

**Deer Antler Supplements, Growth Factors and Possible Cancer Risks**

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**Table of Contents**

<b>Chapter One: Introduction.....</b>	<b>7</b>
<b>Glossary of Relevant Terms.....</b>	<b>10</b>
<b>Abbreviations.....</b>	<b>12</b>
<b>Chapter Two: Literature Review.....</b>	<b>14</b>
<b>IGF-1 and Cancer.....</b>	<b>14</b>
<b>Exogenous IGF-1.....</b>	<b>18</b>
<b>Deer Antler Constituents.....</b>	<b>19</b>
<b>The Effects of Deer Antler.....</b>	<b>23</b>
<b>Deer Antler and Cancer.....</b>	<b>27</b>
<b>Deer Antler and Cancer Treatment.....</b>	<b>29</b>
<b>Deer Antler Toxicology.....</b>	<b>31</b>
<b>Deer Antler Dosage.....</b>	<b>32</b>
<b>Chapter Three: Methodology.....</b>	<b>34</b>
<b>Chapter Four: Results.....</b>	<b>36</b>
<b>What is the Summary of the Current Understanding of the Association Between     IGF-1 and Neoplasia?.....</b>	<b>36</b>
<b>IGF-1 and Longevity.....</b>	<b>40</b>
<b>Does Orally Administered IGF-1 Get Absorbed in the General Circulation?.....</b>	<b>40</b>
<b>What is the Content of IGF-1 in Deer Antler?.....</b>	<b>40</b>
<b>How Much IGF-1 is in Deer Antler Products?.....</b>	<b>41</b>
<b>How does Deer Antler Supplementation Affect Endogenous Hormone Levels in     Human Studies?.....</b>	<b>41</b>

**What were the Observed Effects of Deer Antler on Human Subjects?..... 42**

**What is the Direct Impact of Deer Antler on Cancer?..... 43**

**Other Safety Issues, Dosing..... 44**

**Summary of the Main Results..... 46**

**Chapter Five: Discussion..... 47**

**Limitations of the Current Study..... 47**

**Summary of Findings..... 47**

**Implications for Theory..... 48**

**Implications for Practice..... 48**

**Future Recommendations and Conclusion..... 49**

**References..... 51**

**Appendix: IRB Approval Letter..... 60**

### Abstract

**Background:** Deer Antler has been used in Asia for millennia as a precious substance to nourish Yang energy, increase vigor, stamina and promote longevity. Its popularity has been fueled by publicity of the high profile professional sport scandal and the ever-present demand for athletic and sexual performance enhancing substances. Frequently marketed as the natural source of growth factors, some Deer Antler users question its safety in terms of increased cancer risk.

**Aim:** The aim of this paper is to explore the possibility of higher chance of getting cancer among healthy individuals who take Deer Antler supplements. **Method:** This is a literature synthesis of the current understanding of Deer Antler's chemistry with the emphasis on Insulin –like growth factor-1, pharmacology, toxicology and its effects on cancer. **Results:** Although the hypothetical risk of cancer associated with Deer Antler can be inferred from the current scientific theory, there is no evidence supporting the hypothesis of increased risk of cancers in healthy Deer Antler users.. **Conclusion:** Cautious use of Deer Antler supplements is advisable due to the insufficient scientific evidence, lack of human trials and even the possibility of using illegal, adulterated products.

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## Chapter One: Introduction

The use of Deer Antler for medicinal and health promoting purposes can be tracked down for two millennia. Deer Antler was included in Divine Farmer's *Materia Medica*, the earliest Chinese pharmacopeia compiled during the Han dynasty. Practitioners of Chinese medicine have prescribed it as a Kidney Yang, Jing and Blood tonic. Preparations of Deer Antler have been revered in Asia as powerful tonic for weak, old, overworked, emotionally taxed people. *The Essence of Medical Prescriptions*, a Japanese compilation of Chinese texts from the tenth century states "that there is nothing better than Deer Antler to cause a man to be robust and unaffected by age, not to tire in the bedroom, and not to deteriorate either in energy or in facial coloration" (Teegarden, 1998, p. 125).

Deer Antlers are cranial appendages that develop after birth on the protuberances on the frontal bone of male deer. It is the only mammalian organ that can fully regenerate in an annual rhythm coordinated with the reproductive cycle. Unlike horns, antlers are secondary sexual characteristic whose function is to attract mates and fight other males. The whole process of growth to rejection and shedding takes only 90 days. Some deer species can grow spectacular, 100-pound heavy appendages at the rate of more than an inch of daily growth. Deer are the only animals that grow antlers and they should not be confused with horns. Horns are just keratinized tissue that grows from their base. Antlers are organs composed of skin, nerves, blood vessels, cartilage, fibrous tissue and bones (Price, Allen, Faucheux, Althnaian, & Mount, 2005). Antler regeneration is a stem cell process with the involvement of the whole matrix of growth factors which are mostly concentrated in the tip. During this period of intense growth all tissues develop simultaneously: bone, cartilage, nerves and blood vessels.

These magnificent examples of male prowess in the animal kingdom have been held in the great regard by humans and still intrigue modern day scientists. Antler research can help us understand why mammals lost the ability to regenerate appendages and find the ways to overcome this shortcoming. Researchers' ultimate goal is to enable regrowth of human limbs lost through trauma or surgery (Kierdorf and Kierdorf, 2010). Some authors with interest in antiaging science go even further and consider the cycle of Deer Antler growth and apoptosis to be potential model to better understand human life stages. Researching the forces that drive development, rejection and shedding of antlers might help us to better understand growth, development, senescence and death (Huo, Huo and Zhang, 2014).

The primary source of Deer Antler is farmed deer. China and New Zealand are the two biggest producers of antlers in the world. In China, Jilin province is the main deer farming area. The global production is around 1300 tons per year and rapidly growing to meet demands of the world markets (Sui, Zhang, Huo and Zhang, 2013). Two main deer species used for farming in China are Sika deer (*Cervus nippon* Temminck) and red deer (*Cervus elaphus* Linnaeus). The primary material collected at deer farms is usually called velvet. Originally, velvet was referred to fine hair covering antlers, but in the deer antler industry velvet is stage of growth before ossification. Deer antlers are cut off while the animals are under local anesthetics. Ossified and naturally shed antlers are collected and used as a cheaper substitute for velvet. Cut antlers are immersed in boiling water and then dried by air or low temperature baking. Deer antler usually comes to Chinese herbal shops as thinly sliced chips. Traditionally antlers are not cooked with all other herbs, but taken as a powder with decoction. Deer Antler supplements are available as capsulated powder, liquid extract and lately as an oral spray.

Throughout the millennia Deer Antler has been used in treatment and in prevention of various conditions like cardiovascular diseases, infertility, gynecological problems, immunodeficiency, blood cancers, tissue repair and overall health promotion (Wu, Li, Jin, Li, Ma, You, Li and Xu, 2012). In modern times Deer Antler supplements have been heavily promoted as athletic performance boosters to increase strength and endurance during workouts and help muscle recovery. It is often marketed as a sexual enhancing substance. Many supplement companies have been touting Deer Antler as a natural source of Insulin Like Growth Factor 1 (IGF-1), supposedly it's the most important active ingredient.

IGF-1 has been on the list of banned substances by the National Football League (NFL), Major League Baseball, and the World Anti-Doping Agency. Deer-antler spray became the hot topic of media in the days leading to Super Bowl XLVII after *Sports Illustrated* published an article about Baltimore Ravens' linebacker Ray Lewis' alleged use of the substance to help in the healing of his torn triceps. Google search trend graph shows a huge spike in Deer Antler interest in those early months of 2013. Higher sales of Antler supplements followed, as well as consumption by athletes, body builders and anyone searching for strength and vigor.

Being a practitioner of medical traditions that brought Deer Antler to modern times, I have been approached on numerous occasions by people curious about Deer Antler benefits and sometimes they express concerns about its safety. Those inquires on potential side effects and my inability to provide satisfactory answer gave me an inspiration for the research question for this study:

Can Deer Antler supplementation increase the risk of cancer in otherwise healthy subjects?

There is perceived risk from taking Deer Antler supplements among some users. Presence of IGF-1 in antlers is the most common reason for the concern, especially by people who have done a little bit of research beyond the sales pitch. IGF-1 is an endocrine hormone, the most common mediator of Growth Hormone (GH). It is a protein secreted by the liver, with a similar structure to insulin. The GH/IGF-1 epidemiological studies have suggested association between GH/IGF-1 and cancer, although not with tumor induction (Jenkins, Mukherjee and Shalet, 2006).

The objective of this research synthesis is to explore the correlation between Deer Antler use and possible increased cancer risk in healthy individuals. I hope the results of this study will be of value for the practitioners of Chinese Medicine and other medical modalities to become more familiar with Deer Antler and get a better understanding of safety issues related to this unique substance. General population, patients of Traditional Chinese Medicine, athletes, body builders and anyone else using Deer Antler as a supplement hopefully will get more information on the potential risks.

