Crimson Publishers
Wings to the Research

Research Article

Use of *Viscum album* in the Integrative Treatment of Cholangiocarcinoma in a Dog (*Canis familiaris*)- Case Report

Ana Catarina Viana Valle[1,2]*; Luciana Lima[3]; Leoni Bonamin[4]; Hilana Brunel[5]; Aline Barros[1]; Aloisio Carvalho[1,4] and Rosangela Vieira Andrade[2]

[1]IDIS/Lamasson Institute, Brazil

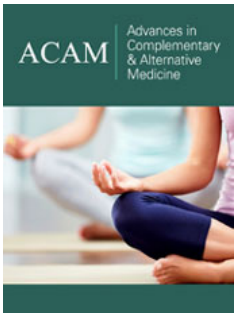
[2]Catholic University, Brazil

[3]CVAN, Brazil

[4]Paulista University, Brazil

[5]Bioinnova, Brazil

ISSN: 2637-7802



***Corresponding author:** Ana Catarina VV, IDIS/Lamasson, Catholic University, Brazil

Submission: December 16, 2019

Published: January 07, 2020

Volume 5 - Issue 4

How to cite this article: Ana Catarina V, Luciana L, Rosangela Vieira A, Leoni B, Hilana B, et al. Use of Viscum album in the Integrative Treatment of Cholangiocarcinoma in a Dog (Canis familiaris)- Case Report. Adv Complement Alt Med. 5(4). ACAM.000619.2020.
DOI: 10.31031/ACAM.2020.05.000619

Abstract

Cholangiocarcinoma is a malignant neoplasm originated in the bile ducts or gallbladder. It is considered quite aggressive and usually metastasizes for regional lymph nodes and lungs. The treatment is by surgical resection and chemotherapy, which are very invasive and aggressive methods. *Viscum album* (VA) extract has immunomodulatory and cytotoxic properties capable of acting directly on the tumor and its microenvironment, as well as in other systems. *Viscum album* improves the quality of life as it does not present significant side effects compared to the traditional allopathic treatment. A case of Cholangiocarcinoma in a dog with pulmonary and splenic metastasis is reported in the present study. The patient was treated by subcutaneous and intravenous administration of ultra-diluted *Viscum album* for 11 months. The *Viscum album* administration improved the quality of life of the animal and decreased the tumor growth speed.

Keywords: Tumor; Quality of life; Metastasis

Introduction

Cholangiocarcinoma (CCA) or carcinoma of the bile ducts is a malignant neoplasm originated mainly in the intrahepatic and extrahepatic ducts or gallbladder [1]. CCA has already been described in dogs, cats, sheep, cattle, equines, and goats [1]. Its highest occurrence appears to be in elderly dogs and cats [2], with a prevalence of 10% among all cancers in dogs [3].

The etiology of CCA is unknown in domestic animals. However, there are some risk factors associated with its occurrence, and disease incidence is higher in castrated dogs as compared to intact females or males [1]. The main risk factors are parasites, such as *Platynosomun concinum*, responsible for chronic lesions in the bile system [4]; chemical agents, such as plutonium and nitrosamines, intestinal parasites, such as *Ancylostoma sp*. and *Trichuris vulpis*; and chronic inflammations which may increase bile duct epithelial cell proliferation [1].

CCA clinical signals are unspecific and similar in dogs and cats. Lethargy, anorexia, vomiting, weight loss and dyspnea are more often reported when the animal is affected by this type of tumor and in hepatocellular carcinoma. Increased serum levels of the enzymes alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (AF) are important biochemical findings. Regarding bile duct tumors, 10 to 40% of dogs and cats may show clinical signs of icterus [5].

