https://doi.org/10.17221/87/2025-CJAS

The mechanism of *N*-carbamylglutamate promoting arginine synthesis and its application in pig production: A review

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Citation: Mao P., Gao M.M., Hu N.Z., Zhang X.L., Yan C.G., Song C.S., Ma W.F. (2026): The mechanism of *N*-carbamylglutamate promoting arginine synthesis and its application in pig production: A review. Czech J. Anim. Sci., 71: 299–307.

Abstract: Arginine (Arg) is an essential amino acid that can improve the reproductive capacity, intestinal development, and growth performance of pigs. *N*-carbamylglutamate (NCG) and *N*-acetylglutamate (NAG) can activate carbamyl phosphate synthetase I and the Δ1 pyrrolin 5 carboxylate synthetase in mitochondria, promoting the synthesis of citrulline from glutamine and proline, citrulline is the main precursors for the synthesis of Arg, and subsequently increasing the endogenous synthesis of Arg to produce nitric oxide (NO) and polyamines. Compared with Arg, NCG has a longer half-life and does not inhibit the absorption of basic amino acids such as histidine or lysine; thus, it has been developed as a feed additive. This paper reviews the application of NCG as a feed additive in pig production and its possible theoretical mechanism.

Keywords: amino acid substitute; feed additive; performance; swine

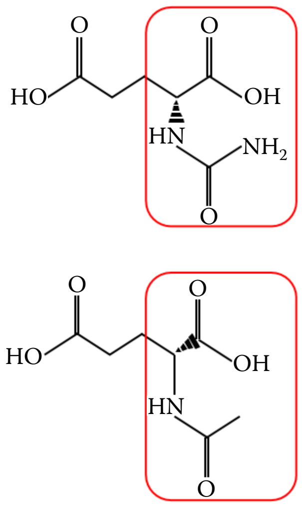
INTRODUCTION

Arg is a conditionally essential amino acid in mammals and is essential during pregnancy, lactation, and weaning period. Arg has a variety of functions, including participating in the synthesis of bioactive substances, such as nitric oxide (NO), creatine, agmatine, and polyamines, which promote embryo implantation, improve the foetal survival rate and growth of lactating animals, and enhance antioxidant and immune functions (Li et al. 2022). In pharmacokinetic studies on Arg, it has been demonstrated that the half-lives of Arg in adult, lactating, and newborn pigs after intravenous administration are 1.06 h, 0.75 h, and 0.65 h, respectively (Ye et al. 2017).

N-carbamylglutamate (NCG) is similar to N-acetylglutamate (NAG) in molecular structure, as shown in Figure 1 (Ah Mew et al. 2009). NCG can also play a similar physiological function

Supported by the Foundation for University Young Key Teacher Programme of Henan Province (Grant No. 2025GGJS047).

https://doi.org/10.17221/87/2025-CJAS



$C_6H_{10}N_2O_5$, 190.15
CAS No.: 1188-38-1
NCG
(*N*-carbamylglutamate)

$C_7H_{11}NO_5$, 189.17
CAS No.: 1188-37-0
NAG
(*N*-acetylglutamate)

Figure 1. Chemical structural formulas for NCG (*N*-carbamylglutamate) and NAG (*N*-acetylglutamate)

to NAG in animals. The biological function of NCG is closely related to the urea cycle, and NCG can activate the activity of carbamyl phosphate synthetase 1 (CPS1) in the intestine (Zhang et al. 2014). In addition, the CPS1 is a key rate-limiting enzyme in the urea cycle and can catalyse the conversion of glutamine and glutamic acid into citrulline, which is an important precursor of arginine (Arg), and thus promote the endogenous synthesis of Arg, as shown in Figure 2 (Ah Mew et al. 2009). Compared with the NAG, there is no specific hydrolase in the gastrointestinal tract of animals to degrade NCG, so the proportion of NCG entering the blood through the epithelial cells of the small intestine is about 80%, which makes the half-life of NCG longer and about 8–10 h in rats (Kim et al. 1972).

