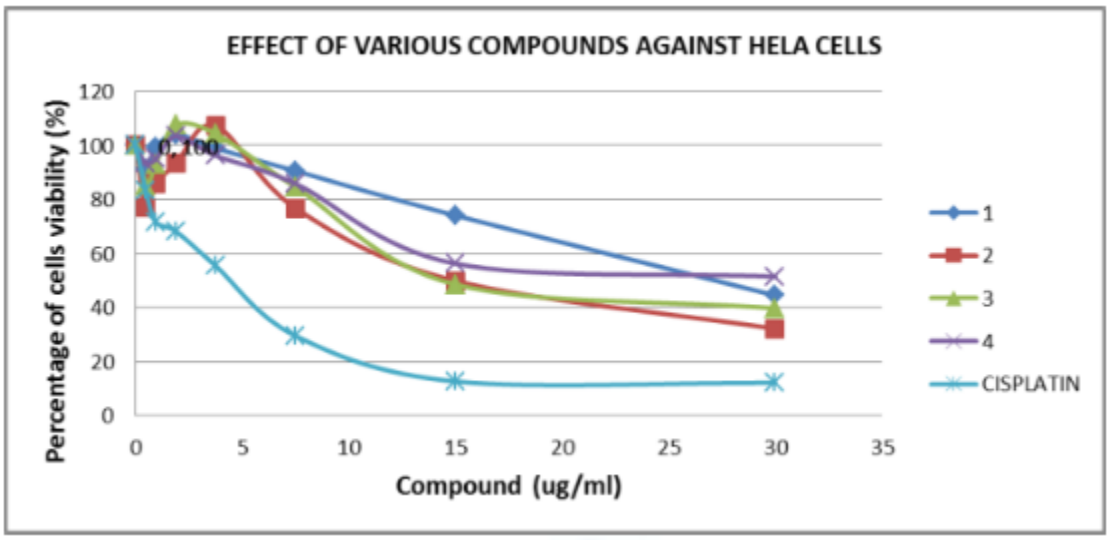

Figure 2: Effect of various extracts against HELA cells. Adopted from Saidi *et al*., 2014.

* [1]: Ethyl Acetate Tuber; [2]: Ethanol Tuber; [3]:Ethanol Leaves; [4]: Ethanol Bark

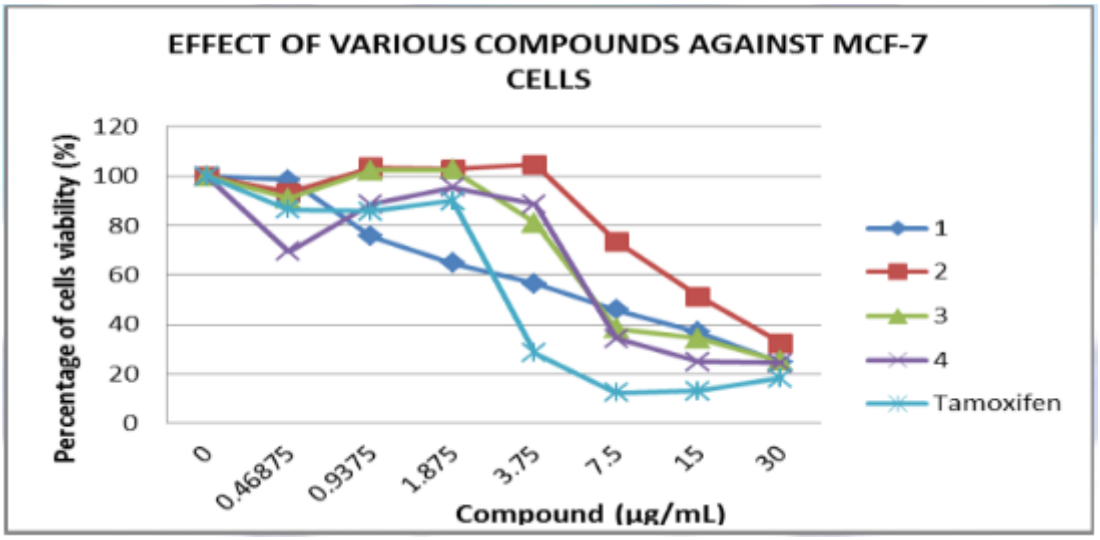

Figure 3: Effect of various extracts against MCF-7 cells. Adopted from Saidi *et al*., 2014.