### **Glossary of Relevant Terms**

**Anabolic** is substance, usually a hormone used to repair body tissues, increase appetite and the growth of muscles (NCI Dictionary of Cancer Terms).

**Androstenedione** is anabolic steroid hormone of weaker potency than testosterone (Medilexicon).

**Angiogenesis** is the formation of new blood vessels (NCI Dictionary of Cancer Terms).

**Apoptosis** is sometimes called programmed cell death. It is a series of molecular steps in a cell by which the body gets rid of abnormal or unneeded cells (NCI Dictionary of Cancer Terms).

**Autocrine** is referred to cellular self-signaling, where specific receptor is on the same cell that produced the signaling factor (Medilexicon).

**Erythropoietin** is a hormone produced by kidneys. It is a sialic acid containing glycoprotein that stimulates formation of red blood cells in the bone marrow (Medilexicon).

**Glycosaminoglycans** are long, unbranched polysaccharide molecules, major structural components of cartilage (NCI Dictionary of Cancer Terms).

**Osteoclastic** is pertaining to osteoclasts; large cells that absorb and remove bone tissue (Medilexicon).

**Kinase** is a type of enzyme that can activate or deactivate other molecules, such as sugars or proteins by transferring phosphate group (NCI Dictionary of Cancer Terms).

**Liposome** is a spherical particle of lipid substance suspended in aqueous medium. It is used as a drug delivery system to enhance therapeutic effect (Medilexicon).

**Mammalian target of rapamycin** is a protein kinase which is central regulator of cellular metabolism, growth and survival in response to hormones, growth factors, energy, nutrients and stress signals (Universal Protein Resource).

**Myelosuppression** is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells and platelets (NCI Dictionary of Cancer Terms).

**Paracrine** is referred to cellular signaling to nearby cells (Medilexicon).

**Polymorphism** is a common change in the genetic code in DNA. Polymorphisms can have a harmful effect, a positive effect, or no effect at all.

**Protein kinase C** is any of a number of cytoplasmic calcium activated kinases involved in hormonal binding, platelet formation, tumor promotion and numerous other processes (Medilexicon).

**Sialic acids** are family of nine carbon acidic monosaccharides that occur naturally at the end of sugar chains attached to the surfaces of cells and soluble proteins (Wang and Miller, 2003).

**Sirtuins** are family of proteins that are localized in mitochondria. Sirtuins are linked to lifespan regulation (Sack and Finkel, 2012).

**Uronic acids** are acids derived from monosaccharides by oxidation of primary alcohol group (Medilexicon).

**Villous adenomas** is tumor of colonic mucosa, it can frequently become malignant (Medilexicon).

**V02max** is the measure of maximum volume of oxygen than an athlete can use.

**Zoledronic acid** is a drug used to treat high blood levels of calcium caused by cancer (NCI Dictionary of Cancer Terms).

### **Abbreviations**

**GH:** Growth hormone

**IGF:** Insulin-like growth factor

**IGFBP:** Insulin-like growth factor binding protein

**IGFR:** Insulin-like growth factor receptor

**FGF:** Fibroblast growth factor

**FGFR:** Fibroblast growth factor receptor

**GAG:** Glycosaminoglycan

**MAPK1:** Mitogen-activated protein kinase 1

**MMP:** Matrix metalloproteinase

**PKC $\beta$ :** Protein kinase C  $\beta$

**S6K:** S6 protein kinase

**TOR:** Target of rapamycin

**VEGF:** Vascular endothelial growth factor

**VEGFR:** Vascular endothelial growth factor receptor

## **Chapter Two: Literature Review**

In this chapter I will present all the scholarly literature used in this project. The literature has been grouped in seven sections in the effort to cover all the relevant aspects of the research: The connection between IGF-1 and cancer, the impact of exogenous IGF-1 on human body, the actual constituents of Deer Antler, the effects of Deer Antler, the relationship between Deer Antler and cancer, Deer Antler toxicology and finally, dosaging of Deer Antler.

### **IGF-1 and Cancer**

In their seminal paper “The Hallmarks of Cancer”, Douglas Hanahan and Robert A. Weinberg lay down the rules that govern transformation of normal human cells into malignant cancers. They suggest that most, if not all human cancers share the same set of acquired capabilities, similar molecular, biochemical and cellular traits. To be precise, Hanahan and Weinberg suggest six alterations in cellular physiology that drive tumorigenesis: self sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, unlimited potential to replicate, sustained angiogenesis and tissue invasion and metastasis. Normal cells require growth signaling for proliferation. This is in strong contrast to tumor cells, which are not dependent on exogenous growth stimulation. Tumors tend to generate their own growth signals, reducing their dependence on stimulation from their normal neighboring tissue microenvironment. IGF-1 and IGF-2 do not affect directly tumor cells proliferation, but are clearly part of the antiapoptotic machinery. These growth factors can affect dynamic of tumor development through activating survival signaling circuit (Hanahan and Weinberg, 2000).

IGF signaling system operates at a whole organism on cellular and subcellular levels. In the past it was believed that all IGF-1 originated in liver and was distributed by endocrine

mechanisms throughout the body. Now we know that IGF-1 can be produced in other organs. Higher levels of IGF-1 signaling are associated with quickening of the aging processes in the organism as a whole. Proliferation and metastasis of cancer is increased by activation of IGF-1 receptors, either because of a higher level of circulating IGF-1 in the body, or increased autocrine production by cancer cells. Converging results from epidemiological studies and in vivo models point to the conclusion that high levels of IGF-1 are associated with increased risk of several common cancers (Pollak, Schernhammer and Hankinson, 2004). Renehan et al. (2004) found in their overview of population studies association between high concentrations of IGF-1 and increased risk of prostate and premenopausal breast cancers. The same study showed modest, non-statistically significant positive association between IGF-1 and colorectal cancer risk. The authors identified 21 eligible studies, which included 3609 cases and 7137 controls. The cases in this meta analysis included prostate, colorectal, premenopausal and postmenopausal breast and lung cancers. Pollak et al. (2004) talk in their review on some factors that may influence circulating IGF-1 levels. There is a significant variation of circulating levels of IGF-1, IGF-2 and IGFBP between normal healthy individuals. Genetic factors influence levels of IGF-1. Polymorphic variations of genes encoding dozens of proteins involved in regulation of IGF-1 levels could influence circulating concentrations. Nutrition has important influence on IGF-1 levels. Starvation reduces levels of IGF-1. This might be evolutionary mechanism to minimize energy and protein consumption in the times of inadequate nutrition. High levels of protein or energy intake have mild effect on IGF-1 levels. Exogenous and endogenous steroid hormones have influence on GH/IGF-1 system. Oral estrogen replacement therapy suppresses IGF-1 levels. This might be result of estrogen direct delivery to the liver and suppression of hepatic IGF-1 gene expression. Acromegalics have very high levels of IGF-1, but surprisingly the increased

cancer risk is quite modest. The lack of extreme cancer risk in people with acromegaly might be related to increased levels of IGFBP3, which is believed to attenuate IGF-1 signals. Pollak et al. (2004) conclude their paper with warning on possible detrimental effects of GH therapy. GH supplementation to increase IGF-1 levels above age specific norms might have short term positive, anabolic and anti-aging effects. The evidence of association of IGF-1 and cancer warrants caution over the long term of GH therapy.

It is interesting to mention that in contrast to cancer, risk of cardiac disease seems to vary inversely with circulating IGF-1 levels.

Cytosine-adenine (CA) repeat polymorphism in the human IGF-1 gene was the focus of many studies, primarily because of its proximity to the promoter. (CA) 19 polymorphism was implicated as higher cancer risk factor, and the studies had been inclusive. Chen et al. (2008) conducted their meta-analysis on (CA) 19 association with cancer. Eligible studies totaled 8800 outpatients and 13900 controls. The authors stratified the data by ethnicity (Asians and Caucasians) and type of the cancer (breast, prostate, colorectal). The meta analysis did not reveal significant association between (CA) 19 polymorphism and cancer risk.

Pooled individual analysis of 17 prospective studies published in 2010 showed that plasma concentrations of IGF-1 were positively associated with breast cancer risk. The association was weakly positive for premenopausal women, but strongly positive for postmenopausal women. IGF-1 was inversely associated with age, although without sharp decline around age of 50, which suggests that menopause does not have significant effect on IGF-1 levels. IGF-1 was higher in taller women. Women with BMI of 25.0 to 27.4 kg/m<sup>2</sup> had higher levels of IGF-1 than thinner or more overweight women. Possible explanation might be that thinner women do not get enough nutrients to the liver to synthesize enough IGF-1, while

obese women might have compromised liver function. Women who drank a small amount of alcohol had higher levels of IGF-1 than women who did not drink or drank more substantial amounts. The association of IGF-1 with the risk of breast cancer was limited to estrogen receptor positive tumors only. The odds ratio for IGF-1 is smaller than the odds ratio for both estrogens and androgens. High concentrations of estrogen and testosterone can double breast cancer risk. In this collaborative analysis, adjustment for estradiol and testosterone had no or very little effect on the association of IGF-1 with breast cancer risk in postmenopausal women. There is a need for better understanding of the joint effect of hormones on breast cancer risk (The Endogenous Hormones and Breast Cancer Collaborative Group, 2010).

