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**C Vinaya Sree**
Assistant Professor, Department of Veterinary Physiology, College of Veterinary Science, Korutla, PVNRTVU, Telangana, India

**Swathi Bommu**
Professor, Department of Veterinary Physiology, College of Veterinary Science, Mamnoor, PVNRTVU, Telangana, India

**Kala Kumar B**
Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science, Mamnoor, PVNRTVU, Telangana, India

**Ashok Kumar D**
Associate Professor, Department of Veterinary Biochemistry, College of Veterinary Science, Mamnoor, PVNRTVU, Telangana, India

**Corresponding Author:**
**C Vinaya Sree**
Assistant Professor, Department of Veterinary Physiology, College of Veterinary Science, Korutla, PVNRTVU, Telangana, India

# L-Homoarginine: An overview and its application in animal nutrition

**C Vinaya Sree, Swathi Bommu, Kala Kumar B and Ashok Kumar D**

**Abstract**
L-Homoarginine (hArg) is a non-essential cationic amino acid that is synthesised from its arginine by transamination or by means of lysine catabolism involving the enzymes of ornithine transcarbamoylase (OTC), an enzyme from the urea cycle or the arginine: glycine amidinotransferase (AGAT), an enzyme from the creatine biosynthesis pathway. These enzymes are tissue-specific, hence they synthesised L-hArg in animals and human organs such as the liver, kidneys, brains, and the small intestines. L-hArg plays some important roles in the pathophysiological conditions, endothelial functions, and the energy metabolic processes in different organs. However, the applications of the L-hArg in both human and animal studies is in its juvenile stage, and the mechanism of action in this vital amino acid is not fully substantiated and requires more research attention. Hence, we review the evidence with the perspective of the LhArg usage in the monogastric and human nutrition and its related health implications.

**Keywords:** L Homoarginine, Arginine, Lathyrus sativus, animal nutrition

## 1. Introduction
L-Homoarginine (hArg), a non-protein cationic amino acid, was the first to be characterized from *Lathyrus sativus* seeds but had been ignored because of its toxic attributes in lathyrus. Homoarginine is now recognized as a normal metabolite in humans and its role in human health is becoming increasingly important. Homoarginine has been even believed for at least 50 years to be an exogenous compound with no significance at all for humans or animals. Yet, things changed only very recently, when hArg was measured in human blood and its concentration was found to correlate with functional parameters, suggesting potential physiological functions in humans (Valtonen *et al.* 2008) [1]. Although the first report on the biological importance of hArg appeared only very recently (Valtonen *et al.* 2008) [1], hArg attracts the increasing attention of scientists from various disciplines, and the number of scientific reports dealing with hArg increased exponentially. By analogy, hArg has also been tested as a potential substrate for nitric oxide synthase (NOS), which catalyzes the conversion of Arg to nitric oxide (NO) and l-citrulline (DimitriosTsikas, 2015) [2]. The potential utility of hArg as a substrate for NOS has early led to the assumption that, hArg would have a biological role, that would be due to its function as an NO precursor. Apart from it being the precursor of NO an exerting biological functions, L Homoarginine directly also participates in many of the organs functional status like it has been established as a potent bio marker in cardio vascular diseases, renal diseases and the death associated with them (Seidu *et al.* 2019) [3]. The role of L Homoarginine do not limit to the above mentioned but it is also associated with the bone health, energy metabolism, brain metabolism reproduction etc.
Considering the studies and reports pertaining to the multi-faceted role of L Homoarginine in the patho physiological functions and their health implications, the role of L homoarginine is evaluated in the present study.

### 1.1 History
Off late the very existence of the hArg was that of the wallflower in the scientific community though its artificial synthesis is dated back to 1926 by Steib [4], credited for being a naturally oocuring substance by Stevens and Bush 1950 and was isolated and characterised from lathyrus sativus by Rao *et al.* (1964) [5].

