A SYSTEMATIC REVIEW ON CURCUMIN AS AN ANTI CANCER TREATMENT IN CANINE PROSTATE CARCINOMA

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CERTIFICATION

This is to certify that we have read this research paper entitled **'A Systematic Review on curcumin as an anti-cancer treatment in canine prostate carcinoma'** by Aruut Sudarr A/L Prim Kumar, and in our opinion it is satisfactory in terms of scope, quality and presentation as partial fulfillment of the requirement for the course DVT 5436 – Research Project.

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Family

Friends

Thank you

DEDICATION

I glad to dedicate my thesis to my family, especially my father, Prim Kumar A/L Retnam and my mother, Pechayee A/P Supramaniam for their belief and support. Also my sister, Arrull Molyy A/P Prim Kumar and my brother, Arul Amutan A/L Prim Kumar for always encouraging me and setting great examples.

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ABSTRACT

An abstract of the research paper presented to the Faculty of Veterinary Medicine, Universiti Malaysia Kelantan, in partial requirement for the course DVT 5436 – Research Project.

Canine prostate carcinoma is a malignant cancer that is able to rapidly proliferate and metastasize to other body systems. It has low prevalence; about 1%. It is mostly diagnosed in median age dogs especially in dogs aged more than 10 years age. Canine prostate carcinoma has poor prognosis with limited treatment options and poor outcomes of these treatments. Curcumin (diferuloylmethane) is a derivative of Curcuma longa, from family Zingiberaceae. It is contains polyphenolic compound, curcuminoids that is a potent tumor suppressor due to its property of stimulating apoptosis by triggering cell cycle arrest and suppress oncogenic pathway. The collective information on the use of curcumin for canine prostate carcinoma treatment is disjoined and not readily accessible for clinical and academic reference. This is a systemic review to summarise the researches done with curcumin as a potential anti-cancer treatment for canine prostate carcinoma. Thus, a total of 2,154 publications were collected from Science Direct and PubMed using 12 search phrases. 19 published articles have met the set research criteria. Even though, there aren't any published articles on curcumin as anti-cancer treatment for canine carcinoma, it shows great potential to be used in treatment for canine prostate carcinoma. Several researches are already been conducted in human prostate cancer using curcumin as anti-cancer treatment that shows promising outcome. Study and research on curcumin as canine prostate carcinoma treatment should be at prompt given its great potential to work alone and work synergistically with practicing anti-cancer treatments.

Key words: Curcumin, Prostate cancer, Canine, Therapy

Abstrak

Abstrak penyelidikan dikemukakan kepada Fakulti Perubatan Veterinar, Universiti Malaysia Kelantan, untuk memenuhi sebahagian daripada keperluan krusus DVT 5436 – Projek Penyelidikan.

Kanser prostat anjing adalah kanser malignan yang mudah sebar ke seluruh sistem badan. Kelaziman kanser prostat dalam anjing adalah 1% dimana ia kerap dijumpa dalam anjing berumur lebih daripada 10 tahun. Prognosis kanser ini adalah kurang baik. Rawatan untuk kanser prostat anjing yang sedia ada adalah terhad dan prognosisnya kurang baik. Curcumin (diferloylmethane) diperolehi daripada *Curcuma longa*, dari keluarga Zingiberaceae. Kandungan curcumin adalah kompaun curcuminoid, yang boleh rawat kanser melalui memberhentikan kitaran sel, apoptosis dan sebagainya. Kajian dan rekod yang sedia ada, menyatakan potensi curcumin sebahagain agen anti- kanser tidak sesuai untuk dirujuk oleh kilink dan penyelidikan. Dalam pengajian ini sejumlah 2,154 artikal pengajian telah diperolehi daripada 'PubMed' dan 'Science Direct'. 19 artikal menyatakan curcumin mempunyai potensi yang tinggi untuk digunakan sabagai rawatan kanser. Kebanyakan artikel diperolehi telah merekodkan kegunaan curcumin dalam rawatan kanser kelenjar susu. Walau bagaimanpun, artikal yang menunjukkan kegunaan curcumin dalam rawatan kanser prostat belum diterbitkan. Pengajian ini memunjukkan potensi tinggi curcumin untuk digunakan sebagai rawatan untuk kanser prostat anjing. Pengajian ini juga menyatakan bahawa curcumin memberi prognosis yang lebih baik apabila digunakan dengan rawatan kanser yang sedia ada. Potensi yang tinggi telah didemonstrasi oleh curcumin, sebagai rawatan anti kanser. walaubagaimanpun banyak lagi pengajian perlu dibuat untuk mendapatkan konklusi yang signifikan.

Kata kunci: Curcumin, kanser prostat, Anjing, Rawaten

1.0 Introduction

Curcumin (diferuloylmethane) is a derivative of Curcuma longa from family Zingiberaceae. It is obtained from the roots of turmeric and appears naturally yellow. It's a phytochemical which has potent tumor suppressor activity due to its property where it stimulates apoptosis, triggers cycle arrest and suppress oncogenic pathway (Imran *et al.,* 2017). The polyphenolic compound or curcuminoids represents 2- 4% of the dry weight of the medicine are known for their anti-cancer, anti-inflammatory, anti-oxidanr, anti-viral, anti-parasitic, anti-bacterial, anti-fungal and low toxicological properties (Ali *et al.,* 2006).

Turmeric has been long known for its use as spice, food preservative, anti-inflammatory properties, blood purifier, antiseptic properties, cosmetics, and colouring agent and so on. It is now being known for its anti-cancer effect (Ali *et al*., 2006). Carcinogenesis involves three different yet interrelated stages; they are initiation, promotion and progression. During the stage of promotion inflammatory and oxidative tissue damage plays an essential role. The potent anti-inflammatory characteristics and anti-oxidant characteristics of curcumin prevent cancer by suppressing promotion of tumor. Besides that, curcumin also inhibits growth and induces apoptosis in a range of different cell types; this had been seen in ceased of cancer cells in S, G2/M phase in cell cycle.