Another study was done on 299 male participants who had at least one adenoma at the baseline. There was statistically positive association for serum IGF-1 levels and adenomas with villous histology. Villous adenomas are more often larger adenomas with a more severe degree of dysplasia and malignant transformation. After polyp removal surgeries, the authors observed inverse relation between IGF-1 levels and colorectal adenoma recurrence. This protective action of IGF-1 after polypectomy was unexpected, since it is in contrast to our understanding of IGF-1 as a mediator of body size and risk for colorectal tumors. Possible explanations for these surprise findings might be that IGF-1 acts as an analog to transforming growth factor beta, a negative growth regulator, or just that higher levels of IGF-1 might be associated with healthier organism (Jacobs et al., 2008).

Convincing data show that GH/IGF-1 axis plays a significant role in cancer development, but not with tumor induction. The proliferative and antiapoptotic effects of IGF-1 provide an environment that favors survival of genetically damaged cells. This effect might be weak, but exposure to a large number of damaged cells over many years could accelerate cancerogenesis,

although not inducing cancer per se (Jenkins, Mukherjee and Shalet, 2006). Reducing activity of IGF-1 and growth hormone is a promising target for antiaging therapies. The inhibition of those pathways has been a promising area of studies that might lead to prolonging life span and protection from damages and diseases associated with aging like cancer and diabetes (Puzanov and Hess, 2015).

Longo et al. (2015) in the review of workshop titled “Interventions to Slow Aging in Humans: Are We Ready?” brings the most promising strategies to slow down aging based on the current scientific understanding. The very first intervention listed is pharmacological inhibition of the GH/IGF-1 axis, followed by protein restriction and fasting, inhibition of TOR-S6K pathway, regulation of certain sirtuin proteins, inhibition of inflammation and the use of metformin. Low plasma IGF-1 concentration can predict survival in long-lived people, decreased risk of cancer and diabetes. Pharmaceutical interventions that directly lower IGF-1 levels in adults can improve health and prolong lifespan.

### **Exogenous IGF-1**

Most orally taken proteins and peptides are degraded by enzymes in the gastrointestinal tract, otherwise they cannot pass through the intestinal epithelium. Despite the obstacles, the study on rats showed that 9.3% of orally taken IGF-1 got into systemic circulation. When administered with casein, the bioavailability of IGF-1 jumped to 67% (Kimura et al., 1997).

Kim et al. (2006) conducted a study to explore whether orally administered IGF-1 would be absorbed into circulation and also whether ingested IGF-1 would enhance the growth of tissues, internal organs and whole body. Actually the authors conducted two experiments. In the first experiment mice were fed IGF-1 and subsequently IGF-1 levels were measured during a 24 hour period. The second experiment was designed to investigate effects of repeated oral IGF-1

administration during two weeks on organ and body weights. The first experiment showed that upon oral administration IGF-1 was absorbed in general circulation, serum levels peaked 4 hours later and returned back to baseline level within 8 hours. In the control group, consisting of animals receiving feed without IGF-1, concentration of IGF-1 did not change throughout the 24 hour period. There was no observed whole body growth or organ growth, with the exception of small intestines.

There have been few meta analyses conducted on the correlation between dairy product consumption and cancer risk. Milk may contain not only IGF-1, but also pesticides, which are potentially carcinogenic and high fat content especially saturated fats. On the other hand, dairy products contain vitamin D, calcium and conjugated linoleic acid, constituents associated with anticarcinogenic properties. The hypothesis that IGF-1 in milk is related to breast cancer is less than compelling, primarily because of the lack of evidence (Moorman and Terry, 2004). Overall, the literature review done by Moorman and Terry, 2004, came to the conclusion that published epidemiological data do not provide consistent evidence between dairy products consumption and breast cancer risk. Li et al., 2011, in their meta-analysis found no statistically significant association between dairy intake and bladder cancer risk.

### **Deer Antler Constituents**

Sui, Zhang, Huo and Zhang, (2013), in a review of Deer Antler bioactive components gave a comprehensive list of its minerals, amino acids, proteins and peptides, saccharides and lipids.

**Mineral elements:** Calcium, Phosphorus, Sodium, Potassium, Magnesium, Iron, Zinc, Copper, Chromium, Strontium, Nickel, Cobalt, Manganese, Vanadium and Tin.

**Amino Acids.** 19 amino acids have been isolated from Deer Antler: Arginine, Histidine, Glutamic acid, Proline, Aspartic acid, Serine, Threonine, Glycine, Alanine, Isoleucine, Leucine, Phenylalanine, Methionine, Lysine, Tyrosine, Valine, Cysteine, Hydroxyproline and Tryptophan.

**Proteins and peptides:** Growth factors and their receptors: FGF-2, VEGF, FGFR1, FGFR2, FGFR3, VEGFR-2, soluble proteins, crude proteins, collagen and multifunctional peptides like tripeptide with a molecular weight of 395.1, and Decorin.

**Saccharides:** GAGs, Uronic acid, Chondroitin sulfate, Sialic acid, Keratan sulfate

**Lipids:** Phospholipids, Prostaglandins, Saturated fatty acids, Monounsaturated fatty acids, Conjugated linoleic acid, Polyunsaturated fatty acid, 17 alpha-hydroxyprogesterone, Progesterone and Testosterone. Lu et al., (2013) developed a method for the simultaneous determination of eighteen steroid hormones in Deer Antler: 17 $\alpha$ -Ethinylestradiol, 17 $\alpha$ -Estradiol, 19-Nortestosterone, Estriol, Testosterone, Androsterone, 17 $\beta$ -Estradiol, Estrone, 17 $\alpha$ -Hydroxyprogesterone, Medroxyprogesterone, Progesterone, Norethisterone acetate, Testosterone 17-propionate, Medroxyprogesterone 17-acetate, Corticosterone, Megestrol-17-acetate, Chlormadinon 17-acetate and 17 $\beta$ -Estradiol-benzoate. These 18 hormones cover four classes of steroid hormones: androgens, estrogens, corticoids and progestogens. Amino acids, polypeptides and proteins are considered the most prominent bioactive components, whose content decreases from the tip to the base section of Deer Antler. Traditionally the tips of the antler have been considered more valuable than lower sections.

Decoctions and medicinal liquors have been traditional methods of preparation of Deer Antler. There are reports showing that hot water and ethanol extractions methods could denature proteins and compromise their effects (Sui et al., 2013). On the other hand, saccharides like uronic acid, sulfated GAGs and sialic acid need higher temperatures to be fully extracted (Je at

al., 2011). Ethanol is more appropriate for the extraction of uronic acid, while water is better for sulfated-GAGs and sialic acid.

With the help of advanced analytical technology and proteomics it was possible to establish correlation between proteome difference and growth stages of Deer Antler. The early growth phases contain more metabolism related enzymes and signal transduction proteins, which are absent in later stages of Deer Antler cycle. The growth slows down in the later phases, and the proteins found have more structural support function (Huo Y.,Huo H. and Zhang, 2014). Kierdorf U. and Kierdorf H. (2010) stated that from in vitro and in vivo studies, IGF-1 is the main hormone behind Deer Antler growth. Bartos, Schams and Bubenik in their 2008 study concluded that testosterone, possibly interacting with other steroids and not IGF-1 is primarily responsible for the intense antler growth. Antler's growth is terminated by increasing levels of testosterone which stimulates osteoclastic activity. Eventual drop in testosterone precludes casting of hardened antlers. There is some evidence suggesting that this effect of testosterone is indirect, after testosterone conversion into estrogen (Kierdorf U. and Kierdorf H., 2010). Levels of amino acids, testosterone, IGF-1, and testosterone plus estradiol were significantly higher in the upper section of Deer Antler than middle and basal sections in the analysis published by Tseng et al., (2014). For example IGF-1 was measured 52.91 ng/g in the upper section, 46.7 ng/g at the middle and 22.9 ng/g in the base. They found testosterone levels to be 1.05 ng/g, 046 ng/g and 027 ng/g for the upper, middle and base sections of Deer Antler. GAGs, cholesterol, iron and copper also decreased from the tip to the base. Calcium levels on the other hand increased toward the base.