CCA can be visualized by ultrasonography (US) and diagnosed by percutaneous thin needle biopsy [6,7]. According to Patnaik [5], Cholangiocarcinomas typically has a multifocal pattern. Macroscopically, the neoplasm presents a large solitary mass or multiple firm nodules. Microscopically, it consists of ducts or rudimentary acini from biliary epithelium, separated by fibrous connective tissue stroma. Metastases are usually observed in the regional lymph

nodes, lungs, and peritoneal cavity [8]. The routes by which cancer cells spread to other organs are lymphatic, hematogenous, and peritoneal dissemination [9].

The elective treatment of CCA is surgical resection associated with radiotherapy and chemotherapy. This treatment is not always efficient and significantly reduces the quality of life of the diseased animals. Therefore, new therapies, as adjuvant or complementary therapies, are necessary to improve the quality of life of these patients [1].

Viscum album (*VA*) is a semi parasitic plant native from Europe. The use of *Viscum album* extract is widespread among the complementary medicine protocols for cancer treatment in Europe, which is indicated for several types of neoplasms [10]. *Viscum album* (*VA)* contains different compounds with immunomodulatory and cytotoxic action. As a result, it may be effective in improving the quality of life of patients with cancer [11]. Viscotoxins and lectins are the better-known active principles of this plant. However, it also contains several alkaloids, triterpenes, and flavonoids [11]. Lectins and viscotoxins are the main antitumor agents [12]. It is known that apoptosis is induced by the activation of the caspase cascade, pathways P13K/AKT, JNK, P38, and MAPK [13]. Nevertheless, not all mechanisms of action of the extract are fully understood.

Ultra-diluted injectable medications have been increasingly used for the care of patients with cancer (13, 2013; Valle et al., 2016) due to their effectiveness and lack of significant side effects [14]. From this perspective, such medications are considered, in many cases, as the first option for the treatment of cancer. Ultra-diluted injectable medications are frequently used solely in the complementary medicine area. However, they may also be used as auxiliary or complementary medications in the integrative medicine, in which they are associated with conventional chemotherapy. In this context, the objective is to reduce the undesirable effects of the latter [10,15]. This study aimed at reporting the treatment and survival of a dog with Cholangiocarcinoma, which was treated at Natural Pet-Integrative Veterinary Clinic, between October 2016 and November 2017.

Material and Methods

A 12-year-old Australian Shepherd female, weighing 27Kg, was referred to the clinic for routine examination. Analyses of complete blood count, ALT, AST, AF, urea, creatinine, and total proteins (Table 1) were requested, as well as an abdominal US. A mass of 6.9x7.0x5.3cm was visualized in the right hepatic lobe in the US examination. Contrast-enhanced abdominal and thoracic computed tomography (CT) images confirmed the presence of an irregular shaped neoformation with a heterogeneous enhancement after intravenous contrast medium administration. The mass measured approximately 7.3x6.9cm in width and 5.3cm in length and was in the right lateral liver lobe parenchyma topography (Figure 1). Suggestive images of multiple isodense nodules of low capitation after intravenous contrast injection were also verified. The nodules measured between 0.4 and 1.3cm in diameter and were randomly distributed along the splenic parenchyma (Figure 2). Additionally, a low captation isodense nodule was identified after intravenous contrast injection. The nodule measured approximately 2.5cm in diameter and was observed in the dorsal peripheral portion of the left lung caudal lobe parenchyma (Figure 3).

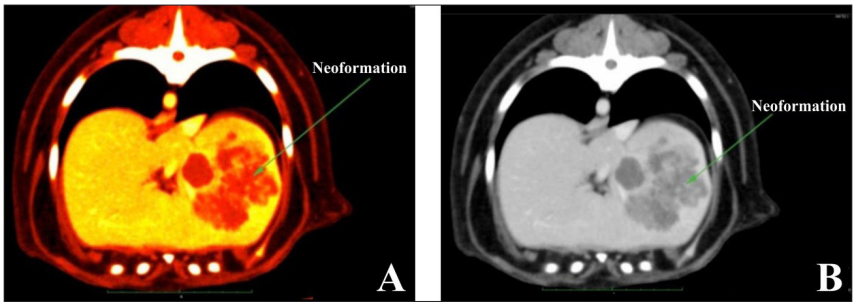


Figure 1: Spleen computerized tomography (10 October 2016). A) Image with contrast: nodule measuring 38.69cm^2; B) Image with no contrast enhancement.