Curcumin are active in several different pathways. These pathways include inhibiting signals through NF-κB, which regulates gene expression, including of COX-2. COX-2 is the enzyme responsible for malignant transformation and inflammation. Curcumin also interacts with many cell regulatory proteins, such as mitogen activated protein cascade; this directly inhibits v-Src, which leads to a decrease in phosphorylation of Shc, cortactin and focal adhesion kinase directly. Inhibition of focal adhesion kinase causes loss of Src mediated cell mobility which helps in to prevent invasion and metastasis. Curcumin also inhibits action of several

cytochrome P-450s, phenol sulphotransferase and glutathione S- transferases resulting in anti-carcinogenic action.

Dysregulated de-differentiation, apoptosis, cellular proliferation, and progression toward the neoplastic phenotype by effects on key signalling pathways are inhibited by curcumin (Asai A, Miyazawa T., 2000).

2.0 Research problem

The bioavailability and extensive metabolism of curcumin that many of its anti-cancerous effects observed in vitro may not be attainable in vivo (López-Lázaro, 2008). The collective information on the use of curcumin for cancer therapies are disjointed and not readily accessible for clinical and academic reference. The available data on the use of curcumin in canine prostate cancer therapy is scant and not necessarily useful for inferential purposes.

3.0 Research questions

I. What is the significance of curcumin to be used as an anti- cancer treatment for canine prostate carcinoma?

II. Does curcumin shows potential as an anti-cancer treatment for canine prostate carcinoma?

4.0 Research hypothesis

I. Curcumin could be a potent anti- cancer treatment in canine prostate carcinoma, given its anti- cancerous properties.

II. Curcumin could be used in combination with clinically practiced anti-cancer treatments to obtain a synergistic effect.

5.0 Research objective

I. To identify the potential of curcumin to be used as an anti-cancer treatment in canine prostate carcinoma.

II. To identify if researches should be continued on curcumin as anti–cancer treatment in canine prostate carcinoma

6.0 Literature review

6.1 Cancer treatment

Cancer chemotherapy is defined as the use of anti-neoplastic agents in the treatment of malignant growth (Studdert *al*.,2012). Mechanisms of action of cancer chemotherapy to cure and treat tumors is through killing rapid dividing cells generally via targeting DNA in the cell nucleus or affect a cell's ability to synthesize protein (Shield, 2016). Chemotherapeutic agents cannot differentiate normal and tumor cells because both normal and tumor cells are active dividing cells (Chun *et al.*,2007). Toxicity is the major concern of side effect caused by cytotoxic chemotherapy drugs. The common toxicities induced are hematopoietic toxicities, gastrointestinal toxicities, hypersensitivity and extravasation. Hepatotoxicity, pancreatitis, cardiotoxicity, uroepithelial toxicity, pulmonary toxicity, neurotoxicity and nephrotoxicity are caused by selected cytotoxic chemotherapy agent (Dhaliwal, 2009).

6.2 Canine prostate cancer

Canine prostatic tumor is rare with prevalence about 1%. It is commonly seen in median aged dogs, where most cases are diagnosed at the age of 10. There is increased risk of canine prostate cancer in neutered dogs (Schrank, Romagnoli, 2020). Shetland sheepdogs, and Scottish terriers. The tumor may arise from glandular epithelium, prostatic duct or prostatic urethra. The cancers rapid proliferation and high risk of metastasis which is reported in 80% of the necropsy studies (Dacvim *et al.,* 2017).

The prognosis is poor as majority of dogs are diagnosed with advanced disease state. Treatment is palliative, focusing on controlling local and distant metastatic disease. Several surgical techniques are available, the preferred being subtotatl intracapsular prostatectomy but poor outcome due to high morbidity and poor outcome (Dacvim *et al*., 2017).

6.3 Curcumin

Curcumin (diferuloylmethane); [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-hepadiene-3,5-dione]), isolated from Curcuma longa. It is a phytochemical with potent tumor suppression activity, which has shown significant efficacy in pre-clinical and clinical studies (Ali *et al.*, 2006b). Curcumin trigger cycle arrest and suppresses oncogenic pathways and cell death. It shows wide efficacy for in vivo inhibition of mutagen-induced tumor formation in the skin, forestomach, stomach, esophagus, duodenum, colon and tongue (Campbell & Collett, 2005).

The pharmacokinetics of curcumin is, in rat about 75% of orally given curcumin is excreted in feces and only traces in urine. In vitro it took 30 minutes for hepatocytes to be metabolized (Ali *et al.*, 2006b).

Angiogenesis is an important mechanism in a number of diseases; such as atherosclerosis and cancer. Curcumin's anti-angiogenic action is mediated by inhibition of vascular endothelial growth factor (VEGF) at a molecular level, angiopoiteins (Ang 1 and Ang 2) and inhibition of fibroblast growth factor induced fibrogenesis (Dulak.J, 2005). Increased bone reabsorption is observed in bone inflammation and cancer diseases. Curcumin is known to inhibit bone resorption and stimulate cell apoptosis (Ozaki K., 2000).

Most of the data supporting the anti-neoplastic properties of curcumin were obtained in vitro. Curcumin is being clinically evaluated as a chemo-protective agent for major cancer targets that include prostate, colon and lungs (Manson *et al*).