* [1]: Ethyl Acetate Tuber; [2]: Ethanol Tuber; [3]:Ethanol Leaves; [4]: Ethanol Bark

4.0 Cytotoxicity Study of *Myrmecodia pendans* on Fibroblast

Myrmecodia pendans (*M. pendans*) with 70% ethanol dried extract showed no sign of toxicity on fibroblast cells accessed by using the MTT assay method. The higher concentration of extract showed an increase in viable cells. The findings may add to the overall value of the herbal medicinal potential of ant nest plant that had been known previously as antibacterial and anticancer, yet does not show any toxic effect on normal cells (Janti *et al*., 2015).

5.0 Toxicity Study of *Myrmecodia platytyrea* in Male and Female Albino Mice

A single oral administration was performed at 2000 mg/kg body weight in both male and female mice and observed for 24 hours for mortality. The results showed no signs of toxicity such as general behavioral changes and changes in gross appearance. No mortality was also reported. The extract also did not exhibit any significant (p> 0.05) effects on body weight, absolute organs weights, hematological and blood chemistry levels in treated mice as compared to the control group. *M. platytyrea* aqueous tuber extract showed no toxicity in male and female albino mice thus, safe for consumption (Maisarah *et al*., 2013).

6.0 Potential of *Myrmecodia pendans* as Anti-Cancer on Tongue Cancer Cells

The results of the study showed cytotoxicity test on tongue cancer cell death percentage of SP-C1 from each treatment fraction continues to increase coincide with the increase of the given concentration. Ethyl acetate and ethanol fraction resulted in the most potent cell growth inhibition compared with hexane fraction and water fraction. Ethyl acetate fraction of flavonoids at a concentration of 1000 µg/ml resulted in a percentage of cell death as much as 64.60%, and the lowest concentration of 7.8125 µg/ml led to cell death by 15.80% of the cells (Harun *et al*., 2014). The graph results of the average percentage number of cell death due to exposure to certain concentrations of four fractions (Figure 4).

Research results by cytotoxicity test obtained LC_{50} of each fraction consisting of ethyl acetate fraction, ethanol fraction, hexane fraction and water fraction, respectively, 452.059; 937.562; 2691.535; 12302.69 µg/ml (figure 5) (Harun *et al*., 2014). In conclusion, *M. pendans* for flavonoid fraction has potential as an anticancer agent on tongue cancer cells (SP-C1) type of Squamous Cell Carcinoma.

