

Human's Bosom Buddy Beagle: As an Experimental Animal Model

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The fundamental purpose of this article is to review the human's bosom buddy beagle dog as a pet animal, as an experimental animal model for basic research methodology, and other uses of this breed in various field. Main focus of this paper is to light up beagle dog anatomical and physiological resemblance to humans with brief idea about disease pathology and treatment. The article collect different diseases that associated to eyes, oral system, CVS and bone joint, from different review articles and research papers, putting all these study in one paper. This animal model gives practical and clinical knowledge about disease pathology, history and mechanism of the drug. Overall conclusion was to describe scope of beagle as an animal model to understand human anatomy and the effect of drug that having similar action on dog as well as humans. This provides platform to develop novel drug on various diseases and assessment of their safety and efficacy. With this ,the review paper explain that beagle is not only human's a true hearted buddy but also the great companion animal that help in research work to go beyond the limit of experiment to serve good health to mankind and environment.

Keywords: Beagle Animal Model; CVS; Drug Pathology in Heart; Osteoarthritis; Ocular Lesions; Periodontitis.

Beagle is the family friendly dog breed. This dog is small in size and having short hair, belonging to family name as "*canidae*", their genus is "*canis*". In past they were famous for hunting purpose as they possess strong sense of smell; because of this their owner takes them for searching a rabbit and foxes. Beagle is very popular as a pet animal due to their small size, good temper and friendly nature with human and this is also

very famous in research purpose. Modern breed of beagle was developed around 1830s, these breed were developed from Talbot hound (this is North Country beagle) and harrier (this one is the southern hound). This particular breed (beagle) is well known since Elizabethan times. Now a days this breed often seen in television and comic books.

History about origin of beagle is not known, William the conqueror in eleventh century

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cross breed Hubert dog (bloodhound, sleuth hound) and Talbot dog with Britain breed dog Grey hound to give haste for running and improve strength for hunting purpose. Miniature breed of beagle were known from 11th to 14th century, they were small about eight to nine inches (20-23cm) at shoulder. Elizabeth describe dog as a singing beagle as she used to entertained guest at her royal table by allowing her beagle cavort amid their plates and cup.

The beagle hound general appearance in terms of colour are lemon & white, tri-colour, white & tan, chocolate tri, chocolate and white etc. very rarely beagle found with single or two colour. But they are many times they have three colours. Tri colour beagle found in number of shades like large black colour with light brown colour, "classic Tri, black Tri, faded Tri". Some beagle slowly changes their colour during their life span and afterwards they may lose their black shade permanently. Talking about beagle temperament, this animal is friendly, clever, calm, gentle and temperamental. Generally they seem like miniature Foxhound but they having slightly broader head and their muzzle are shorter, legs are also shorter as compare to body. Beagle having domed shape skull, square cut muzzle and black nose or gumdrop nose. They are having strong jaw. The upper teeth perfectly fit to lower jaw and arrangement look like square to the jaw. Beagle eyes are large and brown in colour. Beagle having short length neck that is easy to them to bend at ground and smell scent, little skin folding at neck site. "Stern" is the tail of beagle with white tip called flag. Beagle characteristic is they have great senses of smell. Their long ear and large lips help them for trapping the scents closer to their nose area. American kennel club is the varieties of beagle. Beagle can gives birth to average 6 puppies. Pups weigh about few ounces.

In United State the beagle dog used in agriculture department for detecting the food items in luggage. This dog having pros that is they are small in size, intelligent and easy to care. Beagle dogs are used in ministry of agriculture department and forestry department in different countries. For identifying explosives these animals are not suitable. They are also useful in detecting cosmetics, medical and chemical test. Beagle is widely used in research purposes like - basic

biological research, medicine for veterinary and human uses are tested¹.

Scope of beagle dog for research purpose:

Beagle dog are prominently used to study the etiology and therapeutics of several diseases that are resemblance with human. Beagle dog in ophthalmology; this breed is famous to evaluate drug toxicity to eyes. In ocular toxicity study histopathology of eye is crucial part, to study structural variation and compare that with human eye is therefore necessary. Beagle dog eye having physiological resemblance with that of human eye and hence it is best animal model for ocular study. Beagle dog is concern for tapetum which is reflective tissue for choroid layer of eye. Drug associated tapetum degradation is mostly studied with this animal eye. Tapetum degeneration also called as toxic tapetopathy².

