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Review Article

## Medicinal Uses of L-Lysine: Past and Future

Meenu Singh<sup>\*1</sup>, D. Muralidhara Rao<sup>2</sup>, Shivansh Pande<sup>3</sup>, Sowjanya Battu<sup>4</sup>, Mahalakshmi. K<sup>4</sup>, K. Rajeswar Dutt<sup>4</sup>, M. Ramesh<sup>5</sup>

<sup>1</sup>Department of Pharmacy, NIMS University, Shobha nagar, Jaipur- 303121, Rajasthan, India

<sup>2</sup>Dept. of Biotechnology, S. K. University, Anantapur, Andhra Pradesh, India

<sup>3</sup>Apollo Hospitals, Jubilee Hills, Hyderabad, Andhra Pradesh, India

<sup>4</sup>CMR college of Pharmacy, Medchal Road, Hyderabad-501401, Andhra Pradesh, India

<sup>5</sup>Department of Biotechnology, JNTUK, Kakinada, Andhra Pradesh, India

### ABSTRACT

L-Lysine is an essential amino acid that has to be available in sufficient amounts in feed-stuffs to meet the nutritional requirements of animals and humans. This supplementation is realized by the direct addition of Lysine and, as a result, a tremendous growth in the market has taken place in the past ten years. L-Lysine is a necessary building block for all proteins in the body. L-Lysine plays a major role in calcium absorption, building muscle protein, recovering from surgery or sports injuries and the body's production of hormones, enzymes, and antibodies. This review describes the clinical significance of L-Lysine in the treatment of various pathological conditions like herpes simplex virus (HSV) infection, osteoporosis, anxiety and mood disturbances, migraine etc. Clinical studies producing contradictory results on the effects of oral L-Lysine supplementation as prophylaxis or treatment of herpes simplex virus infections have been discussed in detail. This review also discusses the safety profile and scientific rationale behind the alleged physiological benefits of its tremendous increase in its uses in the intervention of drug therapies like in Alzheimer's dementia, hair loss, shingles, cancer, cardiovascular diseases and aging. The benefits of using L-Lysine as a diet supplement in relation to future prospective are also covered.

**Keywords:** L-Lysine; Herpes simplex virus (HSV); Migraine and Osteoporosis.

### INTRODUCTION

L- Lysine is an essential amino acid in human nutrition, meaning the body cannot produce it, therefore, it must be obtained through diet or supplementation (Budavari S, 1989). Lysine was first isolated from casein (a milk phosphoprotein) in 1889 by the German dentist Heinrich Drechsel (Dorland, 1965). It was first introduced in the US market as Lysine hydrochloride in 1955 (Flodin NW, 1997). There was an interest in fortifying bread with Lysine to target populations with Lysine-poor diets. However, the US Food and Drug Administration refused to modify the standards of identity for white bread (L-Lysine. Monograph, 2007 and Flodin NW, 1997). It is estimated that more than 600,000 metric tons of Lysine are produced annually and, owing to the exploitation of new uses in pharmaceuticals, cosmetics and polymer materials, the market shows a growth potential of 7–10% per year (Mattheos Koffas and Gregory Stephanopoulos, 2005). Lysine is important for proper growth, and it plays an essential role in

the production of carnitine, a nutrient responsible for converting fatty acids into energy and helping to lower cholesterol. One of the key building blocks of muscle tissue, this amino acid is commonly used by athletes to support lean mass building and the overall health of muscle and bone.

### CLINICAL SIGNIFICANCE OF L-LYSINE

#### Potential Role in Herpes Simplex Virus (HSV) Infection

According to University of Maryland Medical Centre (UMM), it indicates that lysine taken regularly prevent from developing cold sores and genital herpes. Studies have been mixed, yielding both positive and negative results, and more are required to establish any benefit. In the year 1978, Griffith RS *et al.*, had done a multi-centered study of lysine therapy in herpes simplex infection and found a beneficial effect from supplementary lysine in accelerating recovery from herpes simplex infection and suppressing recurrence. Tissue culture studies have demonstrated an enhancing effect on viral replication when the amino acid ratio of arginine to Lysine favours arginine. The opposite, preponderance of lysine to arginine, suppresses viral replication and inhibits cytopathogenicity of herpes simplex virus. The codons characterizing herpes simplex DNA apparently specify production of viral capsids at the expense of host cell histones (Griffith RS *et al.*, 1978). Other study in the year 1980, followed 65 individuals, found