Liu, Zhang, Li and Dou (2011) conducted the successful study to employ and enzyme-linked immunosorbent assay (ELISA) to detect the content of IGF-1 in Deer Antlers. In the past,

IGF-1 content in antler was determined mainly by radioimmunoassay (RIA). RIA has some disadvantages like costly equipment, short-lived radioactive isotopes and possible radioactive contamination and technician exposure. ELISA protocol is considered relatively simple, reliable, rapid and economical. To measure IGF-1 content in this study, the deer blood samples were taken from upper, middle and base sections of Deer Antlers. The results showed the highest level of IGF-1 is in the upper section decreasing downward toward the base. IGF-1 content was significantly higher ( $P < 0.01$ ) in the upper section compared to the bottom section. A Korean study from 2007 demonstrated that IGF-1 in Deer Antler can be partially purified and quantified using classic protein isolation methods. The study measured total amount of 0.291 grams of IGF-1 in 20 grams of starting weight of Deer Antler tissue (Gu et al., 2007). Proteome analysis of red Deer Antlers done by Park et al. (2004) did not confirm presence of growth factors including IGF-1. The authors did find several proteins involved in growth factor signaling pathways such as PKC $\beta$  and MAPK1.

Cox and Eichner (2013) in their research article analyzed IGF-1 content in six Deer Antler supplements. Four supplements were liposome solutions, one tincture solution in 35% alcohol and one supplement was unprocessed bulk Deer Antler powder. All products were marketed as all natural source of IGF-1 with significant health benefits. For this study IGF-1 was extracted from all six supplements using chloroform and acetonitrile precipitation methods. IGF-1 is a 70 amino acids protein. Human and deer IGF-1 share very similar sequence, the difference is only in two positions out of 70. IGF-1 can be analyzed as intact protein or as peptides after trypsin digestion. Ultra-performance liquid chromatography/tandem mass spectrometry (UPLC/MS/MS) methods were developed to measure intact IGF-1 protein and IGF-1 trypsin peptides using a triple quadruple mass spectrometer. The researchers found in all four liposomal

solutions presence of pharmaceutical human IGF-1. Pharmaceutical IGF-1 can be produced by using recombinant methods or by just using crude preparations of IGF-1 from cow, dog or pig. Whichever of the two methods was used it is considered adulteration. Three of liposomal supplements had on the label high amounts of Deer Antler IGF-1: 5000ng, 10000ng and 100000ng per 1 fl. oz. bottle. Analysis of these three supplements did not confirm any deer IGF-1 only pharmaceutical human IGF-1 in the amounts 10 to 20 times smaller than labeled by manufacturer. It is possible that analytical methods were not adequate or that IGF-1 did go through the process of natural degradation. Only one out of four liposomal solutions contained small amounts of deer IGF-1. This can be explained either by too small amounts to be detected or by too long of a time between antler harvest and supplement production that allowed degradation of natural proteins. Deer IGF-1 and human IGF-1 could not be confirmed in tincture supplement and bulk Deer Antler powder. Adding recombinant protein of unknown purity may pose danger for the customers and it is definitely considered an illegal act by manufacturers (Cox and Eichner, 2013).

Suttie et al. (2004) argue for the need to develop a simple quality standard and effective product label that consumers can trust and make their purchase choices with confidence. Most natural products that are offered for retail sales do contain the concentration of what is believed to be the active ingredient or they are standardized to a particular marker substance. Deer Antler is an extremely complex mixture and no specific active ingredient is associated with a specific effect.

### **The Effects of Deer Antler**

Zhang et al. (2013) in their comprehensive review of Deer Antler bioactive components and their pharmacological properties, list the following effects of Deer Antler:

immunomodulatory, anti-cancer, anti-fatigue, anti-osteoporosis, anti-inflammatory, anti-oxidation, wound healing and regeneration promoting and finally, cardioprotective effects. The studies they used to support their conclusions on Deer Antler pharmacological effects are exclusively murine, animal studies from China. Wu et al. (2013) in the review of traditional uses, chemistry and pharmacology of Deer Antler base found it to possess immunomodulatory, anti-cancer, anti-fatigue, anti-osteoporosis, anti-inflammatory, analgesic, anti-bacterial, anti-viral, anti-stress, anti-oxidant, hypoglycemic, hematopoietic modulatory activities and the therapeutic effect on mammary hyperplasia. There are no human studies included in this review, only studies on rodents. All the studies are from China. Deer Antler pharmacopuncture is a Korean style treatment that applies Deer Antler extract on an acupuncture point or a hypersensitive epidermal point. Lee, Hwangbo, Kwon and Seo (2013) reviewed the known studies on the subject of Deer Antler pharmacopuncture and its effects on arthritis, anti-osteoporosis, anti-oxidation, anti-aging, anti-ischemic effects, anti-cancer, growth promotion, increased immunity, neurogenesis, analgesic effects, and anti-stress effects. Most of the studies were experiments on animals. The authors concluded that more clinical trials are necessary to substantially support the experimental effects of Deer Antler pharmacopuncture.

Sleivert et al. (2003) conducted a well-designed, double blind study on the effects of Deer Antler extract or powder supplementation on aerobic power, erythropoiesis, muscular strength and endurance characteristics. The purpose of the study was to determine whether taking Deer Antler extract or powder enhanced the strength and muscular endurance during 10 weeks of a strength training program in male athletes. The second goal was to determine whether any changes in the levels of anabolic hormones occurred that could explain any enhancement in muscular strength or endurance. The third purpose was to determine if Deer Antler supplements

had erythropoietic properties that might affect athletic performance. All the participants were men, 19 to 24 years old, physical education students, active in sports and no dietary supplementation. Subjects were assigned capsules of either Deer Antler extract (300 mg per day), Deer Antler powder (1500 mg per day) or placebo capsule. They were taking the capsules for 3 months and the dosages were based on traditional doses used in Chinese medicine. The main finding of the study was that isokinetic strength and muscular endurance improved in the group taking Deer Antler powder. There were no significant differences in IGF-1 or testosterone in any of three groups as a result of the supplementation or strength training. In addition, there were no significant changes in VO<sub>2</sub>max or erythropoietin. The authors gave one possible speculative explanation for increasing muscle endurance with no increase in testosterone or IGF is that Deer Antler provided analgesic effect that masked the pain during endurance tests.

A 2004 double blind study investigated the physiological and potential performance enhancing effects of 1350 mg twice a day Deer Antler supplementation in men during 10 weeks of resistance training. The researchers found that Deer Antler supplementation in athletes might be effective in five areas: 1) fat mass losses; 2) enhancement in upper and lower body strength; 3) possible prevention of declines related to over-training; 4) enhancement of aerobic capacity; 5) significant reduction in LDL cholesterol (Broeder et al., 2004). Authors found the most interesting finding increased aerobic capacity in Deer Antler group measured as VO<sub>2</sub>max. This study unfortunately had a high dropout rate which weakened statistical significance of its results.

A 2005 study examined the effects of Deer Antler supplementation on the hormonal response to exercise in male and female rowers. The rowers, both male and female were given 560 mg daily of Deer Antler or placebo for 10 weeks. There was no significant difference between Deer Antler and placebo groups in hormonal response after a 2000 m race. Testosterone

(men only) and growth hormone (both men and women) were higher at 5 minutes after the race, but returned to baseline at 60 minutes. Cortisol was higher at 5 and 60 minutes, compared to rest for both genders, and was higher 60 minutes post exercise after 5 and 10 weeks of training (Syrotuik, MacFadyen, Harber and Bell, 2005).

A New Zealand double blind, randomized, placebo controlled study explored the effects on Deer Antler supplementation on sexual function in men and their partners. At the end of 12 weeks of study, there were no significant differences in the hormone level of two groups (Deer Antler and placebo) of men at baseline; neither were there any significant changes in hormone levels from the beginning to the end of the study. Study showed no significant effect of Deer Antler supplementation on the measured sexual function in a group of heterosexual men between the ages of 45 and 60, in steady relationships (Conaglen H., Suttie and Conaglen J., 2002).

Triple blind, placebo controlled clinical trial examined the effects of Deer Antler on joint pain and swelling, functional ability, quality of life, blood levels of C-reactive protein and adverse events in patients with stage 2 to 3 of rheumatoid arthritis. Some patients after 6 months study did report improvements with their symptoms, but there were no statistically significant differences between the groups (Allen, Oberle, Grace, Russell and Adewale, 2011).

The systematic review of randomized controlled studies by Gilbey and Perezgonxales, (2012) on health benefits of Deer Antler supplements returned 724 articles. After excluding duplicates, the remaining 478 articles were narrowed down to only seven articles that met all inclusion criteria. Those seven articles were already presented in this chapter. The included studies scored between 3 and 5 points on the Jadad scale. The conclusion of the review was that

claims that Deer Antler supplements had beneficial effects for any human condition were not supported by convincing clinical data from human trials.