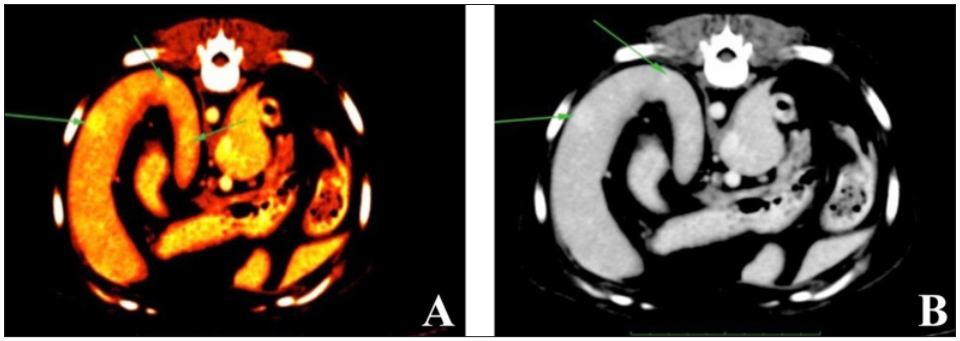


Figure 2: Spleen computerized tomography (10 October 2016). A) Image with contrast: micronodules varying from 0.31 to 1.32cm^2; B) Image with no contrast.

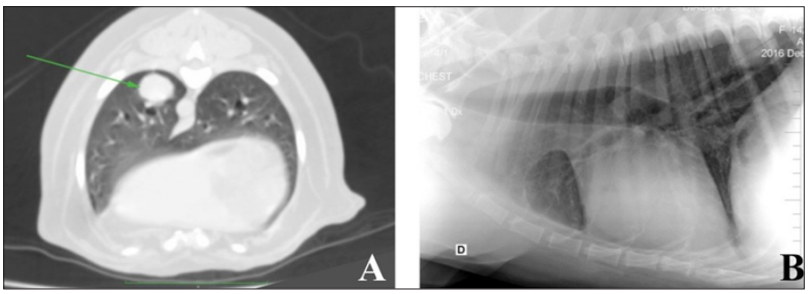


Figure 3: A) Lung computerized tomography: nodule of 4.9cm^2 in diameter (10 October 2016); B) Lung x-ray-nodule of 15.96cm^2 (21 November 2016).

Table 1: Results of the laboratory blood analysis.

	10/20/2016	11/17/2016	12/13/2016	4/10/2017	5/27/2017	9/13/2017
Hematocrit	47	42	43	44	44	37
Red blood cells	6.96	6.37	6.24	6.65	6.41	5.98
Hemoglobin	16	14.1	14.7	16	14.6	13.2
Leukocytes	3.6	5.1	7.4	7.4	9.8	5.9
Platelets	157	185	218	150	146	155
ALT	36	57	41	52	220	47
Creatinine	1.2	0.8	0.8	1.2	1	0.7
Urea	--	--	32	--	63	26
AF	91	157	107	290	273	58
Albumin	2.2	2.6	2.4	2.3	2.2	2.2
Globulin	4.3	3.1	3.2	4.4	3	3.8

After imaging diagnosis, the patient was referred to an exploratory laparotomy procedure for a hepatic nodule biopsy. Subsequently, the material collected was referred to a histopathology laboratory for analysis and was diagnosed as hepatic Cholangiocarcinoma. Immunohistochemistry analysis revealed the immune expression of CEA, and no expression of CK7, CK19, CD31, Herpar, and Vimentina, which confirmed the diagnosis. According to Flores et al. [3], CEA marker is the most specific marker for the Cholangiocarcinoma diagnosis.