6.3.1 Anti-inflammatory properties

Curcumin was first described as a potent modulator of inflammatory cell signalling by Aggarwal and co-workers. This showed high potential of curcumin to be used as an anti-cancer drug because tumorigenesis requires angiogenesis, survival, proliferation, metastasis and invasion (Coussebs, L. M., 2002). Curcumins anti-inflammatory effects are mainly done by inhibiting nuclear factor – κB (NF- κB) signalling pathway by inhibiting proteasome function. Curcumin is able to target several components in this pathway. NF – κB regulates expression of greater than 450 genes such as numerous oncogenes, anti-apoptotic genes like Bcl-2 and X linked inhibitors of apoptosis (XIAP), tumor cell proliferation like cyclins, angiogenesis like vascular endothelial growth factor (VEGF), invasion potential like matrix metalloproteinases, growth factors like epidermal growth factor (EGF) and tumor necrotic factor (TNF α) (Marin, M. E., 2007). This polyphenolic compound was proven to suppress activation of IκBα kinase (IKK), the degeneration and phosphorylation of IκBα and nuclear translocation and phosphorylation of p5 subunit in several cancer and premalignant cell types. Similar results were shown in multiple myeloma patients and pancreatic cancer patients. Curcumin also effects molecular events involving inflammation and subsequent tumor promotion; such as inflammatory cytokines TNF α, interleukines IL-8, IL-1 and IL-6, inflammatory transcription factors (STATs) and inflammatory enzymes like Cyclooxygenase (COX) – 2 , 5- lipoxygenase (LOX). The inhibition of NF – κB and STAT1 suggested to be resulting in inhibition of COX-2, reactive oxygen generating enzymes in inflammatory pathway (Wang *et al.*, 2009).

6.3.2 Tumor cell proliferation and invasion

Carcinogenesis involves oxidative stress, hormonal imbalance and chronic inflammation. Curcumin mainly affects the tumorigenesis by decreasing proliferation of cancer cells by arresting cell cycle. This effect was seen in prostate, neck, mammary and lung cancer. Curcumin triggers the cyclin-dependent kinase (CDK) expression by inhibiting p16, p21, and p 27. It also inhibits cyclin E and cyclin D1 expression as well as hyperphosphorylation of retinoblastoma (Rb) protein. Eventually these events results in cell cycle disruption and cell death by apoptosis (Srivastava *et al.,* 2007).The central seven carbon chains of curcuminoids are essential for the anti -proliferative property. Modulation in cyclin is affected by curcumin on the Wingless (Wnt) signalling pathway, through modulation in β-catenin or T-cell factor (TCF) or lymphoid enhancer factor (LEF) as studied conducted in colon cancer, osteosarcoma and mammary gland cancer (Leow *et al.,* 2009). Decrease in β-catenin or TCF transcriptional activity was observed at a nuclear level which resulted in inhibition of tumor growth tested in animal model with adenomatous polyposis. Reduced regulation of phosphatidylinositol 3-kinase (PI3K) or Akt signalling pathways also contributes to cancer cell growth and survival. Thus, by inhibiting these pathways can provide anti-cancer effects. Curcumin demonstrates good inhibition of PI3, which is mammalian target for rapamycin (mTOR) signalling pathway in prostate cancer and other type of cancers. This results in call death through apoptosis and down regulation of downstream effector protein and genes such as NF-κB, p53, eukaryotic initiation factors that initiates protein synthesis. Variants of curcumin also exhibited inhibition of cell proliferation in prostate cancer by disrupting P13 or Akt or mTOR signalling pathways. Curcumin also showed inhibition of proangiogenic components like angiopoietin 1 and 2 gene, Kinase Domain Region (KDR), cell surface expression of vascular cell adhesion molecules (VCAM-1) and matrix metalloproteinases (MMPs), which plays a major role in angiogenesis by neovascularisation, tube formation and

endothelial cell migration when tested in prostate carcinoma, melanoma, mammary gland tumor, and lung tumor. Besides that, curcumin demonstrated down regulation of epidermal growth factor receptor (EGFR), which plays a role in cancer cell proliferation of prostate carcinoma, mammary tumor and colon cancer (Lev-Ari *et al.*, 2006).

6.3.3 Genomic modulator

Epigenic modification like post-translation histone modification and DNA methylation involves acetylation, phosphorylation, methylation, sumoylation and ubiquitylation. DNA methylation is mediated by DNA methyltransferases (DNMTs) (Liu *et al.,* 2009).The catalytic thiolate of the C1226 of DNMT1 is blocked by curcumin through covalent bond, that results in DNA hypomethylation leading to subsequent death of tumor cells. Besides that, histone deacetylase (HDAC) and histone acetyltransferase (HAT) and, histone acetylation is essential for chromatin remodelling and regulation of gene transcription. When studied the epigenic mechanism, curcumin demonstrated to be a potent inhibitor of p300/CREB Binding Protein (CBP) histone acetyltransferase that inhibit histone hypoacetylation by blocking HAT by promoting proteasomal degradation (Ropero *et al.,* 2007).

6.3.4 Mechanism of induced cell death

Apoptosis is the main modulation of curcumin to induce tumor cell death. But, poor prognosis is shown id cancer cells that are resistant to apoptosis. However, along with apoptosis mitotic catastrophe mechanism inducing cell death is shown by curcumin (Woo, J. H. *et al.,* 2003).

6.3.4.1 Apoptosis

Apoptosis is initiated by extracellular ligands and intracellular stress signals due to DNA damage and stress. Curcumin is able to downregulate anti apoptotic protein and promote pro apoptotic proteins. This induces opening permeability transition pores in mitochondria. This releases cytochrome c and activates apoptosome and cleavage of caspase 3, caspase 6, polymerase (PARP) and Poly (ADP-ribose) that leads intrinsic apoptosis and cancer cell death. Besides that, activation of cell membrane receptors (Fas, TRAIL) induces extrinsic apoptosis pathway by assembly of death inducing signalling complex (DISC) (Anto, R.J *et al.,* 2008).