Apart from eye beagle dog also useful in tooth related diseases like periodontitis, photodynamic study and gingival infection³. This infection is common in both dogs as well as in humans. So this animal model gives brief pathophysiological study of periodontitis and their treatment. *H. pylori* is the gram negative bacterium, it causes chronic gastritis and peptic ulcer. And furthermore it commences gastric mucosa related cancer. Antisecretory agent and antibiotics are the therapy used for these conditions. But there are adverse effect seen with this therapy as development of drug resistance, also there is possibility to recurrence. To overcome this problem the vaccine invented since last decades. The beagle dog is very suitable animal to study safety and efficacy of such vaccine⁴. The body structure of beagle dog stomach and peptic ulcer pathophysiology likeness to human hence this animal provide accurate therapeutic treatment with reliable result.

In basic research especially on cardiovascular studies dog species are preferred due to their likeness in heart connectivity and size to human heart. Beside this dogs also used in discovery of the insulin which is used in treatment of diabetic, blood transfusion procedure and for electrical defibrillator to normalize heart rhythm⁵. Dogs are very convenient animal to study the efficacy of some newly developed anticancer drugs with same cancer that happen to humans, this one

is beneficial to both field veterinary and medical science.

Some structural differences among laboratory animals are mentioned below:

Conducting histopathology of the eye is crucial need in ocular toxicity. For this study knowing structural variation of laboratory animals are therefore necessary. Any ocular lesions found in animal's eye compare to anatomy and physiology of human eye.

Albino rat

In this animal there is absence of melanin in the eye fundus. This can be observable through ophthalmoscopy. Due to absence of melanin, light induced retinal degeneration studied can be performing by using this animal model⁶.

Dog

The shiny reflective tissue present in choroid layer of eye is called "tapetum lucidum" this contain reflecting crystal and with this there is high level of Zn found. This is best animal model to study drug induced tapetum degeneration (toxic tapetopathy). The benefit to use dog as animal model for ocular toxicity is that, larger eye size as compare to other experimental animals, which

provide excellent brief observation of eye parts. Fundus having two parts, first one is the tapetum lucidum, and another one is non tapetum also called tapetum nigrum. The tapetum is the main characteristic of dog species². The test also required less time in case of dog i.e., up to 1 year⁶.

Monkey

Macula present in eye of monkey and that is likeness to humans. This animal is suitable for study the drug induced macular lesions^{2,7}.

Beagle dog as an animal model to study various disease pathophysiology and treatment that resemblance to humans are described below:

Oral diseases

The veterinary data supports that there is high risk of dog to develop periodontitis as their age increases and with decrease in bodyweight⁸. Animal diet, behavior, environment and genetics factors play crucial role here. A periodontal disease is most commonly seen in dog that is similar to humans⁹. Periodontal disease is the inflammation cause to periodontium, which are surrounding tissue that supports the tooth. This periodontium are composed of gingival, cementum, periodontal ligament and alveolar bone etc¹⁰.