The animal was referred to Natural Pet-Integrative Veterinary Clinic (Brasilia, DF, Brazil) on 10 November 2016. On this date, the homeopathic treatment with subcutaneous *Viscum album* extract (INJECTCENTER®, Ribeirao Preto, SP, Brazil) injections was instituted. A pre- established daily protocol comprised of 1 mL applications of each *Viscum album* concentration, was organized as follows: $1x10^{-3}+1x10^{-6}$ (day 1), $1x10^{-9}+1x10^{-12}$ (day 2), $1x10^{-30}+1x10^{-3}$ (day 3), and so on, during 30 days. "D" is the serial decimal dilution of the aqueous plant extract. The patient was conducted to the clinic once a week for chromotherapy and autohemotherapy sessions, in addition to the *Viscum album* injectable treatment. The auhemotherapy sessions were associated with intramuscular applications of 1mL of *Viscum album* $1x10^{-3}$. Five drops of a prepared homeopathic complex were also orally administered once a day. The complex had the following composition: *Taraxacum officinale* $1x10^{-60}$, Phosphorus $1x10^{-60}$, and *Carcinosinum* $1x10^{-400}$. Moreover, Vitamin D_3 3000IU and Omega-3 2000mg (one capsule of each) were administered once a day; and one capsule containing dry extract of *Curcumin* 150mg, *Piperine* 400mg, and *Momordica charantia* 150mg was administered twice a day. Furthermore, a ketogenic diet based on 30% animal protein, 50% saturated fats, and 20% vegetables was offered.

The animal was intensely assisted by its tutors, and the patient was not left alone from the beginning of the treatment onwards. On 20 December 2016, the animal exhibited eczematous dermatitis in the paravaginal region. This type of alteration often occurred during the patient's life. The disease was treated with injectable antibiotic therapy (Convenia® 4mg kg^{-1} - single dose). Chromotherapy sessions were suspended from 20 April 2017 due to the impossibility of the tutor of going to the clinic. The orally administered medications and *Viscum album* subcutaneous applications continue to be performed. As of 20 July 2017, *Viscum album* applications were carried out on alternate days.

Signs compatible with hemorrhagic gastroenteritis were observed on 05 August 2017, and the animal was treated with antibiotic therapy (Stomorgyl 20®, 1 capsule, SID, 6 days). Except by these two occurrences, the patient had a normal life with no evidence of pain or discomfort, as if she did not have the disease. There were no further complaints from the tutors until October 2017, when respiratory distress associated with emetic episodes were reported. The tutor of the animal signed a free consent term on 02 December 2017, allowing the publication of this clinical data.

Results and Discussion

Some of the clinical signs and biochemical changes most described in the literature were not observed until the fifth month of treatment. The serum levels of hepatic enzymes showed a slight initial oscillation, but they recovered to normal values throughout the treatment. The patient did not demonstrate clinical evidence of icterus at any time, as it is frequently observed in CCA cases.

According to [1,4,8], the presence of fluid in the abdominal cavity is commonly observed. It occurs in chronic liver diseases with fibrosis, due to portal hypertension and hypoproteinemia. However, no fluid was verified in the abdominal cavity in this case.

Malignant neoplasms of bile ducts display a highly invasive growth pattern, often resulting in metastases. The occurrence of the extrahepatic CCA in dogs varies from 60 to 88% [1]. Corroborating the findings of Trigo et al. (1982), the patient showed metastasis in the right lung and spleen (Figure 1). However, no nodules were observed in other organs, such as pancreas, stomach, brain, kidney, bones, thyroid, mediastinum, omentum or regional lymph nodes.