6.3.4.2 Mitotic catastrophe (MC)

MC is aberrant mitosis induced cell death. Curcumin has been reported to have shown mitotic spindle structure disruption. Curcumin showed induction in cell cycle arrest at G2/M by down regulating survivin, a cell division modulator (Holy, J.M. *et al* 2002).

6.3.4.3Synergism with conventional therapy

Curcumin has shown promising synergism with radiation where significant radiation-induced clonogenic inhibition was observed. The combination reduces TNF α mediated NF-κB activity that activates cytochrome c, caspase3 and caspase 9 in prostate cancer cells and colorectal cancer cells. Reactive oxygen species (ROS) and extracellular signal regulated kinase (ERK) was increased that suggest curcumin to be a potent radio sensitizer in prostate cancer (Javvadi *et al.,* 2008).

TNF α related apoptosis inducing ligand (TRAIL) showed increased sensitization when used with curcumin. TRAIL is an inducer of apoptosis and a cytokine that used in advanced prostate cancer. Prostate cancer cells showed resistant to TRAIL when used alone. In

combination with curcumin inhibition of active NF-κB, cleavage of pro-caspase 3, procaspase 8 and procaspase 9 and anti- apoptotic proteins XIAO, Bcl-xL and Bcl-2 (Shankar et al., 2008).

7.0 Methods

Preferred Reporting Items for Systemic Reviews and Meta- Analyses (PRISMA) was used to conduct this systematic review. This is done by using “OR” for alternatives and “AND” for termed to be included. Inclusion and exclusion criteria’s were also set to filer the articles obtained.

7.1 Literature search

PubMed and Science Direct were used as search engines for the literature research. No time frame was set during this research, in order to get a complete data on so far published papers on curcumin been used as anti- cancer treatment to get the potential of it been used in canine prostate carcinoma as anti-cancer treatment. Specific search phrases includes key words, “curcumin as anti-prostate cancer” OR “curcumin as anti- prostate carcinoma” AND “treatment in” AND “veterinary medicine” OR “veterinary practice” OR “veterinary science” we used. The results are tabulated in Table 1 and the summary of the results are tabulated in Table 2.

7.2 Screening, inclusion and exclusion criteria

To ensure the significance of the literature to the interest of study several screening was done. The inclusion criteria were published papers on use of curcumin, in any analogue to treat cancer *in vitro* or *in vivo*. Exclusion criteria were use of curcumin for different treatments other than cancer treatment, use of other anti-cancer agents for cancer treatments, prevalence, diagnosis, overview, books, index and pharmacology. This is to ensure the data collected are published research papers that are reliable.

The search results from PubMed and Science Direct was uploaded to EndNoteWeb to ease the filtration process. EndNoteWeb help to organise the search result in ascending manner based on year of publication. First screening was done by removing the duplicate of searched article obtained from the two resources and with manipulation of search words. Second screening was done manually where only articles that were related to curcumin were kept. Third screening was done to filter out articles that published use of curcumin in cancer treatment. Forth screening was done by reading abstracts of the screened articles to filter out irrelevant articles and also researches that used curcumin as an additive and not primarily for anti-cancer treatment. The process and results are illustrated in Diagram 1.