\* Corresponding Author

Email: meenupharma@gmail.com

Contact: +91-8099334083

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no benefit but they used lower dosages of lysine (Milman N *et al.*, 1980). In 1984, McCune MA *et al.*, investigated the treatment of recurrent herpes simplex infections with L-lysine monohydrochloride in a randomized, double-blind, placebo-controlled, cross-over study of forty-one patients and found that oral ingestion of 1,248 mg a day of L-Lysine monohydrochloride shows evidence of decreasing the recurrence rate of herpes simplex attacks in non immunocompromised hosts. A dose of 624 mg a day was not effective. L-Lysine may also be capable of decreasing the severity of symptoms associated with recurrences. Neither dosage showed any evidence of shortening the healing time compared to placebo (McCune MA *et al.*, 1984). In 1987, Griffith RS *et al.* had studied the treatment and prophylaxis of L-Lysine in frequently recurrent herpes simplex infection in a double-blind, placebo-controlled, multicenter trial of oral L-Lysine monohydrochloride for the prevention and treatment of recurrent herpes simplex (HSV) infection was conducted. The treatment group was given L-Lysine monohydrochloride tablets (1,000 mg L-lysine per dose) 3 times a day for 6 months. A total of 27 (6 male and 21 female) subjects on L-Lysine and 25 (6 male and 19 female) subjects on placebo completed the trial. The L-Lysine treatment group had an average of 2.4 percent less HSV infections, symptoms were significantly diminished in severity and healing time was significantly reduced. L-Lysine appears to be an effective agent for reduction of occurrence, severity and healing time for recurrent HSV infection (Griffith RS *et al.*, 1987). In a report, researchers describe a relationship between lysine and herpes simplex virus (HSV), the amino acid arginine's composition is high in the HSV viral coding thus, replication of the virus requires high consumption of arginine. Lysine appears to be an "antimetabolite," acting as an analogue of arginine, competing for absorption and entrance into tissue and cells. Lysine inhibits HSV replication by limiting arginine (by competing with it) during viral replication. Both cold sores and genital herpes are also caused by a virus called herpes simplex. After infection, this virus hides in certain nerve cells and re-emerges under times of stress. Test tube research suggests that lysine fights this virus by blocking arginine, an amino acid the virus needs in order to replicate (Griffith RS *et al.*, 1981). For this reason, lysine might be most effective when used in conjunction with a low-arginine diet. However, this widely stated claim has not been proven.

When taken in sufficient doses, it appears that regular use of lysine supplements might be able to reduce the number and intensity of herpes flare-ups (Flodin NW, 1997). One double-blind, placebo-controlled study followed 52 participants with a history of herpes flare-ups (Griffith RS *et al.*, 1987). While receiving 3 g of L-lysine every day for 6 months, the treatment group experienced an average of 2.4 fewer herpes flare-ups than the placebo group—a significant difference. The lysine

group's flare-ups were also significantly less severe and healed faster. Lysine prophylaxis was 100% effective in preventing herpetic labialis in patients suffering from frequent lesion occurrence. Treatment for recurrent aphthous ulcers (RAU; acute painful oral ulcers, "canker sores") was also evaluated in this study. Only 1 of 28 patients did not benefit from lysine therapy. Dosing was 500 mg lysine/day for prevention and 1000 mg every 6 hours upon development of prodrome in both treatments. (Wright E, 1994).

#### Potential Role in Osteoporosis

Osteoporosis is a bone disorder in which the bones become weak and brittle particularly in the hips, spine and wrists and increases the risk of falls or fractures. The ability of L-Lysine to encourage calcium absorption may help guard against osteoporosis-related bone loss. L-Lysine plays a role in maintaining healthy bones because it helps our body absorb calcium, while reducing the quantity of calcium that we lose in our urine. According to the University of Maryland Medical Centre (UMM), laboratory research suggests that L-Lysine, used in combination with L-Arginine, boosts the activity of bone-forming cells and increases collagen production. This can help contribute to increased bone strength. Therefore, Lysine may be associated with protection against osteoporosis (Fini M *et al.*, 2001). However, there are no research studies to link Lysine with osteoporosis prevention in humans (University of Maryland Medical Centre, Lysine, 2010). Calcium deficiency contributes to age-related bone loss, consequently, any preventive approach to osteoporosis should include dietary  $\text{Ca}^{++}$  adjustment or supplementation.