Slowly but steadily the hArg is gaining momentum in the research which is evident by plethora of studies ranging from 1968 -69 where in it was documented by Ryan *et al*. [6] that l hArg is synthesised and released from kidney and liver tissues; it was found to be in the circulation; having a role to play in the function of bone, liver GIT, reproduction as it acts as an effective inhibitor of alkaline phosphatase isoenzyme as reported by Fishman and Sie 1971.The revolution in hArg research started to full extent after it was demonstrated as the substrate of Nitric oxide -one of the significant Bio signalling molecule under the influence of NOS family enzymes (nNOS, iNOS and eNOS)by Lambert *et al*. (1992) [7]. Recently the most promising discoveries of the hArg are its effect on Bone formation in which it accelerated the turnover of the bone as reported by Pilz *et al*. (2012) [8] and also it being identified as suitable biomarker in cardio vascular diseases (Atzler *et al*. 2015) [9]. Over time much about hArg's functions has been learned from patients with hyperargininemia. Terheggen *et al*. 1975 [10] reported Hyperargininemia a rare autosomal-recessive hereditary disorder of the urea cycle as a result of deficiency of arginase enzyme, which hydrolyses arginine to ornithine and urea resulting in higher levels of arginine, homoarginine and other guanidino compounds and the symptoms pertaining to them vary from vomiting, irritability, lethargy, seizures, convulsions, intellectual impairment, spasticity and coma (Deignan *et al*. 2010) [11].

### 1.2 Physical and chemical properties

L Homoarginine (6-(aminoiminomethyl)-L-lysine) bears structural homology with arginine except for a methylated group (Adams *et al*. 2019) [12] because of which they share several chemical and physical properties but they slightly differ due to the variations of biosynthesis.

**The physical and chemical properties are listed in the table 1.**

| S. No | Arginine | L Homoarginine |
|---|---|---|
| Chemical formula | C6H14N4O2. | C7H16N4O2, |
| Molecular weight | 174.20 g.mol−1 | 188.231 g.mol-1 |
| Boiling point | 368 °C | |
| Melting point | 260 °C | 213-215º C |

### 1.3 Denovo L-hArg formation

L-hArg is synthesised in the body either from the lysine or the Arg using two pathways i) by using the enzymes from the urea-cycle (Cathelineau *et al*., 1974) [13] in which lysine is used as substrate instead of ornithine for OTC enzyme resulting in the formation of homocitrulline which upon the action of ASS is transformed into homoarginino succinate. Thus, formed homoargininosuccinate I snow transformed into l-hArg under the influence the enzyme ASL (Seidu *et al*. 2019) [3] ii) The second pathway utilises AGAT from the creatine cycle which catalyses the guanidinoacetic acid (GAA) synthesis by means of transfer of amidinos to the glycine which further undergoes methylation to form creatinine under the influence of the guanidinoacetate methyltransferase (GMAT) (Wyss and Kaddurah-Daouk 2000) [13]. If the AGAT catalyses the lysine as amidino receiver instead of lysine it results in the production of h-Arg (Hernandez and Alvarez 2001) [14].

### 1.4 Applications of L-Homoarginine in animal nutrition

The application of L Homoarginine in animal feed and its utilisation depends on the physiological responses and the regulation of the metabolic pathways which are involved in the consumption of feed, digestibility of nutrients, and also the digestive enzymes secretion. There are studies which investigated the effect of L Homoarginine on animal nutrition like a) lysine deficiency was observed in rats supplemented with l Homoarginine [15], as both lysine and L-hArg uses the same membrane transport mechanism b) feed consumption in birds was also decreased (Angkanaporn, [16]) c) Interestingly when L-hArg was supplemented to lysine deficit rats it increased the lysine concentration [17] d) Hara, [18] observed that upon supplementation with protein rich diet along with l-hArg increased in the secretion of the pancreatic enzymes in rats e) In contrast to the above, study done by Hira, [19] stated that upon L-hArg supplementation to rats it decreased the exocrine pancreatic enzyme secretion by regulating the signal transduction pathways that are involved in the pancreatic enzyme secretions. These contrary findings could not cement the facts indicating the relation between the L-hArg supplementation and nutritional reflexes including the microbial composition and the relationship with health status of the animal.

## 2. Conclusion

The synthesis of L-hArg in the body is in very minute quantities but occurs in different parts of the body. This prompted its use in various physiological and pathological conditions. Keeping in view of the various organs involved in the synthesis of L-hArg and their role in overall wellness of the host organism it explains the vital role of L-hArg in general well-being of the host. But the literature pertaining to the application of L-hArg in animals is very limited, hence further studies are highly recommended to study the role of L-hArg on digestive physiology including the intestinal microbial component, neurochemicals, transport of nutrients and metabolic disorders.

## 3. Conflict of Interest

No conflict of interest.

## 4. Reference


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