### **Deer Antler and Cancer**

The astonishing growth rate of Deer Antlers has been intriguing researchers to explore whether antlers are susceptible for tumor formation. Antler formation in male deer is well coordinated process exhibiting no growth abnormalities associated with malignant tumors. Even antlers of castrated animals seem to be resistant to malignant growth (Kierdorf and Kierdorf, 2010). It has been argued that the ability for epimorphic regeneration is associated with resistance to malignant tumor formation. Tumors tend to occur in reverse relationship to the tissue capacity to regenerate itself (Prehn, 1997).

Clark et al. (2004) reported on the ability of Deer Antler extracts to promote angiogenesis both in vitro and in vivo. An in vitro cell proliferation assay was performed on human umbilical vein endothelial cells that were treated with Deer Antler extract. In vitro ability of Deer Antler to promote migration of bovine aortic endothelial cells was reported, too. Wound healing is a complex process in which angiogenesis plays an important part. In vivo studies on rats show that Deer Antler extracts in saline solution at dose rates 2 mg/ml, 10 mg/ml and 100 mg/ml significantly improved the rate of wound closure. Only the smallest dose of 0.1 mg/ml show no significant effect. Both boiled and not heated Deer Antler extracts exhibited similar responses. Angiogenesis is not only the process by which new blood vessels develop, but it is also the method by which cancers grow and spread. Fraser et al. (2010) investigated the possibility of Deer Antler supplement to promote growth and metastases of colon cancer. This New Zealand study was done on rats with colon cancer. Chemical carcinogen azoxymethane (AOM) was used to induce colon cancer in rats. AOM is selective for distal colon and rectum, which is common

distribution of colon cancer in humans. Rats were randomly assigned in two groups, treatment and control. The treatment group was given Deer Antler powder in gelatin cubes, 1 gram per kilogram of body weight for 26 weeks. The control group received gelatin cubes without Deer Antler in them. The results showed that there was no statistically significant difference after 26 weeks between two groups in the volume of colon tumors, multiplicity (incidence) of colon tumors or multiplicity of tumors at all sites. The significant difference between groups was that the Deer Antler group had a higher incidence of lower grade colon tumors and for tumors at all sites. The tumors were evaluated on Astler-Coller grading system. The important separation is between tumors affecting local lymph nodes and tumors without lymph nodes involvement. Deer Antler treated group had no tumors involving lymph nodes, unlike the control group. The study not only confidently ( $p < 0.0001$ ) concluded that Deer Antler does not increase the incidence, multiplicity, metastases and tumor volume in rats with AOM induced colon cancer, but showed less metastases and a higher proportion of lower grade colon tumors.

The following case control study published in the British Journal of Cancer is not on Deer Antler, but on related topic: Men who use muscle building supplements that contain creatine or androstenedione may have up to 65% increased risk of developing testicular cancer. The odds are even higher for men who started using this supplements before age of 25 or who had taken them for the period longer than 36 months. Testicular germ cell cancer is the most common solid cancer in men aged 15 to 39 years. The incidence of it increased significantly in recent decades; so far no other known factors beside muscle building supplements can explain the increase (Li et al., 2015).

### **Deer Antler and Cancer Treatment**

Li, Cheng and Du (2008) mention Deer Antler in multiple instances in their comprehensive book *Management of Cancer with Chinese Medicine*. They list Deer Antler with other materia medica as an accessory treatment for alleviating side effects of chemo and radiation therapy. Deer Antler is mentioned as beneficial for promoting the production and enhancing the function of leukocytes and macrophages. The authors included Deer Antler on the list of materia medica that promotes humoral immunity. The book references a Chinese study by Cheng et al. on the positive effects of oral administration of Yi Xue Teng (Tablet for Augmenting the Generation of Blood) in the treatment for bone marrow suppression after chemotherapy for leukemia. Hemoglobin, white blood cell count and platelets came back to normal faster in the group taking the herbal formula than in the control group. Formula Yi Xue Tang contains beef bone marrow, deer blood, human placenta, deer antler, donkey hide gelatin, deer antler gelatin, turtle shell gelatin, codonopsis and astragalus. *Management of Cancer with Chinese Medicine* recommends using Deer Antler for damage to renal function due to chemotherapy.

Study published in Chinese language by Yang et al. (2014) came to conclusion that Deer Antler suppresses the over activation of osteoclasts, reduces bone absorption and maintains balance between osteogenesis and osteoclastogenesis. This was study on mice injected with breast cancer cells into shinbone. Some were treated with Deer Antler polypeptide, some with zoledronic acid, and the control group was without treatment. There was no significant difference between the Deer Antler and zoledronic acid groups, but both seemed to inhibit tumor growth. Unfortunately, there were only ten animals per group, which was the weakness of the experiment.

A clinical study, also in Chinese language, investigated the efficacy of oral administration of Deer Antler to treat myelosuppression after chemotherapy. Control and treatment groups were comparable in size, age and gender. All the subjects were treated with chemo for lung cancer, breast cancer or malignant lymphoma. Their Chinese medical diagnosis was Qi and Blood deficiency, Kidney and Spleen Yang deficiency. The control group was getting only chemotherapy, while the treatment group was taking one gram twice a day of powdered Deer Antler in addition. The author concluded that Deer Antler showed promising efficacy as a treatment for chemotherapy induced myelosuppression based on white blood cells count, Karnofsky performance status scale and body weight change after treatment (Duan, 2007).

There has been safety concern related to using Deer Antler in hormone sensitive conditions like breast cancer and endometriosis. There has been belief that Deer Antler should be avoided for women with hormone sensitive issues. Kim et al. (2012) in this South Korean study investigated the effects of Deer Antler extract on adhesion and migration of human endometriotic cells. The establishment of endometriotic cells in abdomen requires adhesion, migration, invasion and proliferation of the ectopic endometrial tissue. The study was done in vitro, using human endometriotic cells and human peritoneal mesothelial cells in the presence (treatment group) or absence (control group) of Deer Antler extract. The Deer Antler group demonstrated anti-adhesive effect and significantly reduced migration of endometrial cells. Deer Antler extract significantly suppressed expression of matrix metalloproteinases (MMP). MMP-2 and MMP-9 are important enzymes in ectopic adhesion, invasion, implantation and vascularization of the endometrium. The study also found that Deer Antler extract reduced the levels of inflammatory cytokines TNF- $\alpha$  (tumor necrosis factor alpha) and IL-6 (interleukin 6). The authors concluded with the suggestion that Deer Antler extract might be effective in treating

endometriosis and might be a potential anti-adhesive and anti-metastatic agent. Endometriosis shows many characteristics of benign neoplasia with the potential for malignant transformation. Endometriosis and ovarian cancer share similar predisposing factors like genetic susceptibility, immune and angiogenic dysregulation, and environmental toxic exposure. Cancer and endometriosis displays features of atypia, adherence, invasion and metastases (Varma, Rollason, Gupta and Maher, 2004).

### **Deer Antler Toxicology**

Zhang et al., (2000) explored in this New Zealand study the potential toxic effect of acute and subacute dosage regimens of Deer Antler powder in rats. No acute toxicity was found at the dose levels of 0.5, 50, 500 and 2000 mg/kg given for 7 consecutive days. There were neither gross pathological findings, nor histopathological evidence of acute toxicity. Subchronic oral administration of 1000 mg/kg for 90 days produced no signs of toxicity. There was no change in weight. No significant differences were seen between the Deer Antler group and the control group in red blood cell count, hemoglobin, platelets, and white blood cell count. There were no observable effects on carbohydrate metabolism, liver function and kidney function. The autopsy of rats treated with Deer Antler did not show any gross or microscopic changes of heart, liver, lungs, stomach, small and large intestines, pancreas, kidneys, bladder and spleen. Authors concluded with confidence that any potential accumulation of active constituents resulting from Deer Antler consumption does not lead to toxicity. The mg/kg doses were by far greater than dosages anticipated in humans. It is likely that no acute or subchronic toxicity would occur in humans. Since this study was done on rats, not on human subjects, this conclusion should be taken with caution. Similar study done on mice and published in Chinese language also showed no evidence of subchronic toxicity (Lei, Ding, Wang and Jiao, 2010). Another Chinese language

study done by Dong et al. (2008) concluded that Sika Deer Antler capsules are safe food without toxicity. Rats were given for 30 day Deer Antler on dosage 150 times higher than human dose without any impact on hematology, blood chemistry, body weight and histopathological tests. Wu et al. (2013) in their review of Deer Antler base summarized the toxicity chapter with the statement: “In short no known contraindications for the use of Deer Antler base have been found.” The study on dogs that were injected with Deer Antler extract showed no effect on the cardiovascular system. The eleven cardiovascular parameters were studied before and after Deer Antler administration including cardiac output, stroke volume, heart rate, mean arterial pressure, pulse pressure, central venous pressure and total peripheral resistance (Clifford, Lee, Kim and Lee, 1979).

Rollin, (2001) submitted his ethical commentary to *The Canadian Veterinary Journal* on animal welfare versus food safety in collecting Deer Antler. Cutting antlers might be painful for animals, since the tissue is alive at the time of collection. For the reasons of animal welfare and easier handling, animals are anesthetized for the collection and provided with analgesic after the procedure. This practice raises questions of possible anesthetic residue and subsequently the safety of Deer Antler products for the consumer.