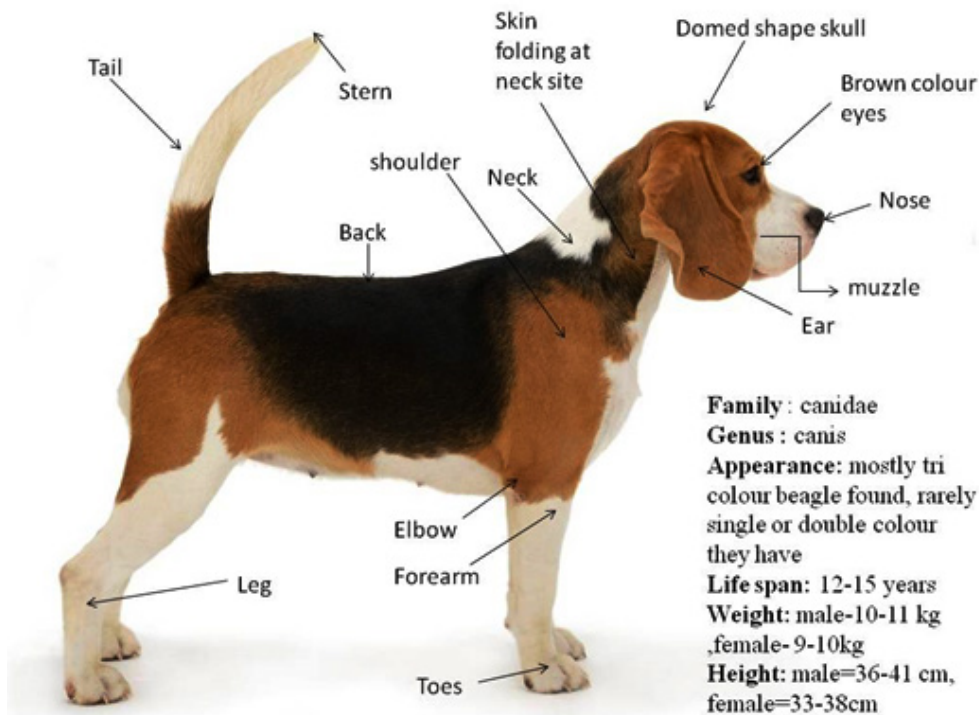


Fig. 1. Beagle dog Anatomical representation with biological salient characteristics

This disease condition occurs due to formation of plaque on surface of tooth. Plaque formation commence in 3 steps. At First there is pellicle formed due to adherence of salivary glycoprotein to tooth, that result into bacterial adhesion and in last step plaque maturation take place. When this plaque get mineralized it form calculus this provide new surface to adhere new plaque over it. Further Inflammation and tissue damage is due inappropriate regulation of immune response to bacterial infection^{11,12}. In periodontal disease two conditions commonly observed one is gingivitis and another is periodontitis¹³. In case of gingivitis there is inflammation and redness to gingiva. In periodontitis the supporting tissue of tooth become swollen, that resulted in lose the attachment to tooth and destruction of ligament, cementum and alveolar bone¹⁴. Gingivitis is reversible condition and periodontitis is irreversible but still there are some manageable treatments are available on this condition¹⁵. There are several types of periodontal infection that occur to humans are- chronic periodontitis and aggressive periodontitis. In chronic conditions that occur in adolescence but it get slowly progressive & initially it is not clinically

relevance. Aggressive periodontitis is progress fastly and alter pre-pubertal juveniles. It is concern that there are some other factors too that induces plaque formation and influences host's s response to the infection¹⁶. As like to humans these factors are modifiable such as behavioral or environmental that includes stress, nutrition and oral hygiene. In an early stage of this disease condition it is not so painful but as the disease get progress it get extremely painful with periodontal abscesses and mucous membrane damage. In addition there is loss of attachment of periodontium to tooth that result in increase in mobility to tooth and further it tooth lost. There are some physiological changes observed with this disease are, pain in tooth , weight loss, abnormal aggressive behavior , abnormal eating behavior, gingival bleeding, shaking of the head etc. severity of this disease in mainly associated with pathological changes in vital organs of the body¹⁷.

Cardiovascular diseases

Beagle dog having resemblance of heart with humans heart, this provide scope in Cardiovascular related disease understanding and also for understanding the drug mechanism acting