The ideal  $\text{Ca}^{++}$  supplement would yield the greatest bioavailability. Studies in animals have shown that dietary supplements with certain amino acids, particularly L-lysine, can increase  $\text{Ca}^{++}$  absorption. In one study, the acute effects of an oral  $\text{Ca}^{++}$  load (3 g as  $\text{CaCl}_2$ ) administered with or without 400 mg of L-lysine were compared in 15 healthy and 15 osteoporotic women. In all cases, the oral  $\text{Ca}^{++}$  load determined a progressive increase in serum total  $\text{Ca}^{++}$  and a concomitant decrease in neophrogenous c-AMP. As expected, a progressive increase in urinary  $\text{Ca}^{++}$  excretion was also observed, except in the L-Lysine-treated healthy subjects, who exhibited a blunted calciuric response to the  $\text{Ca}^{++}$  load. In a second study, the effects of a short-term dietary supplementation with L-Lysine, L-Valine, or L-Tryptophan (800 mg/day) on  $^{47}\text{Ca}^{++}$  fraction absorption were compared in 45 osteoporotic patients. L-Lysine but not L-Valine or L-Tryptophan significantly increased the intestinal absorption of the mineral (Civitelli R *et al.*, 1992).

#### Potential Role in Anxiety and Mood Disturbances

L-Lysine has a known anxiolytic action through its effects on serotonin receptors in the intestinal tract. One study on rats showed that overstimulation of the  $5\text{-HT}_4$

receptors in the gut is associated with anxiety-induced intestinal pathology (Smriga and Torii, 2003). L-Lysine, acting as a serotonin antagonist and therefore reducing the overactivity of these receptors, reduced signs of anxiety and anxiety-induced diarrhoea in the sample population. Another study showed that lysine deficiency leads to a pathological increase in serotonin in the amygdala, a brain structure that is involved in emotional regulation and the stress response (Smriga *et al.*, 2002). L-Lysine appears to diminish long-term anxiety in individuals who fail to get an adequate amount L-Lysine in their diet. Human studies have also shown negative correlations between reduced Lysine intake and anxiety. A population-based study in Syria included 93 families whose diet is primarily grain-based and therefore likely to be deficient in Lysine. Fortification of grains with Lysine was shown to reduce markers of anxiety, including cortisol levels, and also led to potentiation of benzodiazepine receptors (Smriga *et al.*, 2004). According to a randomised, double-blind trial, fortification of Lysine in a wheat-based (L-Lysine deficient) diet significantly reduced anxiety score in males, but not females with high baseline anxiety. It is suspected that L-lysine's action as a 5-HT<sub>4</sub> receptor antagonist and benzodiazepine receptor agonist are responsible for the observed effect. In contrast, a prospective study of 29 133 men (aged 50-69 years) found no association between L-Lysine intake and depressed mood. A study performed in the year 2007 concluded that L-Lysine when combined with the amino acid L-Arginine appears to relieve mental stress and anxiety (Smriga M *et al.*, 2007).

Due to lack of sufficient data it is difficult to predict the use of L-Lysine in the treatment of anxiety and mood disturbances hence further studies are required in this field to understand the mechanism and to provide firm evidence for its uses as antianxiety agent.

### Potential Role in Migraine

The process of inflammation is crucial in migraine, and several non steroidal anti inflammatory drugs (NSAIDs) are effective in the treatment of migraine attacks. Despite their efficacy, the routine use of NSAIDs is limited by side effects as well as incomplete efficacy in some patients. Lysine acetylsalicylate is a form of aspirin, a chemical with pain-relieving properties (Krymchantowski A V, 2005). In April 2011, the journal "Neurology" published the findings of a study that measured the effectiveness of lysine acetylsalicylate against severe headaches. The researchers start by acknowledging the well-established fact in the scientific community that this substance alleviates the usual acute migraine attack. The study concludes that lysine acetylsalicylate is also powerful against strong headaches brought on by chemical withdrawal (W. Weatherall *et al.*, 2010). Lysine clonixinate is a nonsteroidal anti-inflammatory drug. Some of its formulation comes from nicotinic acid: niacin, or vitamin B<sub>3</sub>. In 2001, the Brazilian journal "Arquivos de Neuro-Psiquiatria" --