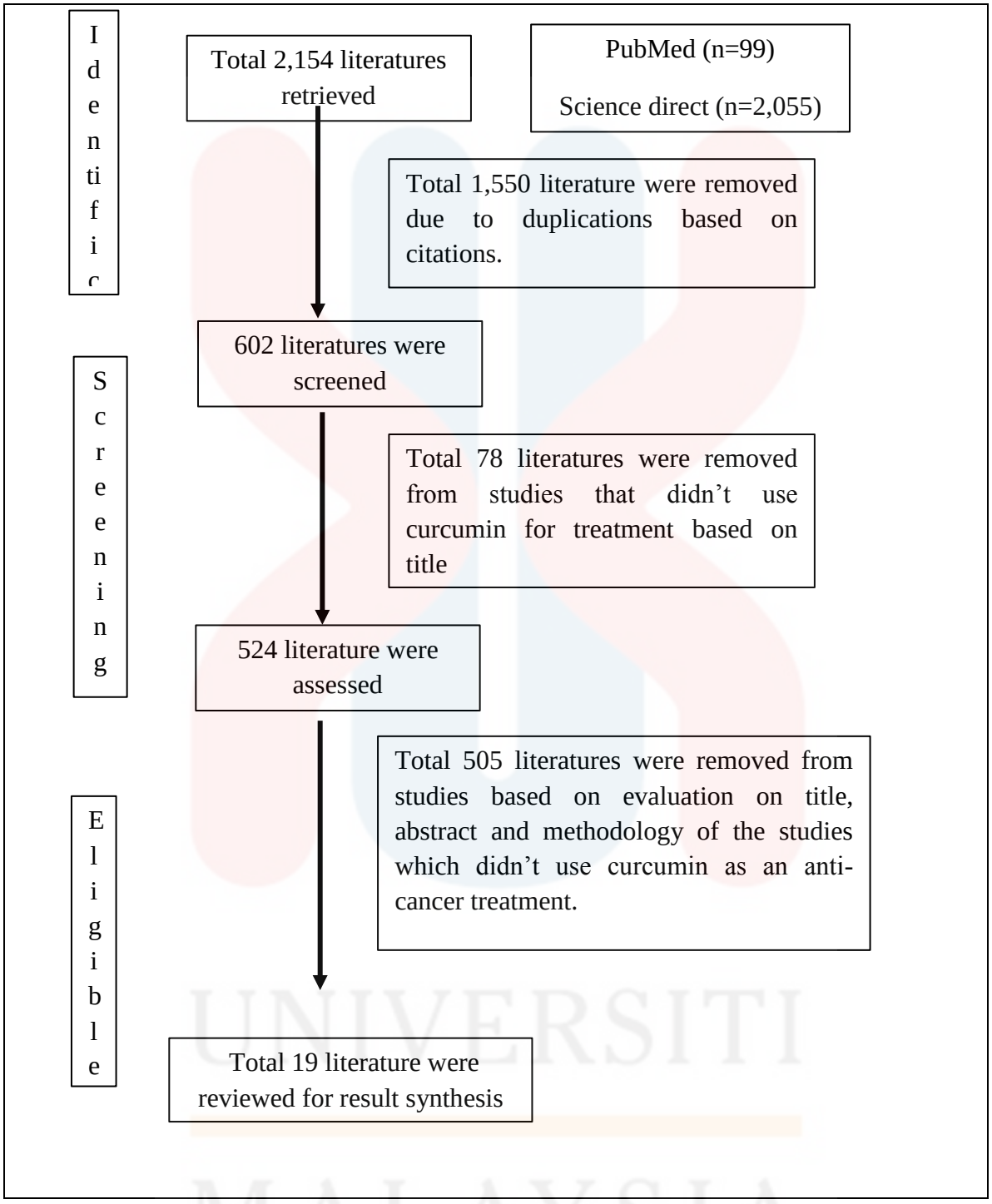

Diagram 1

7.3 Result synthesis

Search results from PubMed and Science Direct are tabulated below:

Search words	Database		
	PubMed	Science Direct	Total
Curcumin as anti- prostate cancer treatment in veterinary medicine	4	146	150
Curcumin as anti- prostate cancer treatment in veterinary science	3	143	146
Curcumin as anti- prostate cancer treatment in veterinary practice	0	37	37
Curcumin as anti- prostate carcinoma treatment in veterinary medicine	0	95	95
Curcumin as anti- prostate carcinoma treatment in veterinary science	0	95	95
Curcumin as anti- prostate carcinoma treatment in veterinary practice	0	37	37
Curcumin as anti-cancer treatment in veterinary medicine	43	467	510
Curcumin as anti-cancer treatment in veterinary science	34	461	495
Curcumin as anti-cancer treatment in veterinary practice	2	139	141
Curcumin as anti-carcinoma treatment in veterinary medicine	8	177	185
Curcumin as anti-carcinoma treatment in veterinary science	5	182	187
Curcumin as anti-carcinoma treatment in veterinary practice	0	62	62
Total	**99**	**2,055**	**2,154**

Table 1: Result of searched articles from PubMed and Science Direct

8.0 Result

From research conducted a total of 2,154 articles were obtained from Pubmed and Science Direct. First screening had discarded 1,550 of duplicate articles using EndNoteWeb, resulting in 602 articles. . Second screening, which was done manually to obtain only articles that were related to curcumin resulted in 524 articles. Third screening was done to filter out articles that published use of curcumin in cancer treatment resulted in 130 articles. Forth screening was done by reading abstracts of the screened articles to filter out irrelevant articles and also researches that used curcumin as an additive and not primarily for anti-cancer treatment resulted in 19 articles.

Therefore 19 articles were chosen to be reviewed for this study, about 99% of the search results were removed because there are high amount of studies and papers published on the use of curcumin on non-cancer treatments given its wide medicinal properties like anti-parasitic use, anti-viral use, treatment for ulcerative colitis, anti-oxidant use, anti-microbial use, anti-fungal use, anti-coccidial use, treatment for alcoholic fatty liver disease, heartworm treatment, anti-toxin use and use in improvement of production animals, mainly in poultry.

Out of the 19 articles obtained 40% were on mammary gland tumor treatment using curcumin. Next, 15% of the results were on colorectal cancer treatment using curcumin. 10% were on lung cancer treatment and osteosarcoma treatment using curcumin each. Pancreatic cancer treatment, hepatic cancer treatment, mucoepidermoid carcinoma treatment, canine melanoma treatment, gastrointestinal cancer treatment and bladder cancer treatment using curcumin carried about 5% each from the total obtained articles.

Different studies used curcumin and its analogues which had clearly demonstrated curcumins use in different forms its great potential to be an anti-cancer treatment. Curcumin had also reported synergistic effects with multiple other anti-neoplastic drugs and with already

practicing anti-cancer treatment. The reviewed articles had also demonstrated different mechanism of action of curcumin to give cancer suppression. This shows that's curcumin is able to hit multi targets in cancer treatment.

Author, year of publication	Targeted study	Route	Form	Mechanism of action	Sp.	Result	Conclusion
Singletary,Keith (1996)	Mammary gland tumor	IP	Curcumin (diferoylmethane)	Down regulates initiation stage of DMBA – induced mammary tumorigenesis of rat.	Rat	Decrease in palpable mammary tumors and mammary adenocarcinoma. When administrated at dose of 50 mg/kg to 200 mg/kg.	Curcumin administration intra peritoneal in female rat prior to dosing with DMBA showed association with a potent inhibition of mammary carcinogenesis and the vivo formation of mammary DMBA-DNA adducts.
Jutooru, Indira (2010)	Pancreatic cancer	IP	Curcumin (98% pure)	Inhibition of NF – κB, apoptosis induction, anti-angiogenesis, inhibit expression of p65 and p50 proteins along NF – κB dependant transactivation and down regulates Sp4, Sp3 and Sp1 transcription factor. Which lead to knock	Nude mice	Curcumin was able to induce apoptosis of cancer cells by cell cycle disturbance.	Curcumin is a potent anticancer component.