Ultra-diluted injectable *Viscum album* has been used worldwide in homeopathic and anthroposophical preparations. In Brazil, this extract is frequently used as a homeopathic medicine and presents several dilutions ($1x10^{-3}$; $1x10^{-6}$; $1x10^{-9}$; $1x10^{-12}$ and $1x10^{-30}$). The immunomodulatory action observed in the aqueous extract of this plant is also identified in homeopathic dilutions [16]. In this case report, immunomodulatory effects were observed right after the first autohemotherapy session associated with *Viscum album* $1x10^{-3}$, seven days after the beginning of the treatment (Table 1). Continuous and expressive increase in the white blood cell count was verified, which agrees with Kuttan [15]. The counter proof of this observation is given by the reduction of *Viscum album* application frequency with white blood cell count reduction (Table 1).

A 64% tumor growth rate increase (Table 2) and (Figure 4) was verified between October and November 2016 (37 days), when the animal was not following any type of treatment. A reduction of 13% in the tumor growth rate was verified in January 2017 compared to the previous period (October-November 2016). No tumor growth was detected between January and February 2017 (Figure 5 & 6), and its size and dispersion remained unchanged. From February to May 2017, the patient began to relapse, and a 37% tumor growth rate occurred in 94 days (Figure 6 & 7).

Table 2: Results of the image exams ultrasonography (US) and x-ray.

	10/10/2016	11/21/2016	1/23/2017	2/23/2017	5/27/2017
	TC (cm^2)	US (cm^2)/x-ray	US (cm^2)	US (cm^2)	US (cm^2)
Liver Nodule I	38.69	63.64	72.21	72.21	99
Liver Nodule II	Not visualized	Not visualized	Not visualized	Not visualized	0.96
Lung	4.9	15.96	Not performed	Not performed	Not performed
Spleen	Multiple nodules 0.31 to 1.32	Not visualized	Not visualized	Not visualized	1.05

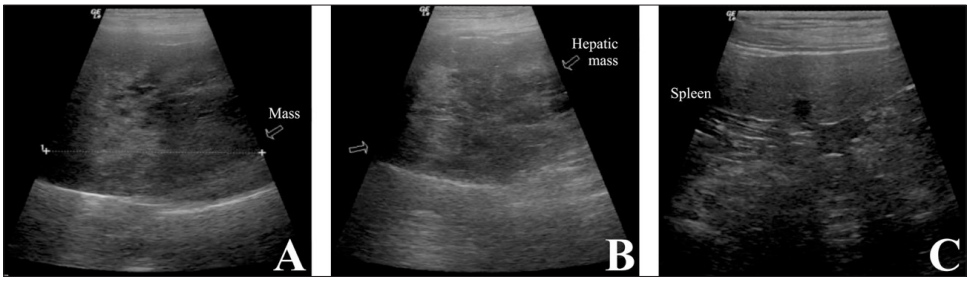


Figure 4: Abdominal ultrasonography (21 November 2016). A-B) Liver: nodule measuring 63.64cm^2. C) Spleen: no change worthy of note.

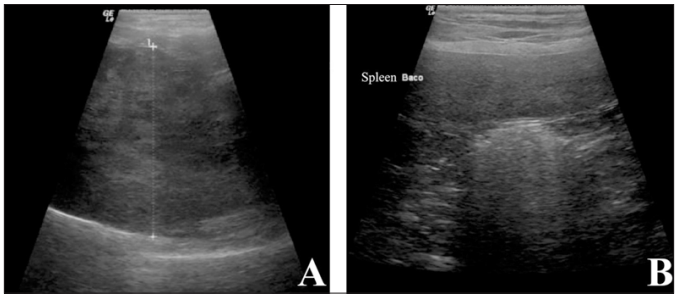


Figure 5: Abdominal ultrasonography (23 January 2017). A) Liver: nodule measuring 72.21cm^2; B) Spleen: no change worthy of note