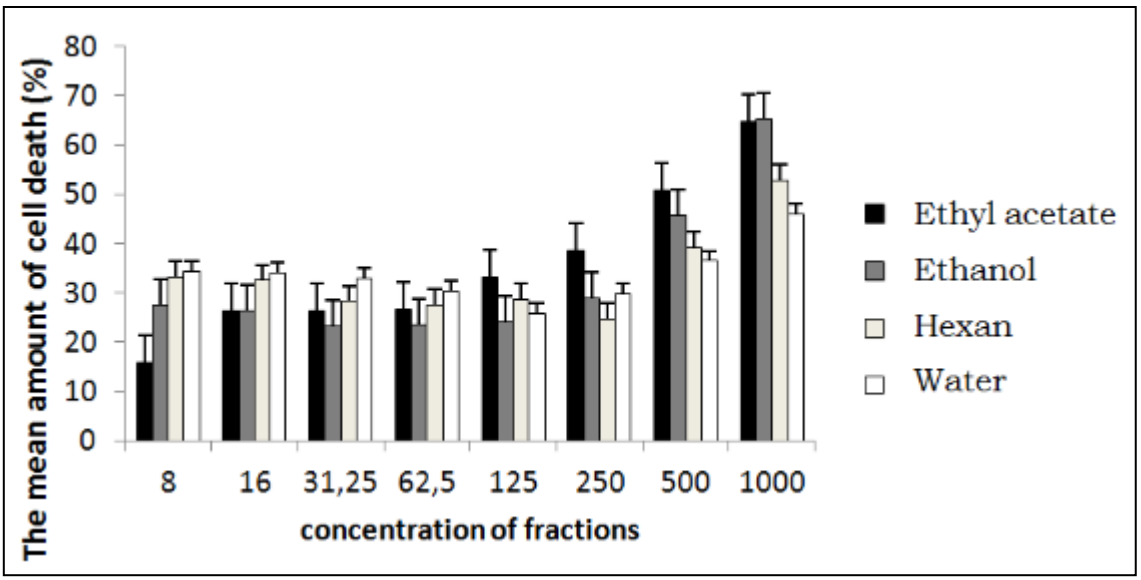

Figure 4: Effect of cytotoxic ant nests (*M. pendans*) ethyl acetate, ethanol, hexan, and water hexan fraction to tongue cancer cells *SP-C1*. Adopted from Harun *et al*., 2014.

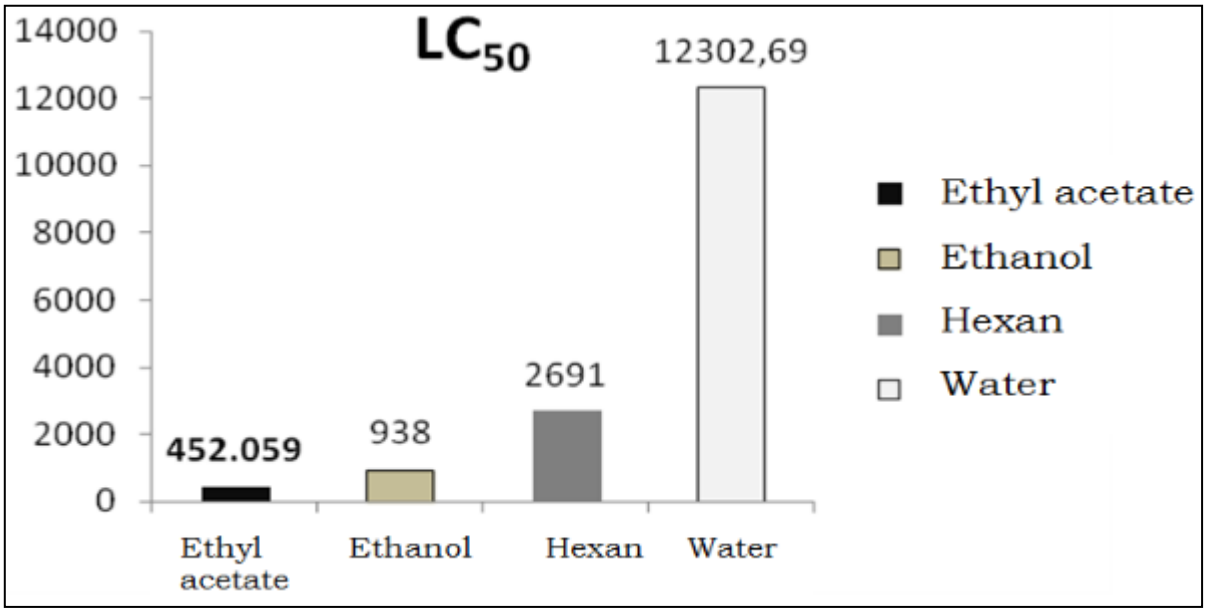

Figure 5: Results of cytotoxicity assay LC_{50} in each flavonoid fraction. Adopted from Harun *et al*., 2014.