				down by RNA interference. Curcumin also reduces mitochondrial membrane potential and induced ROS.			
Agashe, Hrushikesh (2001)	Lung cancer	IV	Curcuminoid 4-[3,4-bis(2-chlorobenylidene – 4 – oxo – piperidine – 1 –yl) – 4 –oxo – 2-butenoic acid] / CLEFMA	Induces apoptosis in lung cancer cell by inhibiting IkappaB.	Nude rat	Tumor volume significantly reduced after CLEFMA i.v. treatment. 94% of tumor was inhibited. No liver, lung and kidney toxicity.	Curcumin demonstrate its novel efficacy.
Ibrahim, Abdelazim (2011)	Mammary tumor		Curcumin	Intrinsic apoptosis, increase ROS production and inhibit Bcl-2 oncoprotein.	Nude mice	Mitochondrial uniporter partially inhibited curcumin effects.	Curcumin is a potent anti-carcinogenic compound.
Dhule, Santosh S. (2012)	Osteosarcoma and mammary tumor		Liposomal nanoparticles 2- Hydroxypropyl - $_{\gamma}$ - cyclodextrin 10:1 ratio		In vitro	Has good potential as delivery vehicle of treatment.	
El-Shaht, Mohamed (2012)	Hepatocarcinoma	PO	5% turmeric diet	Mixture of 5% turmeric in standard laboratory.	Rat	Delayed the initiation of carcinogenesis that was induced by	*Curcuma Longa* is a much potent anti-cancer effects compared to

						diethylnitrosamine (DENA), which couldn't be induce by myrrh (*Commiphora molmol*)	*Commiphoramolmol.*
Lee, Heang – Eun (2014)	Mucoepidermoid carcinomas	IP	Dibenzylideneacetone (DBA)	Apoptosis by inhibition of Sp1 protein.	Nude mice	DBA induced apoptosis in mucoepidermoid carcinoma. It also regulated Sp1, Bim and t-Bid without any toxicity.	DBA is a potent anticancer treatment for mucoepidermoid.
Dong, Y. (2016)	Mammary gland cancer		Diabolocurcumin ether (T1) and demethoxybisabolocurcumin ether (T2)	Increase in ROS that leads to apoptosis	In vitro	T1 and T2 induced threefold of anticancer effects compared to novel curcumin.	T1 and T2 were more potent than novel curcumin.
Madan, Esha (2018)	Mammary gland cancer		Curcumin analog HO-3867	HO-3867 covalently binds to mutant p53 and initiates wildtype p53	In vitro	Wildtype p53 is induced by HO-3867, which makes cancer cells more susceptible to treatment.	Curcumins is a potent anticancer agent.

Withers, S. S. (2018)	Canine osteosarcoma, melanoma and mammary carcinoma	IV	Lipocurc (liposome –encapsulated curcumin)	Inhibition of endothelial cell viability, migration and tube formation.	Cancer bearing dog	Anti-angiogenesis properties was shown in the experiment.	Curcumin is has anti-angiogenesis properties that makes it a potent anti-cancer treatment.
Gao, J. (2019)	Canine mammary carcinoma	IV and intratumoral	Curcumin		Dog	The delivery system influences the effectiveness of the drug that leads to reduced clinical dosing and reduce toxicity.	Intravenous and intratumoral administration of curcumin makes it more potent.
Srivastava, N. S. (2019)	Gastrointestinal cancer		Curcumin and quercetin	Apoptosis and inhibition of Wnt/β-catenin	In vitro	Curcumin and quercetin showed synergistic effect on promoting cancer cell apoptosis.	Curcumin and quercetin has synergistic anti – cancer effects.
Ashrafiadeh, M. (2020)	Lung cancer	IP	Curcumin	Anti- angiogenesis and NF – κB	Mice	Curcumin targets rapamycin, PI3/Akt, microRNAs and noncoding RNAs in lung	Curcumin is able to induce better anti-cancer effects in combination with conventional

						cancer treatment and promotes apoptosis. It also increases radiotherapy efficiency.	cancer treatment.
Ashrafiadeh, M. (2020)	Bladder cancer		Curcumin	Disturbs signalling pathway PI3K, Akt, mTOR, VEGF		Curcumin was able to inhibit metastasis and invasion of bladder cancer cells.	Curcumin is a potent treatment for anti- cancer treatment in bladder cancer
Ashrafiadeh, M. (2020)	Mammary tumor		Curcumin	Synergistic effects with PTX	In vitro	Curcumin was able to work synergistically with paclitaxel (PTX) and enhanced anti-tumor activity and reduces the adverse effects.	PTX in combination shows better anti- cancer effects.
Kuo, I. M. (2020)	Colorectal cancer	PO	Nano sized curcumin	Apoptosis	Rat	Modulated electro-hyperthermia (mEHT) works synergistically with curcumin and induces apoptosis and increase in	Curcumin shows synergistic effects with mEHT.

					serum level of curcumin.	
Raashekaraiah, Rashmi (2020)		Curcumin	Apoptosis, cell cycle arrest, DNA demethylating activity.	In vitro	Curcumin showed synergistic effects with – thioguanine encapsulated chitosan nanopracticles (6-TG-CNPs) by reversing epigenetic dysregulation by DNA demethylation.	Curcumin showed synergistic effect with 6-TG-CNPs
Elbadawy, M. (2021)	Colorectal cancer	Amorphous curcumin	Cell cycle arrest, induce apoptosis.	In vitro	Amorphous curcumin inhibited phosphorylation of ERK signal pathway. Amorphous curcumin showed synergism with colorectal cancer organoids and induced apoptosis.	Amorphous curcumin has better bioavailability and solubility; synergistic effects with CRC organoids make it a potent anti-cancer treatment.

Ojo, O. A. (2022)	Colorectal cancer	Curcumin	Intrinsic and extrinsic apoptosis, autophagy activation and cell cycle arrest.	Curcumin is able to induce apoptosis, cell cycle arrest and autophagy.	Curcumin has great potential for been used as anti – cancer treatment in colorectal cancer.