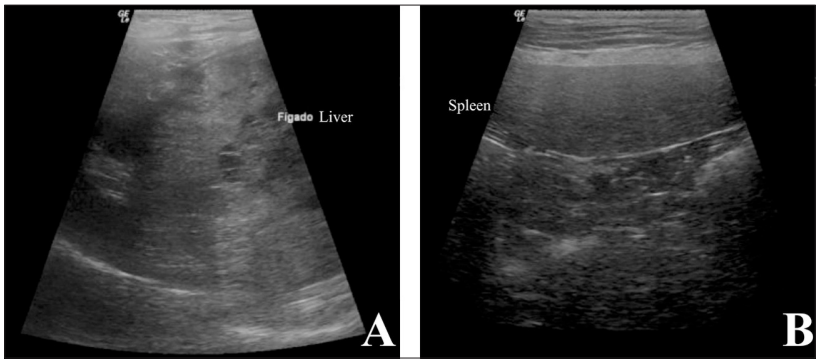


Figure 6: Abdominal ultrasonography (22 February 2017). A) Liver: nodule measuring 72.21cm^2; B) Spleen: no change worthy of note.

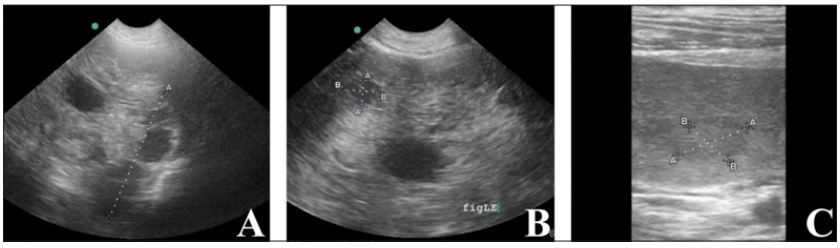


Figure 7: Abdominal ultrasonography (27 May 2017). A) Liver: nodule 1 measuring 99cm^2; B) Liver: nodule 2 measuring 0.96cm^2; C) Spleen: nodule measuring 1.05cm^2.

However, part of the treatment protocol was suspended from April 2017 onwards, as described above, after which the tumor mass began to grow again (Figure 6 & 7). Nevertheless, the size of the nodules was smaller than that recorded in the first month, in which the animal was not following any therapy (64% in 37 days). Additionally, the registered growth rate was of 37% in 91 days when the daily protocol of treatment by oral and subcutaneous applications was maintained (Figure 8).

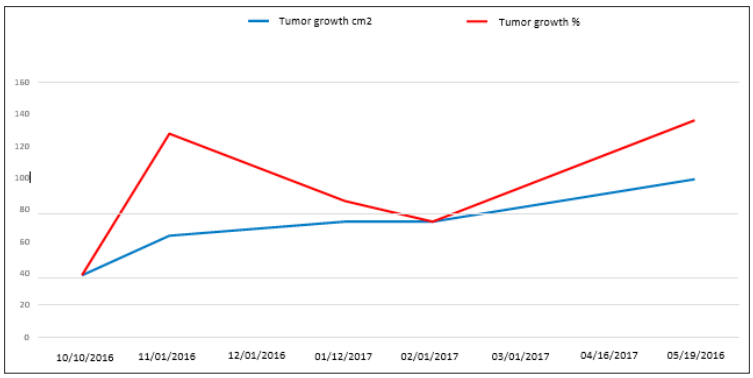


Figure 8: Cholangiocarcinoma tumor growth rate in a 12-year-old Australian Shepherd female, from October 2016 to November 2017, treated with ultra-diluted Viscum album extract.

The treatment here reported was effective in its purpose of increasing the patient's survival. The patient lived 11 months beyond the estimated prognosis described in the literature for this type of neoplasm (from 2 to 6 months) [1]. During the implementation of the complete treatment protocol, a significant reduction was observed in the tumor growth rate and an improvement in the white blood cell count (Table 1). Quality of life parameters showed that the animal was in perfect conditions for 11 months, with no alterations in its daily routine. The patient frequently played, ran, and performed all its functions, with no signs of pain or discomfort.