7.0 Cytotoxicity Study of *Myrmecodia tuberosa* on Oral Carcinoma Cell line

Oral Carcinoma (KB) cells treated with various concentrations of *M. tuberosa* extract were examined by the MTT assay. Relative cell number was evaluated by comparing the absorbance in each cell. It was detected that the more increasing concentration of the extract, the more decreasing the number of viable KB cells based on the colorimetric absorbance values. Data indicated the negative control has the highest absorbance at 1.416 ± 0.05, whereas the positive control (docetaxel IC50 = 12.5 µg/ml) has an absorbance of 0.514 ± 0.20. Concentration of 500 to 1000 µg/ml has the lower absorbance at 0.587 ± 0.04 and 0.365 ± 0.03, respectively (Sartari *et al*., 2016) (table 3). The percentage increase in KB cell growth inhibition by extracts concentration of 62.5, 125, 250, 500 and 1000 g/ml was known at 35.5%, 39.5%, 58.3%, 68.5% and 84.2% compared to the negative control, whereas 12.5µg/ml of docetaxel was detected at 62.4% (Figure 6). In addition, IC_{50} of *M. tuberosa* was found at a concentration 215 µg/ml. These data showed that extract of *M. tuberosa* was effective and has the strong potential to inhibit the growth of KB cells (Sartari *et al*., 2016).

Table 3: Mean and standard deviation of absorbance of KB cell after treatment with the various concentration of *M. tuberosa* extract for 24 hours. Adopted from Sartari *et al*., 2016.

Negative control (Aquadest)	62.5 µg/ml	125 µg/ml	250 µg/ml	500 µg/ml	1000 µg/ml	Postive control (Doxetacel) IC_{50} = 12.5 µg/ml
1.416± 0.05	0.909 ±0.03	0.863±0.01	0.732 ± 0.02	0.587 ± 0.04	0.365 ± 0.03	0.514 ± 0.20

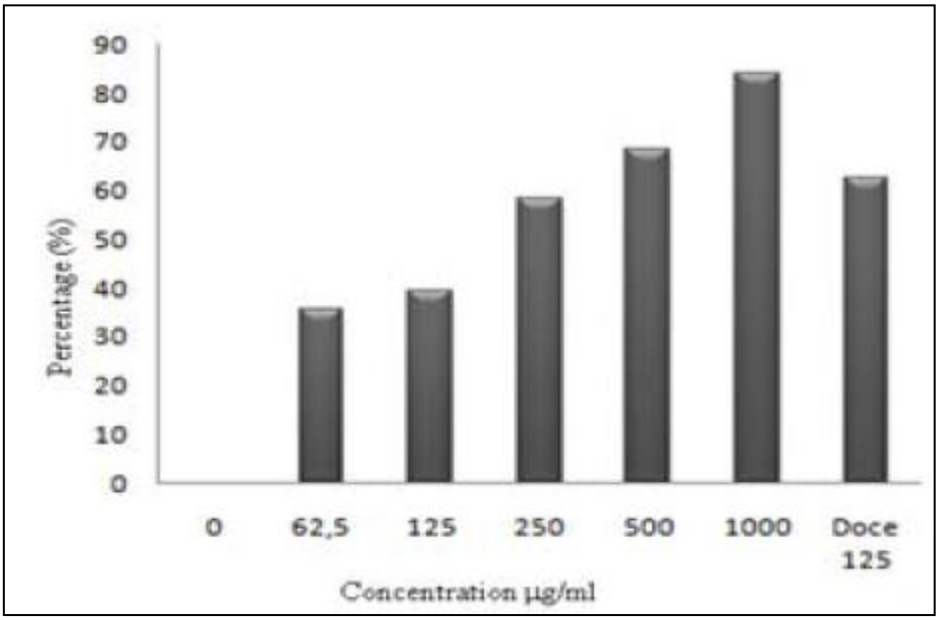

Figure 6: The percentage increase in growth inhibition of KB cells after being treated with various concentrations of extract for 24 hours. Adopted from Sartari *et al*., 2016.

8.0 CONCLUSION

Myrmecodia may have a role in cancer management as a metastasis inhibitor although much more work is needed in this area. It can be concluded that these are important findings that may augment the effectiveness of chemotherapeutic agents and increase the survival of cancer patients.

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