Table 2: Summary of searched articles that used curcumin in cancer treatment from PubMed and Science Direct

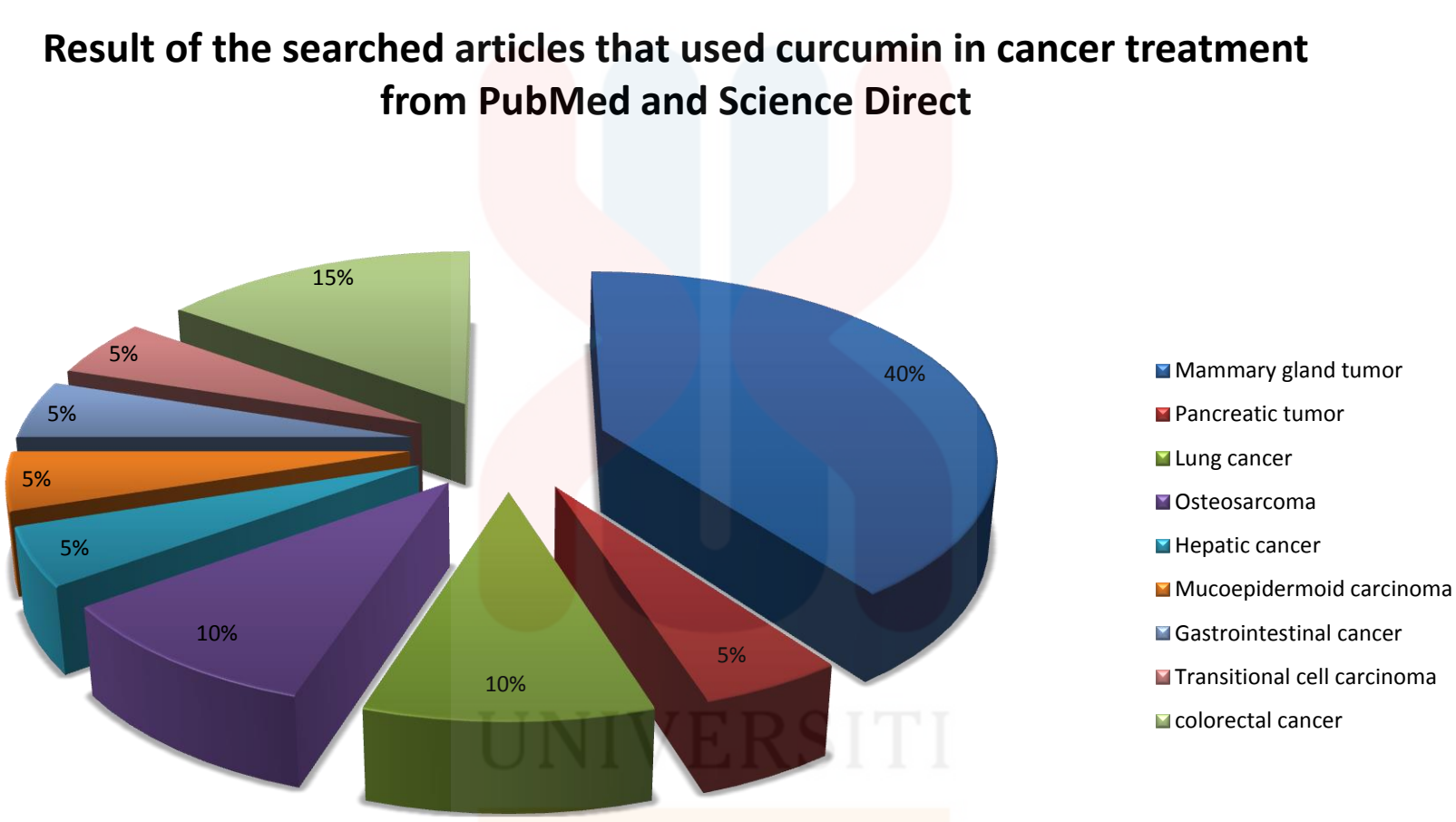

Chart 1: Result of the searched articles that used curcumin in cancer treatment from PubMed and Science Direct

9.0 Discussion

From the research that had been carried out, curcumin shows high potential to be an anti-cancer treatment. Still, there are not any papers published on canine prostate carcinoma treatment using curcumin. This could be due to the fact canine prostate cancer is a rare cancer in canine with the prevalence of 1% (Dacvim *et al.,* 2017). Nevertheless, there still aren't any advancement in treatment options to treat canine prostate carcinoma and about 3% of the cancer developed by male dogs are prostate cancer (Krawiec, Heflin 1992). Also, the available treatment possesses high potential to cause post – operative complications (Bennrtt *et. Al.,* 2018). Luckily, curcumin have been used to treat prostate cancer in human with promising results; it being the highly occurring non- cutaneous cancer in human. About 29% of cancer in American men is prostate cancer (Aditya *et al*., 2014). Research had also showed canine prostate and human prostate are similar in terms of anatomical, physiological and histological similarities (LeRoy, Northrup 2009). Dogs are considered to be an important model for understanding and treating prostate cancer in men (Ryman-Tubb *et al.,* 2021).

Most of the available chemotherapeutic agents available are designed to work on a single intracellular target like to inhibit vascular endothelial growth factor, counteract tumor necrosis factor and so on. In order to overcome cancer a multi-target drug is required to initiate and promote hundreds of gene or signalling cascade. Curcumin, component from Curcuma longa exhibits a wider range of activities given its ability to hit different intracellular targets.