"Archives of Neuropsychiatry" -- reported on research that examined whether lysine clonixinate relieved acute migraine. The substance relieved moderate migraine pain within one to four hours of administration of the drug at a better rate than the placebo used. Regarding its performance against severe migraine, lysine clonixinate also relieved pain, but at the same rate of success as the placebo. On comparison of the combination of lysine acetylsalicylate (equivalent to 900 mg aspirin) and 10 mg metoclopramide (LAS+MTC) with oral sumatriptan (100 mg) and placebo in 421 patients with migraine. LAS+MTC was as effective as sumatriptan with a decrease of headache from severe or moderate to mild or none of 57% and 53%, respectively, for the first migraine attack treated. Both treatments were better than placebo (success rate 24%). LAS+MTC were significantly more effective in the treatment of nausea than sumatriptan and was better tolerated (adverse events in 18% and 28%). LAS+MTC are as effective as sumatriptan in the treatment of migraine attacks. It is also much cheaper (P Tfelt-Hansen *et al.*, 1995).

### OTHER SIGNIFICANT EFFECTS

#### Alzheimer's dementia (AD)

There is a growing body of evidence that implicates the herpes simplex type 1 virus (HSV-1) in the development of Alzheimer's dementia (AD). HSV-1 has been found to be present in the cerebrum of the great majority of older adults, and in many of the same areas of the brain that are affected by AD. When active, the virus may contribute to the formation of the neuro-fibrillary tangles and amyloid plaques characteristic of AD. Like AD, HSV-1 encephalitis may cause long term memory loss. HSV-1 replication is suppressed in Lysine-rich/arginine - poor environments, and population studies suggest that diets high in Lysine and low in arginine may be associated with lower rates of AD. There are no prospective studies of the efficacy of lysine supplementation to prevent or reduce the incidence of AD. Supplementation with adequate doses of Lysine could prevent the development of AD (Rubey RN, 2010).

#### Hair Loss

In addition to calcium, L- Lysine also helps your body absorb iron and zinc. These minerals are important to the health of your skin and hair. According to studies, vegans with a Lysine-deficient diet may have poor hair health and hair loss as a result of decreased zinc and iron absorption. While Lysine alone has not been shown to prevent hair loss, one study described showed that women with iron deficiencies who supplement with both iron and Lysine can reduce iron deficiency-associated hair loss by 50 percent (Rushton DH, 2002).

#### Shingles

Shingles (herpes zoster) is a painful, blistering skin rash due to the varicella-zoster virus, the virus that causes chickenpox. It usually strikes people with weak im-

mune systems and the elderly, causing painful and inflamed blisters. L-Lysine is listed as a purported treatment of the condition, according to the University of Michigan Health Systems.

### Cancer

There are Lysine conjugates that show promise in the treatment of cancer, by causing cancerous cells to destroy themselves when the drug is combined with the use of phototherapy, while leaving non-cancerous cells unharmed (Science Daily, 2008 and Roomi MW *et al.*, 2006).

### Cardiovascular diseases

Limited studies suggest that a high-Lysine diet or L-Lysine supplements may have a moderating effect on blood pressure and the incidence of stroke (Flodin 1997). It may be beneficial in helping ensure heart health because of its ability to inhibit the build up of junk on the walls of our arteries that can prevent blood and the nutrients it carries from arriving at their destinations on time (Mc Beath M, 1993).

### Aging

L-Lysine is instrumental in the formation of collagen, which supports the skin, muscles, and joints. We lose collagen as we age, and the supplementation with L-Lysine may help keep our skin looking young and healthy. Collagen is, of course, also necessary for the repair of all connective tissue (ligaments, cartilage, joints, skin, bones, and teeth) and plays a key role in the growth and repair of many tissues. Thus, healthy collagen may help athletes recover more quickly from intense workouts and protect some of the more fragile tissues of the body (Flakoll P *et al.*, 2004).