Conclusion

The alternative and integrated model of treatment presents certain peculiarities in the evolutionary response of oncological patients, which differ from the conventional approach. Alternative and integrated treatments are primarily aimed at ensuring the quality of life of the animal. The treatment protocol here reported did not result in complete tumor remission but improved the overall condition of the animal and increased survival in 11 months beyond the expected, according to the literature reports. The interruption

of part of the protocol directly influenced the disease evolution, possibly indicating the need for continuous and lifelong treatment to obtain the desired results.

References

1. Cullen JM, Popp JA (2002) Tumors of the liver and gall bladder. In: Meuten DJ (Ed.), Tumors in domestic animals, Iowa State Press, California, USA, pp. 483-508.
2. Kelly WR (1993) The liver and biliar system. In: Jubb KVF, Kennedy PC (Eds.), Pathology of domestic animals. Academic Press, San Diego, California, USA, pp. 319-406.
3. Flores MM, Bianchi RM, Kommers GD, Irigoyen F, Barros CSL, et al. (2013) Prevalence and epidemiological, pathological and immunohistochemical aspects of primary canine malignant hepatic tumors in Rio Grande do Sul, Brazil (1965-2012). Pesquisa Veterinaria Brasileira 33(4): 497-511.
4. Patnaik AK, Hurvitz AI, Lieberman PH, Johnson GF (1981) Canine bile duct carcinoma. Veterinary Pathology 18(4): 439-444.
5. Bonfanti U, Bussadori C, Zatelli A, Lorenzi D, Masserdotti C, et al. (2004) Percutaneous fine-needle biopsy of deep thoracic and abdominal masses in dogs and cats. Journal of Small Animal Practice 45(4): 191-198.
6. Mischke R, Hoinghaus R, Lutkefels E, Buhl K, Gerhardt A, et al. (2003) Immunocytological confirmation of bone marrow metastases in a dog with cholangiocarcinoma. Journal of Small Animal Practice 44(9): 411-414.
7. Maclachlan NJ, Cullen JM (1998) Liver, biliar system and exocrine pancreas. In: Carlton W, Mcgavin MD (Eds.), Thompson's Special Veterinary Pathology, Artmed, Porto Alegre, Brazil, pp. 95-131.
8. Kienle GS, Kiene H (2010) Influence of *Viscum album L* (*European Mistletoe*) extracts on quality of life in cancer patients: A systematic review of controlled clinical studies. Integrative Cancer Therapies 9(2): 142-157.
9. Delebinsky CI, Twardziok M, Kleinsimoml S, Hoff F, Muslow K, et al. (2015) A natural combination extract of *Viscum album* L. containing both triterpene acids and lectins is highly effective against AML in vivo. PLoS One 10(8): 1-20.
10. Tabiasco J, Pont F, Fournie JJ, Vercellone A (2002) Mistletoe viscotoxins increase natural killer cell-mediated cytotoxicity. European Journal of Biochemistry 269(10): 2591-2600.
11. Carvalho AC, Porto E, Bonamin L (2013) Canine neurofibrosarcoma treatment with *viscum album* in serial dilutions. International Journal of High Dilution Research 12(44): 106.
12. Werner M (2014) Efficacy and safety of mistletoe extract in the palliative therapy of patients suffering from pancreatic cancer (PALM-Pan) study no. 33-04, EudraCT no. 2014-002386-30 Kirschweg 20149.
13. Huber R, Ludtke H, Wieber J, Beckmann C (2011) Safety and effects of two mistletoe preparations on production of Interleukin-6 and other immune parameters-a placebo controlled clinical trial in healthy subjects. BMC Complementary and Alternative Medicine 11(1): 116.
14. Estko M, Baumgartner S, Urech K, Kunz M, Reguero U, et al. (2015). Tumour cell derived effects on monocyte/macrophage polarization and function and modulatory potential of *Viscum album* lipophilic extract *in vitro*. BMC Complementary and Alternative Medicine 22: S27-S28.
15. Kuttan G, Kuttan R, Kaveri S (1992) Immunological mechanism of action of the tumor reducing peptide from mistletoe extract (NSC 635089) cellular proliferation. Cancer Letters 66(2): 123-130.