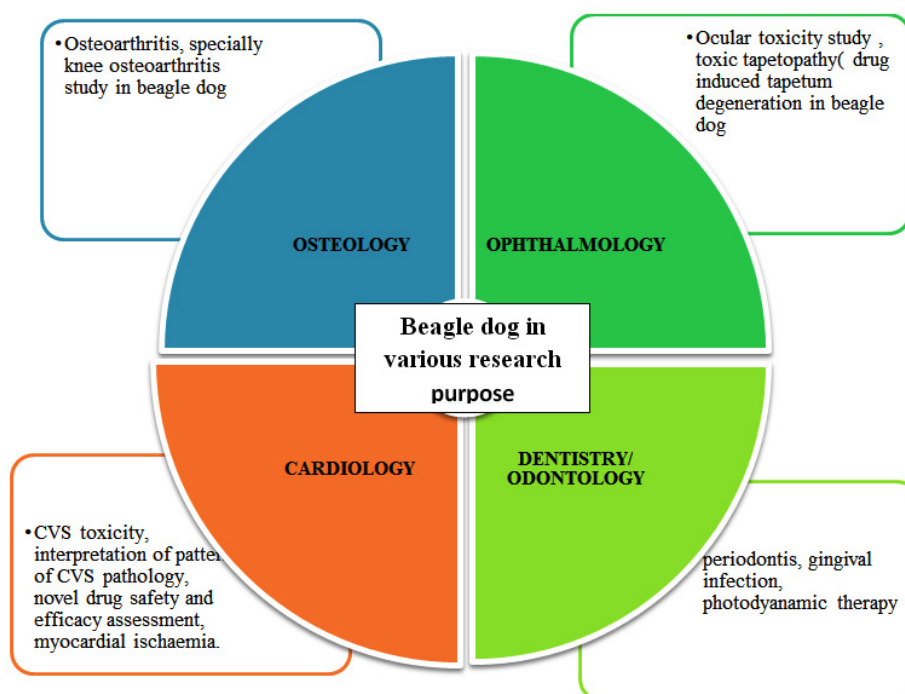


Fig. 2. Diagrammatic presentation of beagle dog in various research purposes with their example

Table 1. Physiological parameters of some experimental laboratory animals

Parameters	Rat	Rabbit	Guinea pig	Mouse	Beagle Dog
Body weight (g)	200-300g	2000-3000 g	500-800 g	25-30 g	Male: 10-11 kg Female: 9-10 kg
Life span	2-3 yrs	4-5 yrs	2 yrs	1-2 yrs	12-15 yrs
Water consumption	35ml/days	200-300 ml/day	250-350 ml/day	6 ml/day	480 ml/day
Food consumption	20g/days	100 g/day	30 g/day	5 g/day	1 cup food/day(one pound/day)
Oestrous cycle	4-5 days	Spontaneous ovulation	15-19 days	4-5 days	Heat cycle 2-3 weeks
Gestation period	21 days	32 days	67 days	19 days	63 days
Breeding age	60-80 days	90-120 days	365days	42-56 days	8 month(American kennel club) Other breed 2 years
Body temperature °C	37.5 °C	38.3 °C	2-4 °C	37.4 °C	38.3 °C
Respiratory rate	80-150 breaths/min	35-60 breaths/min	60-110 breaths/min	90-180 breaths/min	10-35/min
Heart rate	260-450 beats/min	205-308 beats/min	250-300 beats/min	300-750 beats/min	110-140 beats/min
Room temperature	24-27 °C	24-27 °C	24-27 °C	24-27 °C	23-25 °C
Relative humidity (%)	50-60 %	70 %	70 %	50-60 %	65 %

Table 2. Anatomical structure of beagle dog and their specification with research use

Parameters	Heart	Eye	Tooth	Bone joint
Specification	Beagle dog heart anatomy and physiology likeness to human's heart. Human and beagle dog having 4 heart chambers, the upper chamber contain left and right atria and lower chamber contain left and right ventricles. There are 4-5 pulmonary veins present in humans whereas in dog there are about 4-8. Other difference includes size and shape of atrial appendages. Heart beat of dog is 60-160 beats/min, in humans it is 60-100 beats/min. The cardiac diseases that causes to dogs are same as that of humans hence it is best animal model to treat heart related diseases in dog and learn their pathology. This is beneficial to both for dogs and humans.	The dogs are specially concern for tapetum lucidum. Eye of dog having structural characteristic similar to human eye. The advantage of using beagle dog for ocular studies are- they having larger eye size, there is clear observation made for lens, vitreous, fundus and whole anterior portion of eye.	Tooth related diseases are common in man and dogs there are various kinds of tooth problems observed in dogs species. To understand pathophysiology of disease and treatment, this is best animal model. The common tooth problems found in dogs are periodontitis, gingival infection. This periodontium are composed of gingival ,cementum periodontal ligament and alveolar bone etc. Gingival infection, periodontitis	The osteoarthritis mainly knee osteoarthritis is common problem that globally affecting people. This disease is also observed in dog species.
Disease that causes to beagle and are similar to humans	Cardiac toxicity ,Ventricular ischemia,Anthypertensive agents at higher doses lead to sub-endocardial and papillary muscle lesions.	Ocular toxicity that occur by various drugs and chemicals, Toxic tapetopathy, Vision related disorder,		Osteoarthritis (mainly knee osteoarthritis)
Use as animal model for	Cardiac toxicity, Drug induced myocardial ischemia in beagle dog.	Drug induced tapetum degeneration, ocular toxicity	Periodontitis, photodynamic therapy for teeth, gingival infection treatment	Knee osteoarthritis