### SAFETY PROFILE OF L-LYSINE

Although L-Lysine is an essential part of the diet, the safety of concentrated Lysine supplements has not been well studied. In animal studies, high dosages have caused gallstones and elevated cholesterol levels (Kritchevsky D. *et al.*, 1984, Leszczynski D.E. and Kummerow F.A., 1982). Maximum safe dosages for young children, pregnant or nursing women, or those with severe liver or kidney disease have not been established. Although rare, abdominal cramps and diarrhoea have been seen with extremely high amounts (15 to 40 grams per day). Increased risk of gallstones and elevated cholesterol have been reported (in animal studies only) where high amounts were used. Lysine supplementation is not advised for children. No known toxicity found with Lysine use. Most people need about 1 g of lysine per day. The requirement may be greater for athletes and people recovering from major injuries, especially burns. It appears to be most effective when taken on an empty stomach with water. For increasing the release of growth hormone, Lysine is recommended before sleep or before exercise (Suminski RR *et al.*, 1997). If taken in a 4:1 ratio with arginine, Lysine

may both prevent infection from the herpes virus as well as prevent flare-ups in those who already have the virus. Deficiency of Lysine has been linked to fatigue/weakness, red eyes, dizziness, decreased attention span, anaemia, enzyme disorders, retarded growth and immune disorders etc. Adverse Reactions Doses greater than 10-15 g/day may cause gastrointestinal discomfort with symptoms of nausea, vomiting and diarrhoea. Clinical tests have found L-Lysine enhances intestinal absorption and decreases renal excretion of calcium. Lysine is contraindicated in people with the rare genetic disorder hyperlysinaemia / hyperlysinuria. High-dose lysine supplements should be used with caution in hypercalcaemic states, and by people with kidney or liver disease. Safety is unknown for high-dose supplements, however, dietary intake levels are safe.

### FUTURE PROSPECTIVES

On the basis of studies it has been shown that the L-Lysine has an inhibitory effect on the multiplication of HSV in cell cultures. It appears to act as an antimetabolite and competes with the viral growth promoting action of arginine. It has been found that if L-Lysine is taken more than 1000 mg three times per day for 6 months or more, it decreases the recurrence rate of herpes simplex attacks and severity of the infection and, promotes healing time of recurrent HSV infection. Although some results are promising, none of the studies are large enough to give conclusive answers. At this point, more evidence is needed to determine whether Lysine is effective for preventing herpes simplex.

In vitro tests with human osteoblasts indicate that L-Lysine has a positive effect on osteoblast proliferation, activation and differentiation. Results suggest that L-Lysine can both enhance intestinal Ca<sup>++</sup> absorption and improve the renal conservation of the absorbed Ca<sup>++</sup>. The combined effects may contribute to a positive Ca<sup>++</sup> balance, thus suggesting a potential usefulness of L-Lysine supplements for both preventive and therapeutic interventions in osteoporosis.

Due to lack of sufficient data it is difficult to predict the use of L-Lysine in the treatment of anxiety and mood disturbances hence further studies are required in this field to understand the mechanism and to provide firm evidence for its uses as an antianxiety agent.

Among the available options for the treatment of migraine, lysine clonixinate (LC) and Lysine acetylsalicylate have proved effective in migraine. With the help of further studies we could find out other formulations of L-Lysine which would be considerably effective over conventional method of treatments.

To access the effective uses of L-Lysine in the treatment or prevention of Alzheimer's dementia, hair loss, shingles, cancer, cardiovascular diseases and aging etc., a significant number of studies have to be performed in order to determine the mechanism and optimum dose of L-Lysine for these pathological conditions.

## CONCLUSION

About 60 years has been passed since the discovery of L-Lysine, an essential amino acid which is capable of preventing many pathological conditions. Since then, several studies have been performed to understand the mechanisms and to titrate the optimum doses of L-Lysine mainly in the treatment of herpes simplex virus infection. A typical therapeutic dosage of L-Lysine, if taken 1 g three times per day or more for 6 months, it may be helpful for herpes infections. This can be taken as a regular part of diet and will prevent herpes flare ups or perhaps at the first sign of attack. Above mentioned studies provided the insight for the use of L-Lysine in the treatment or prevention of osteoporosis, migraine, Alzheimer's dementia, hair loss, shingles, cancer, cardiovascular diseases and aging. L-Lysine serves as a very good candidate for the future studies and it may act as a main target for new drug therapy in aforementioned diseases.

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