### **Deer Antler Dosage**

Both major Chinese herbal reference books used as textbooks in schools of Traditional Chinese Medicine in the US, *Materia Medica* (Bensky, Clavey and Stöger, 2004) and *Chinese Medical Herbology and Pharmacology* (Chen J. and Chen T., 2004) suggest daily dosage for Deer Antler (Lu Rong) at 1 to 2 grams as a powder. Kawtikwar, Bhagwat and Sakarkar (2007) in the review article on Deer Antler state that in Korea typical dose is 1200 mg of sliced Deer

Antler daily, while in China 900 to 1200 mg daily appears to be the prophylactic dose and more than 1200 mg is the therapeutic dosage. In Russia, Deer Antler is taken twice a day as alcohol extract, 1.25 to 2 ml each time. Another study on rats treated with Deer Antler powder for heart failure considers 2g/70 kg to be human clinical daily dose of Deer Antler (Shao et al., 2012). In the literature review of dose levels of Deer Antler products in relation to efficacy, Suttie and Haines (2004) expressed how difficult is to analyze the dosages and come up with a robust recommendation on them. There are significant differences in the quality of antlers, method of product preparation, length of treatment and clinical objective. The authors analyzed dosages of Deer Antler prescribed by medical practitioners, human clinical trials, case studies and animal trials. Despite difficulties in the analytical process the review concluded that 2000 to 3000 mg per day of Deer Antler powder equivalent (20 to 40 mg/kg/day) is needed to effectively enhance performance in healthy individuals. In the same review, the authors thought the dosage of at least 27 mg/kg to be effective. They point out, in addition, that there is no sufficient data for Deer Antler dosage recommendations for unhealthy people or for the possible effectiveness of low dosages (200 to 400mg/day) taken over long time period.

### **Chapter Three: Methodology**

This chapter presents the methodology applied for this literature synthesis research.

The project's objective is to answer the research question stated as:

Does Deer Antler supplementation increase cancer risk in otherwise healthy subjects?

This question originated through my daily work, and my inability to provide the answer to it, so it morphed into the topic of this paper. There was no research hypothesis, just unbiased curiosity and desire to explore the current scientific knowledge on the subject.

The research was conducted in my work office, home office and UCLA biomedical research library. To research peer reviewed articles I utilized Pub Med, Google Scholar, Science Direct and Wanfang Data databases. Published books were also used in the research process. The following search terms were primarily used: "Deer Antler", "Deer Velvet", "Deer Antler chemistry", "Deer Antler constituents", "Deer Antler pharmacology", "Deer Antler toxicity", "Deer Antler supplements", "Deer Antler benefits", "Deer Antler safety", "Deer Antler dosage", "Deer Antler and cancer risk", "Deer Antler and cancer", "Deer Antler and growth factors", "growth factors and cancer", "IGF-1 and cancer" and "exogenous IGF-1". I went through a couple of hundred abstracts, eventually chose 71 full articles from which I extracted the research information. The inclusion criteria for the articles were to be published in past fifteen years in English or Mandarin languages in peer-reviewed journals. Because of the scarcity of research on the topics related to Deer Antler, I did include studies both on human and animal subjects. The articles were organized in seven groups corresponding with the themes that emerged from my research: IGF-1 and cancer, exogenous IGF-1, Deer Antler constituents, the effects of Deer Antler, Deer Antler and cancer, Deer Antler toxicology and Deer Antler dosaging.

Cooper and Hedges (1994), prominent writers on research methodology define research synthesis as “the process of conducting surveys of previously published material.” Science is a cumulative effort where thousands of scientist contribute toward the common goal either as theorists, researchers who collect data and research synthesists who bring all the pieces together.

The focus of my synthesis were research findings and theories related to the subject. The goal was to integrate past literature on to the topic. My perspective was to begin the research process with neutral initial point of view. The aim was comprehensive coverage of relevant and available material that I conceptually grouped by different aspects of the research topic. The intended audience of this research were health practitioners and the general public interested in the topic

The studies varied considerably in subjects and style, exploring different aspects of the topic, which made it impossible to compare data and clearly defined this project as qualitative research. The whole research process was an exercise in inductive logical thinking and simultaneously a learning experience of opening new themes and creating a narrative theoretical analysis in effort to answer the research question. My research could not find any single article directly investigating Deer Antler usage and cancer risk in healthy individuals, thus necessitating inductive inference to integrate all the information collected. David Hume, 18<sup>th</sup> century Scottish philosopher had an opinion that inductive logic, although useful for creating generalizations, is eventually flawed, since it cannot establish unbreakable connections between cause and effects. Kyriacou (2004), argues that medical decision making will always require inference or extrapolation from the available research to the individual patient or specific issue. Depending on the validity, reliability and availability of knowledge, the inferential step from evidence to clinical question can be small to quite large and always (to a greater or lesser extent) theoretical.

## **Chapter Four: Results**

The objective of this chapter is to present the most relevant data and current scientific knowledge in an effort to provide the best answer to the research question: Does the use of Deer Antler supplements increase the risk of cancer in otherwise healthy subjects?

The very recent study (Li et al., 2015) showed strong correlation between long-term use of muscle building supplements containing creatine or androstenedione and testicular cancer. These were not Deer Antler supplements, but products marketed for the similar effects on the body and targeting similar consumer group of athletic minded men. In the case of Deer Antler, IGF-1, it's the most commonly promoted ingredient is perceived by some as the main reason for concern of possible cancer risks. The research results are organized in the groups exploring the links between IGF-1 and cancer, IGF-1 and longevity, IGF-1 and Deer Antler, Deer Antler and cancer, Deer Antler effects, toxicology and dosaging.

### **What is the Summary of the Current Understanding of the Association Between IGF-1 and Neoplasia?**

The following statements are the most important findings on the IGF-1 and cancer relationship extracted from the literature used for this research:

- IGF-1 does not directly affect tumor cell proliferation, but it is clearly part of antiapoptotic machinery.
- Cancer proliferation is increased by activation of IGF-1 receptors in the body, due to increased levels of circulating IGF-1 in the body or increased autocrine production by cancer cells.
- Higher levels of circulating IGF-1 are associated with increased risk of common cancers.

- GH-IGF-1 axis has significant role in the development of cancer, but does not induce tumorigenesis.
- IGF-1 provides an environment that favors survival of genetically damaged cells. The effect is weak, but through the exposure to large number of damaged cells over a prolonged period of time can accelerate cancerogenesis.
- Genetic factors influence individual levels of IGF-1. A diet high in protein and energy mildly increases IGF-1 levels, while starvation has the opposite effect.
- Exogenous and endogenous steroids have important influence on GH/IGF-1 axis. Oral estrogen replacement therapy lowers circulating levels of IGF-1, but transdermal delivery does not. This might be explained by direct suppression of the hepatic IGF-1 gene in the case of oral delivery.

**Population Studies.** Table 1 is the summary of the most significant results of comprehensive overview of population studies published by Renehan et al. (2004).

Table 1: Population studies of serum IGF-1 levels and cancer risk

<b>Study</b>	<b>Study population</b>	<b>Cancer risk related to IGF-1 level*</b>
<b>Colorectal cancer</b>		
Physicians' Health Study	193 cases, 318 controls	0.28
Nurses' Health Study	79 cases, 158 controls	0.28
New York University Women's Health Study	102 cases, 200 controls	1.23
North Sweden Health and Disease Cohort	110 cases, 336 controls	1.75
Chinese men living in Shanghai	135 cases, 661 controls	1.18
<b>Prostate cancer</b>		
Physicians' Health Study	530 cases, 540 controls	Early stage: 1.2 Late stage: 5.1
Baltimore Longitudinal Study of Aging	72 cases, 127 controls	3.11
North Sweden Health and Disease Cohort	149 cases, 298 controls	1.72
The Washington County Serum bank	30 cases, 60 controls	0.60
ATBC Cancer Prevention Study	100 cases, 400 controls	1.00
<b>Breast cancer</b>		
Nurses' Health Study	397 cases, 620 controls	Premenopausal: 2.88 Postmenopausal: 0.89
New York University Women's Health Study	287 cases, 786 controls	Premenopausal: 2.30 Postmenopausal: 0.95
Swedish cohorts	513 cases, 987 controls	Premenopausal: 0.63 Postmenopausal: 1.29
Kaiser Permanente Medical Care Program	126 cases, 126 controls	Premenopausal: 3.49 Postmenopausal: 0.77
Italian cohort (ORDET)	133 cases, 503 controls	Premenopausal: 3.12 Postmenopausal: 0.58
Two prospective cohorts, EPIC and PPHV	149 cases, 333 controls	Premenopausal: no data Postmenopausal: 1.1
<b>Lung cancer</b>		
CARET	159 cases, 297 controls	0.64
Japan Collaborative Cohort Study	194 cases, 9351 controls	1.17
Shanghai	230 cases, 659 controls	0.73
New York University Women's Health Study	93 cases, 186 controls	0.79

- Highest versus lowest quantile relative risk (95% confidence interval).