on the heart. Drug induced structural changes in myocardium of dog, having a specific link to its mechanism of toxicity. Such assessments are based on interpretation of pattern of CVS pathology. Certain changes in cardiac and vascular function, cellular toxicity are the helpful connection. Full evaluation of this requires in vivo or in vitro, physiological, pharmacological, biochemical information. This animal model is best for study of CVS toxicity as this species having hemodynamic changes & pathological alterations in such a way that it give basic idea and result for safe study in humans with novel drug on CVS activity. Beagle dog provide characterization of novel drug to support their safety and efficacy to further carry this study in humans. Identification of dose response for treatment up to maximum tolerance dose. Anatomical distribution of drug provides ranges of drug induced, hence histological examination of heart and blood vessel are necessary criteria. Importances are given to papillary muscle and area that beneath the endocardium for ischemia, endardium and valve, coronary artery exaggerated vasodilatation and vasoconstriction. In dog toxicity study on heart there must be a careful observation of heart rate, B.P and ECG recording in drug plasma concentration¹⁸.

Antihypertensive agents at High doses of calcium channel blockers and vasodilating antihypertensive produces lesion to subendocardial part and papillary muscle in left ventricular of the dog. Minoxidil at higher dose minimizes the systemic and coronary artery pressure, increase rate of heart and elevate O₂ demand, blood supply to subendocardial zone and papillary muscle get altered. Posterior papillary muscles are sensitive to ischemic damage due to its weak blood supply. When heart rate increases 55 beats/min simultaneously arterial pressure decreases at least 30 mm of Hg that time more chances to cause subendo-cardial necrosis. This effect observed with minoxidil in beagle dog. The calcium channel blockers which having effect on papillary muscle and that tend to damage the endocardia is also known to produce hypotension and tachycardia of similar magnitude at higher doses. Such type of condition not seen in humans.

Inotropic drugs are known to alter the contraction force of heart muscle. There is positive inotropic and negative inotropic effect. CVS

drugs which having multiple pharmacodynamic action, shows inotropic effect, Example of this includes adrenergic agonist, cardiac glycosides, phosphodiesterase etc. Phosphodiesterase possess inotropic as well as vasodilating effect. At high doses it produces hypotension, tachycardia and cardiac lesions in dogs. More inotropic effect of drug produces ischemia in endocardia and increases intramyocardial pressure with O₂ demand.

Many study have reported that majority of myocardial ischemia cause are due to high circulating vasopressor agents like- nor-adrenaline, angiotensin. Other reason includes symapathomimetics amine and digoxin administration⁵.

Osteoarthritis (OA)

This is the tremendous public heath related issue it affect both heath as well as finance of individual^{19, 20}. Research of this disease is the crucial need to understand disease progression and diagnosis. Animal model are playing importance role in understanding disease pathology and their chronic effect. Beagle dog are one of the suitable model to study osteoarthritis. The numbers of knee osteoarthritis are increasing globally, this make big concern about developing advance treatment therapy or medicine in treatment of OA disease²¹. Research by using human subject is difficult to study OA and this lead to develop wide scope for including animal models, in degenerative joint disease and modifying anti osteoarthritis agents. Chemicals such as monosodium iodoacetate and collagens are used to induce OA by giving injection intra-articular route. These chemicals induced disease by mechanism of inhibiting the activity of glyceraldehydes-3-phosphate dehydrogenase in chondrocytes, inducing synovial inflammation and supporting structure degeneration. Alternately induction by surgical method includes destabilizing the knee joint. This can be done by transaction of anterior cruciate ligament, fibular collateral ligaments, ligament of humphry etc²¹. The ideal way to manage OA is blocking catabolic activity of the cartilage and promoting regeneration of cartilage. The treatment are based on pain of palliation, discomfort, functional movement improvement, preventing degeneration, thus there is approach to use NSAIDs analgesics^{22, 23, 24}. This is symptomatic treatment, but this not gives any disease modifying effect. So because