Diferuloylmethane or curcumin is a polyphenolic component extracted from rhizome of the plant Curcuma longa. It is also widely used in traditional medication like Hindu and Chinese traditional medicine, Ayurvedic and so on. Current researches show curcumin to be a promising chemopreventive compound that is able to inhibit, reverse or prevent cancer

development by inhibiting specific molecular signalling pathways. Research has also showed poor bioavailability in tissue and plasma even at high doses, 12g / day due to its short biological half-life and poor water solubility at its raw form.

Curcuminoids, demethoxycurcumin are analogues of curcumin has chemical structure that has low hydrogenation and high methoxylation with unsaturation of diketone moiety makes it have high potential of anti-inflammatory and anti-cancer properties. It has a great kinetic stability and therapeutic index due to glycosylation of its aromatic ring, which makes it more water soluble and increased bioavailability in plasma and tissue (Sandur et al., 2007) (Aditya et al., 2014).

To increase the bioavailability of curcumin, formulation of curcumin in nanoparticles, liposomes, phospholipid complex and micelles showed increased in half-life (Shaikh et al., 2009). In addition, adjuvants like soy bean derived quercetin to inhibit sulfotransferases, black pepper derived piperine to inhibit UGTs and p450s and ginistein that inhibits alcohol dehydrogenase helps to overcome detoxification enzyme acted on curcumin metabolism (Shoba et al., 1998).

The pleiotropic targets of curcumin are inflammation, cell death, genomic modulation, cell proliferation and invasion. Curcumin is a great candidate for cancer prevention to be used alone or with combination of conventional therapies given its ability to hit multiple signalling pathways.

Arsenic trioxide was used in combination with curcumin to treat prostate cancer in human which, showed increase in cell apoptosis of prostate cancer cells, decrease in angiogenesis gene and cell growth inhibition (Mirzaei *et al.*, 2022). Curcumin is considered to be a promising anti- cancer treatment for prostate cancer by cell cycle arrest, apoptosis and regulation of inflammatory pathway (Jordan *et al.*, 2016). It also showed higher delivery of

curcumin in nanoparticle formulation. In a research conducted by (Aditya *et al.,* 2014), showed combination of curcumin and genistein to be a potent anti-cancer treatment in prostate cancer following. Similar results were seen in (Ide *et al.,* 2010, 2011).

Adverse effects

Many of the in vitro results cannot be achieved in vivo given the poor bioavailability of curcumin outside gastrointestinal tract post oral administration. Several studies also showed curcumin can induce toxicity and carcinogenic effects (Burgos-Morón *et al.,* 2010). A 2 year study reported curcumin induced clitoral gland, lung and hepatocellular adenoma and carcinoma of small intestine post ingestion of curcumin in an in vivo study. This is reported to be due to α, β unsaturated ketone that induces inactivation of tumor suppressor p 53 and production of ROS (López-Lázaro, 2008). The carcinogenesis effects are due to DNA alteration and chromosome aberrations. The inhibition of ROS leads to blockade of JNK function post curcumin treatment. Thus, further studies are essential to prove the benefits and controversies reported before been used in clinical trial as curcumin had shown to be a potent anti-carcinogenic agent.

In addition to that, the efficacy and potential of curcumin is shown by the reduction in cell mass and potent cancer cell apoptosis (Ashrafiadeh, M., 2020). Curcumin is able to show such potency towards cancer treatment due to the pleiotropic targeting propery, which allows multi-target to be influenced and to initiate and promote hundreds of gene or signalling cascades to cancer cell apoptosis (Teiten *et al.,* 2010).

10.0 Conclusion

In conclusion, curcumins potential as an anti –cancer treatment should be widely explored given its potential, especially for canine prostate carcinoma given its poor prognosis and limited treatment options. It is evident that curcumin possesses high potential to treat canine prostate cancer from the studies done on human prostate cancer since; they both have similar anatomical, physiological and histological properties. As new studies involving nano-treatment using curcumin and researches on synergistic effects with other medication and treatment option are increasing. With this canine prostate cancer treatment should also be researched.

11.0 Recommendation and future work

In this review, it's obvious that curcumin has potential to be treatment to a lot of medical conditions, including cancer. A lot of human cancer researches are been made but not for companion animals. More researches should be done, to fully use the potential of curcumin as an anticancer treatment on its own or in combination with other therapeutic plants or readily available treatment options, especially for diseases with poor prognosis and limited treatment options like canine prostate cancer in order to provide a better life for our companion animals.

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Abbreviation

Akt = Protein kinase B

Ang = Angiopoiteins

CDK = Cyclin-Dependent Kinase

COX = Cyclooxygenase

DISC = Death Inducing Signalling Complex

DNA = Deoxyribonucleic Acid

DNMTs = DNA Methyltransferases

EGF = Epidermal Growth Factor

EGFR = Epidermal Growth Factor Receptor

ERK = Extracellular signal Regulated Kinase

G phase = Growth phase

HAT = Histone Acetyltransferase

HDAC = Histone Deacetylase

IL = Interleukines

KDR = Kinase Domain Region

LEF = Lymphoid Enhancer Factor

M phase = Mitotic phase

MMPs = Matrix Metalloproteinases

mTOR = mammalian Target for Rapamycin

NF-κB = Nuclear Factor kappa light chain enhancer of activated B cells

PARP = Poly Adenosine diphosphate – Ribose Polymerase

PI3K = Phosphatidylinositol 3-kinase

PRISMA = Preferred Reporting Items for Systemic Reviews and Meta- Analyses

Rb = Retinoblastoma

ROS = Reactive Oxygen Species

S phase = Synthesis phase

STATs = Signal Transducer and Activator of Transcription

TCF = T-cell factor

TNF = Tumor Necrotic Factor

TRAIL = TNF α Related Apoptosis Inducing Ligand

VCAM = Vascular Cell Adhesion Molecules

VEGF = Vascular Endothelial Growth Factor

XIAP = X linked inhibitors of apoptosis