The table shows correlation between higher levels of IGF-1 and increased risk of colorectal, prostate and breast cancer. Lung cancer studies did not establish that association. The possible explanation is that even higher levels of IGF-1 are insignificant in comparison of exposure to high levels of carcinogens: The lung cohorts were comprised primarily of heavy smokers.

The most relevant findings of pooled analysis of 17 prospective studies are presented in Table 2 (The Endogenous Hormones and Breast Cancer Collaborative Group, 2010).

Table 2: Odds ratio (OR) for breast cancer associated with IGF-1 levels, data from 17 prospective studies.

<b>Factor and subset</b>	<b>Cases/Controls</b>	<b>OR (95% CI)</b>
<b>All studies</b>	4790/9428	1.25
<b>Menopausal status</b>		
Premenopausal	1937/4096	1.18
Postmenopausal	2853/5332	1.30
<b>Age at diagnosis</b>		
<50	1071/2286	1.15
≥50	3719/4352	1.28
<b>Estrogen receptors</b>		
Positive	1414/2702	1.38
Negative	479/948	0.80

Circulating IGF-1 is positively associated with breast cancer risk. It appears that this association is confined only to estrogen positive tumors. The association is stronger in postmenopausal and older women.

The third population study used is on characteristic of baseline adenomas by tertile of IGF-1 (Jacobs et al., 2008). Subjects in the highest tertile of circulating IGF-1 had 30 % occurrence of villous histology in baseline adenomas compared to 16.2% in the lowest tertile.

The unexpected finding was an inverse relation between IGF-1 and colorectal adenoma recurrence after surgical removal. This puzzling finding might point to possible protective action of IGF-1.

### **IGF-1 and Longevity**

Reducing the activity of GH/IGF-1 axis is considered by longevity experts one of the most validated and consistent interventions to extend mouse lifespan and health span. The total lack of circulating IGF-1 is lethal, reduction in IGF-1 levels and action can extend lifespan in animal models. Low plasma levels of IGF-1 can predict survival in long-lived people, especially in women with a history of cancer (Longo et al., 2015).

### **Does Orally Administered IGF-1 Get Absorbed in the General Circulation?**

IGF-1 is a polypeptide and like other proteins and peptides has to be broken down by digestive enzymes in order to pass through the intestinal wall. Despite that, study on rats showed that 9.3% of orally taken IGF-1 did get into systemic circulation.

The transient increase in serum IGF-1 levels after oral IGF-1 administration indicates that the physiologically significant amount of exogenous IGF-1 gets absorbed into general circulation in weanling mice and adult rats. Mean serum IGF-1 concentrations was greater ( $p < 0.01$ ) in the IGF-1 fed group than in the control group.

### **What is the Content of IGF-1 in Deer Antler?**

Table 3 shows the example of measured content of IGF-1 in three sections of antlers taken from sika deer (Tseng et al., 2014). The content of IGF-1 is significantly higher in the upper section compared to the base ( $p < 0.01$ ). Estradiol and testosterone follow the same pattern, the upper portion has the highest content of both hormones, basal section the lowest.

Table 3: Chemical analysis of three sections of Deer Antler

Constituent	Upper section	Middle section	Basal section
IGF-1	52.91 ± 7.60 ng/g	46.70 ± 7.54 ng/g	22.90 ± 8.71 ng/g
Estradiol	2.13 ± 0.47 ng/g	1.61 ± 0.56 ng/g	1.02 ± 0.46 ng/g
Testosterone	1.05 ± 0.04 ng/g	0.46 ± 0.12 ng/g	0.27 ± 0.11 ng/g

### How Much IGF-1 is in Deer Antler products?

Deer Antlers are extremely complex substances and no specific ingredient has been associated with the specific effect. Despite that fact, many manufacturers of Deer Antler supplements single out IGF-1 as an active ingredient and keep promoting their products as natural source of IGF-1. Deer Antler products usually come to the market as powdered Deer Antler, tinctures and liposome solutions that are often offered as oral sprays.

The study that I used for this paper (Cox and Eichner, 2013) found no Deer Antler IGF-1 in the majority of products tested and low content of Deer Antler IGF-1 in only one out of six products chosen. The amounts of deer IGF-1 might have been present in concentrations too low to be detected. There is a possibility that analytical methods were not adequate, or that IGF-1 levels degraded over the time and extraction process.

Human IGF-1 was detected in some products. Natural, non-adulterated products cannot show any human IGF-1, which is a pharmaceutical protein.

Certain manufacturers claimed high concentration of IGF-1 on the product label, but analysis of the actual product found much lower amounts of human IGF-1.

### How does Deer Antler Supplementation Affect Endogenous Hormone Levels in Human Studies?

**IGF-1/GH.** A ten week strength training program with concurrent supplementation with either 300 mg of Deer Antler extract or 1500 mg of Deer Antler powder did not show any

difference in IGF-1 levels before and after the ten week training program compared to group receiving placebo (Sleivert et al., 2003).

GH levels at rest and after a race were no different in rowers taking Deer Antler supplement during a ten week training program compared to rowers taking a placebo (Syrotuik et al., 2005).

**Testosterone.** Taking Deer Antler powder supplement for 12 weeks did not cause significant change in testosterone levels or measured sexual function parameters (Conaglen et al., 2005).

Deer Antler supplementation did not affect testosterone levels in a strength training study or a study on hormonal responses in rowers (Syrotuik et al., 2005).

**Erythropoietin and Cortisol.** Levels of these two hormones seem also not be affected by taking Deer Antler supplements (Sleivert et al., 2003).

### **What were the Observed Effects of Deer Antler on Human Subjects?**

All the available research on human subjects did not show any significant effect of Deer Antler on anabolic hormone levels, erythropoietin and cortisol. Consequently and as expected, alteration in muscular strength and performance, isoinertial strength and rowing performance were not observed in those studies. The only unexplained finding was an increase in isokinetic strength and the mechanism behind it, since there were no hormonal changes. Possible explanation was an analgesic effect of Deer Antler that might have enabled athletes to push harder through the exercises (Sleivert et al., 2003).

There was no effect of Deer Antler supplementation on  $VO_{2max}$ , erythropoietic activity and oxygen carrying capacity (Sleivert et al., 2003).

In male subjects' sexual behavior, Deer Antler did not change thoughts, desire, arousal, initiation, pleasure, satisfaction, problems affecting sexual function and preferences (Conaglen et al., 2005).

### **What is the Direct Impact of Deer Antler on Cancer?**

Based on the available evidence, Deer Antlers as organs are seemingly resistant to develop cancer. It appears that tissues resist oncogenesis in direct proportion to their epimorphic regenerative ability. The question is: Does this resistance to tumors in nature somehow get replicated when using Deer Antler as a supplement or medicinal substance? Chinese studies do show the benefits of Deer Antler in myelosuppression secondary to chemotherapy. Knowing the deep cultural reverence for Deer Antler and its benefits in the East and relative obscurity in the West, it was no big surprise for me that there were no available studies investigating the direct association between intake of Deer Antler supplements and risk of cancer.

The following three studies and their findings might be considered keystone, because they offer the most direct insight in possible impacts of Deer Antler on cancer:

- Deer Antler extracts are able to enhance the growth and migration of endothelial cells in vitro and exhibit potent wound healing ability in vivo. In another words, Deer Antler promotes angiogenesis, which facilitates spread of tumors as new blood vessels provide growth factors and nutrients for further growth and metastases (Clark et al., 2004).
- The study done by Fraser et al., (2010) clearly demonstrated the opposite and unexpected: Rats with azoxymethane induced colon cancer treated for 26 weeks with high oral doses of Deer Antler (1g/kg) had significantly less metastases and higher proportion of low grade tumors compared to control group.

- The observed in vitro effect of Deer Antler extract to inhibit endometriotic cells migration and adhesion to mesothelial cells supports the possibility of Deer Antler as anti-metastatic agent. Treatment with Deer Antler extract significantly decreases metalloproteinases expression, which plays a major role not only in endometriosis, but also in cancer progression and metastases (Kim et al., 2012).

**Other Safety Issues, Dosing,**

Deer Antler seems to have almost no known toxicity. Studies on animals that were given much higher than regular human adult dosages (equivalent of up to 140 grams daily for an adult) did not produce any observable toxic effect. On the other end of the spectrum, the dosages below 2 grams per day for an adult might not be sufficient to produce desired positive effects. Under dosing might have undermined significance of some studies used in my research project. It seems that Deer Antler might have potentially quite broad safe therapeutic range, from about 2 grams per day to at least 70 grams per day over a 90 day period for an adult (Table 4).