of this there is necessity to introduce new agents that prevent further destruction of cartilage and promote their regeneration. For this reason there is scope to develop effective cartilage preserving technique with cell sources. The isolated chondrocytes expansion and implantation technique are commonly known as fundamental solution²⁵. The limitation of this chondrocytes is lacking characteristics of producing hyaline like cartilage. In dog model it is observed that cultured autologous chondrocytes limit for returning hyaline cartilage. Cell of adipose derived MSCs are injected intra articular site in humans that lead to improve function, reduce pain and regeneration of hyaline cartilage²⁶. Mesenchymal are not found in normal synovial fluid. But this is found during osteoarthritis condition, as they having important role in regeneration of tissue and act as anti-inflammatory. As the ages increases this mesenchymal cells are decreases with decreasing their ability to divide and differentiate. The decreasing count of healthy mesenchymal cell is one of the reasons for worsening osteoarthritis condition. It also having anabolic effect due to presence of the fibroblast growth factor & transforming growth factor beta. They are capable of enhancing wound healing and extracellular matrix remodeling by stimulating angiogenesis. It is reported that platelet rich plasma has synergistic effect with mesenchymal cells that is proven by using animal dog model²⁷. Female beagle dog were choose for investigating pathology of osteoarthritis. For inducing osteoarthritis most animal models required opening of knee joints and surgical procedures, this OA result in alteration of weight bearing and instability to joints. The stresses act on joint that causes change in morphology and metabolism of cartilages. The certain factors that should be taking into consideration are inflammatory mediators, genetic predisposition, hemorrhage into joint etc. to induced experimental osteoarthritis osteotomy of hind limb have been used as animal model to causes OA in dog (beagle). Some research paper have demonstrated that inducing osteoarthritis in young beagle (female) dog by performing valgus osteotomy of upper tibia that alter biomechanical condition of the knee, reason to use only young beagle dog is to avoid the age related osteoarthritis, and advantage is, they don't have degenerative cartilage problem at this age. This model gives brief idea about

early changes of osteoarthritis, and changes that are necessary to improve surgical procedures osteotomy²⁸.

Beagle dog in ophthalmology

The eye is the sensory organ, their structure is so unique. In humans the eye function are most necessary for living quality of life, As it gather about 80% of external information through vision. Impairment of vision in human due to medicine or chemicals is absolutely having effect on social life of the person^{29, 30, 31}. Therefore ocular toxicity of drugs is crucial to perform under several guidelines of non clinical toxicity studies. This observation of eye is made through ophthalmoscope. For evaluation of drug ocular toxicity there is need to obtain data of from clinically, ophthalmoscopically, and also the histopathological observations etc. There is structural variation of eye among species of animals. By studying and understanding structural criteria of eye, it makes easy to assess ocular lesions. The eye divided into three layers, the outer layer contain transparent cornea and white, opaque sclera. The middle layer contains iris at anterior site and choroid at posterior site. The last one is the inner layer this is comprises of retina. The ophthalmic lesions are not impulsive in beagle dog in comparison to other animals like rat and mice. The previous studies on ocular toxicity of beagle dog have suggested that there is an infrequent spontaneous lesion observed in beagle dog. Due to this reason there is limitation to use other dog species in toxicity studies; the beagle is only preferred species for this kind of study³². Tapetum toxicity also observed after administration of several drugs in beagle dogs. The research study shows that administering zinc pyridinethione, B- adrenergic blocker, chymotrypsin inhibitor, antipsychotics to beagle dog shows alteration of tapetal and simultaneously degeneration of tapetum lucidum but there is no retinal lesions were found. Tapetum lucidus of dog comprises of Zn elevated level, the toxic tapetopathy in beagle eye having correlation to zinc chelation. Another drug i.e., ethambutol, administration of this drug induce de-colouration of tapetum along with swelling and disorientation of rods in tapetal cells, this observed through electron microscopy. Toxic cataract have been observed with various drugs and chemical agents used in toxicity study on beagle. Drug affecting Na-K-ATPase pump, cell permeability,

osmotic balance, resulting toxic cataract formation within lens. This toxic cataract formed at anterior or posterior cortical region of dog eye. HMG-CoA reductase inhibitor at high doses in dog produces anterior and posterior subcapsular cataracts. High galactose diet in beagle leads to accentuation of anterior and posterior sutures of lens and that that further tend to sugar cataract².

CONCLUSION

The conclusion of this review article is to provide detailed information about beagle dog from their history as a pet animal to recent uses in biomedical research as experimental animal model. This dog breed i.e., beagle is the convenient animal model to study ophthalmological diseases, cardiac related diseases, osteoarthritis, periodontitis, due to presence of structural and functional similarity of dog to humans this is beneficial to both for veterinary science and biomedical science. This model gives strong experimental and clinical proof. This paper underlines the wide scope of beagle in research purpose that would be fruitful for advance research in novel drug investigation. Beagle as an animal Model is very convenient to know brief about the disease pathophysiology and therapeutic major followed by drug mechanism of action in preventing disease condition.

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Conflict of interest

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