**Table 4: Daily dosage of Deer Antler**

Daily Dosage*	Duration	Subjects	Comments
0.56 g	10 weeks	Humans	No observed effect on rowing performance and hormonal response (Syrotuik et al., (2005).
1 g	12 weeks	Humans	No effect on sexual behavior or hormonal levels (Conaglen et al., 2002).
1.5 g	10 weeks	Humans	Study on athletes, no change in hormonal levels, aerobic power, erythropoiesis, but isokinetic strength and muscular endurance improved (Sleivert et al., 2003).
1 g to 2 g	varies	Humans	Common dosage range in TCM books and practice.
2 g	4 weeks	Rats	Comparable effects to drugs in reversing changes in functional parameters and BNP levels in rats with heart failure (Shao et al., 2012).
2 g	10 days	Humans	Significant efficacy observed in treating myelosuppression after chemotherapy (Duan, 2007).
2 g and above		Humans	The dosage recommended by New Zealand review (Suttie and Haines, 2004).
2.7 g	10 days	Humans	Promising results on upper body strength, body fat, protection from overtraining, aerobic capacity, and cholesterol. No adverse effects on liver and kidney function (Broeder et al., 2004).
70 g	26 days	Rats	Deer Antler did not increase incidence, multiplicity, metastases or volume of colon cancer Fraser et al., 2010).
70 g	90 days	Rats	Study on subchronic oral toxicity: No toxicological and histopathological changes were observed (Zhang et al., 2010).
140 g	Single dose	Rats	Study on acute oral toxicity: No toxicological and histopathological changes were observed (Zhang et al., 2010).

- Dosage converted to g/70kg (adult dose).

Table 4 is an effort to put in perspective and easily compare dosages and treatment duration of Deer Antler used in various articles for better understanding of its efficacy, therapeutic range and toxicity. All the dosages have been prorated to the average human (70 kg) dose.

## Summary of the Main Results

The statements listed below further summarize the most important research findings into 10 key points:

- Antlers are resistant to tumor induction in live animals.
- Deer Antler does contain growth factors, including IGF-1. The highest concentration is in the tip.
- Higher circulating levels of IGF-1 are associated with higher incidence of tumors, but do not induce tumorigenesis.
- Some exogenous IGF-1 when taken orally does get into systemic circulation.
- Deer Antler supplements seem to contain very little IGF-1.
- Certain Deer Antler products might be adulterated with pharmaceutical IGF-1.
- Oral supplementation with Deer Antler seems not to increase levels of anabolic hormones including IGF-1.
- Deer Antler promotes angiogenesis in vitro.
- Very high dosages of Deer Antler did not increase incidence, multiplicity, volume and metastases of colon cancer in rats.
- Deer Antler in vitro limits endometriotic cells migration and adhesion. There is a possibility of Deer Antler being anti-metastatic substance.
- There has been no observed acute or subchronic toxicity associated with oral intake of very high dosages of Deer Antler.

These are the distilled findings of dozens of surveyed studies. The research result on Deer Antler use and cancer risks is absent, because there is no known study on the subject available.

## **Chapter Five: Discussion**

### **Limitations of the Current Study**

This literature synthesis has not produced definite answer to the research question. The main reason is that there is neither human nor even animal trial to examine directly the impact of taking Deer Antler supplements by healthy subjects on oncogenesis. It has been all circumstantial evidence that I had to rely on in the effort to elucidate the association between Deer Antler supplementation and cancer.

### **Summary of Findings**

The IGF-1 content in Deer Antler has been the primary concern for the possibility of increased cancer risk. Deer Antler is by far much more than just IGF-1. It is a rich mixture of various growth factors and other proteins, peptides, amino acids, hormones, GAGs, lipids and minerals. This extremely complex chemistry does not produce antler cancer in nature, despite the fact that both tumors and blastema of regeneration involve undifferentiated stem cells. IGF-1 by itself has definitely been associated with cancer development although not with the induction of tumors. Reducing activity of GH/IGF-1axis has been target of anti-cancer drug research. In recent years there have been multiple preclinical studies and clinical trials on cancer treatments targeting IGF-1 receptors using antibodies or small molecule inhibitors (Puzanov and Hess, 2015). There is a consensus in longevity research community that decreasing IGF-1 and GH activity is one of the key interventions that can prolong life span and postpone age related diseases. Roughly 10 % of orally taken IGF-1 seems to get in systemic circulation, although without any observable effect on body or organ growth (Kim et al., 2006). In human studies, at least at the dosages of Deer Antler used, there was no significant increase of anabolic hormones levels upon taking Deer Antler supplements in the course of several weeks. Analysis of Deer

Antler supplements in a New Zealand study found almost no human IGF-1. This can be explained either as inadequacy of lab tests to detect IGF-1 in the complex matrix of Deer Antler or more likely explanation is that IGF-1 does get denatured through the extraction processes and overall handling of the products. Toxicological studies on animals showed absolutely no signs of toxicity after exposure to very high dosages of Deer Antler over the period of up to 90 days.

### **Implications for Theory**

All these pieces of evidence, summarized above, although indirect and based on limited research do point to the conclusion that the chance that Deer Antler can increase the risk of cancer in healthy individuals is very unlikely. It appears that Deer Antler has almost opposite effect on cancer: Giving Deer Antler to rats with colon cancer reduces the number of metastases and severity of tumors. Available literature gives the impression that Chinese researchers and practitioners of traditional medicine do not have concerns about Deer Antler and possible carcinogenesis. To the contrary, Deer Antler in China is often used in integrative oncology especially for myelosuppression secondary to cancer treatments.

### **Implications for Practice**

Since antlers contain numerous hormones, common sense dictates constrain from prescribing Deer Antler for patients with hormone dependent cancers like prostate or breast.

Possible increased risk of cancer in healthy individual taking Deer Antler products is hypothetical with no research-based evidence supporting it. Should the practitioner of Traditional Chinese medicine or anyone else prescribing or using Deer Antler supplement be cautious? The answer is definitely yes. We simply do not know enough. Proper dosing is the way to exercise caution. It seems that dosages of Deer Antler powder or the equivalent extract dosage at 2g /70 kg and higher are needed to produce desired effects. Traditionally in Korea, Deer Antler is

usually prescribed for two weeks, 8g daily for an adult (Suttie and Haines, 2004). It is very likely that much higher dosages are safe at least if taken over period of up to 90 days. (There are no data available for possible toxicity of Deer Antler if taken over 90 days). On the other end, we do not know anything about effectiveness and safety of low dosages (500mg) if taken over long time. Based on current knowledge, it might be safer to use high doses of Deer Antler either occasionally or over relatively short period, rather than taking very small doses over many months. The possible theoretical explanation for such dosing strategy would be our current understanding of IGF-1 and cancer. IGF-1 impact on cancer is not strong, unlike estrogen for example, but that weak antiapoptotic effect, many times repeated over long time period can favor cells with damaged DNA, prevent them from dying and facilitate carcinogenesis (Jenkins et al., 2006). We definitely do not want to possibly contribute to elevated levels of IGF-1 with daily routine of taking Deer Antler supplements.

Study by Cox and Eichner (2013) on content of IGF-1 in Deer Antler supplements did find adulterated products spiked with pharmaceutical IGF-1, which is unethical, illegal and potentially dangerous practice. Some products had deceptive and false content claims on the labels. These findings are quite disturbing and potential Deer Antler users should always look for products of reputable manufactures who follow FDA's strict and comprehensive Current Good Manufacturing Practice (cGMP) in manufacturing, packaging and labeling (Guidance for Industry, 2007).

### **Future Recommendations and Conclusion**

Rollin, (2001) raised the question over possible anesthetic residue in Deer Antlers, since the animals are anesthetized for antler collection. Concerns like this might in the future open the

whole new field of research in animal welfare and safe, organic practices in commercial deer farming and subsequently high quality, toxin free raw material for Deer Antler products.

Deer Antler is magnificent organ with a long history of use as a medicine and health-promoting supplement in the East. In modern days its story intertwines directly or indirectly with some of the trendiest topics in biomedical science like stem cells, regenerative medicine and cancer research. In order to step out of its relative obscurity in the West, Deer Antler still needs more high quality, human trials to prove itself as a possibly efficient and safe supplement.

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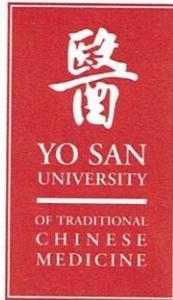
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Appendix



September 22, 2014

Borna Ilic  
1642 Franklin St  
Santa Monica, CA 90404

Dear Borna,

Your research proposal has been approved, with no additional recommendations effective through March 31, 2016.

Should there be any significant changes that need to be made which would alter the research procedures that you have explained in your proposal, please consult with the IRB coordinator prior to making those changes.

Sincerely,

Penny Weinraub, L.Ac.  
IRB Coordinator