Therefore, NCG is often added to feed as an Arg supplement in livestock production (Liu et al. 2012). Moreover, The L-glutamic acid is uniformly used as the starting material for the synthesis of NCG and NAG, and then the finished products of NCG and NAG are directly locked in the L configuration. This review summarises the mechanism of NCG in the urea cycle and its potential role as a feed additive in pig diets, which were reviewed to provide theoretical reference for the application of NCG in pig production.

BIOLOGICAL FUNCTIONS OF NCG

NCG promotes endogenous arginine synthesis. NAG is an essential cofactor of CPS-I, which is the key enzyme in the first step of the urea cycle.

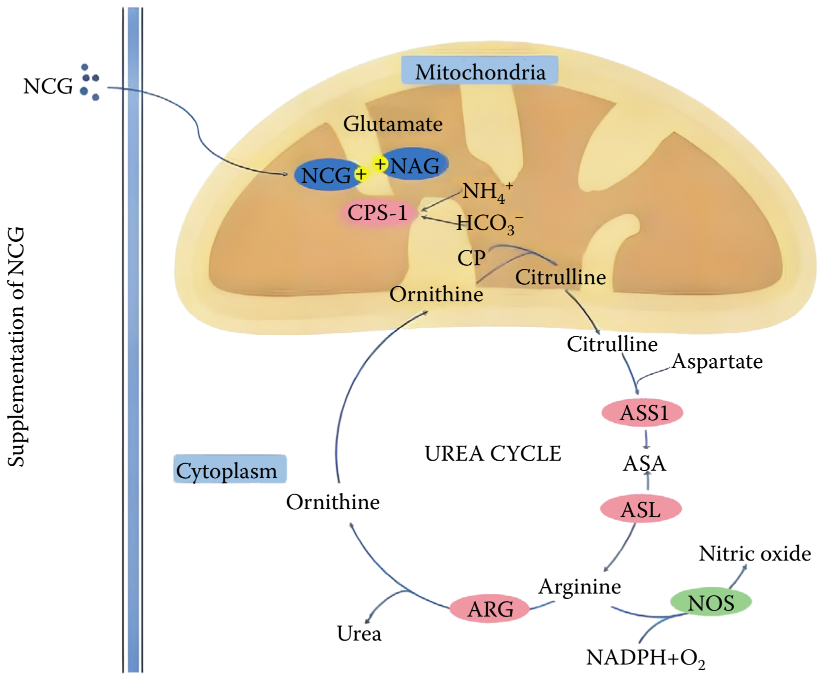


Figure 2. NCG involved in the pathway of arginine synthesis

ARG = arginase; ASA = argininosuccinic acid; ASL = argininosuccinate lyase; ASS1 = argininosuccinate synthetase 1; CP= carbamyl phosphate; CPS1 = carbamyl phosphate synthetase 1; NAG = *N*-acetylglutamate; NCG = *N*-carbamylglutamate; NOS = nitric oxide synthase

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NCG is also a functional analogue of NAG and can play a similar physiological function in mammals. Therefore, NCG can also replace NAG to activate CPS-I and P5CS in mitochondria, promote the synthesis of citrulline from glutamine, glutamate and proline, and citrulline is the main precursor for Arg synthesis, thereby promoting the endogenous synthesis of Arg (Wu 1995).

Compared with NAG, NCG is more likely to enter the mitochondria, and is not easily hydrolysed by acyl amino acid acylase, with a longer half-life (Kim et al. 1972). NCG can convert excess ammonia into urea through the urea cycle. Urea is less toxic to the body and easy to be excreted by the liver (Ah Mew et al. 2009). Therefore, NCG was first used to treat hyperammonemia caused by insufficient or absent NAG activity to restore blood ammonia concentration to normal.

NCG can improve reproductive performance. At present, the mechanism of NCG regulating reproductive performance of mammals is mainly focused on the pathway influenced by Arg and its metabolites, as shown in Table 1. Some studies have shown that dietary supplementation of NCG or Arg in pregnant sows can increase the litter birth weight of newborn piglets (Liu et al. 2012). Arg is catalysed by nitric oxide synthase (NOS) to produce nitric oxide (NO), which is a key regulatory factor of placental angiogenesis (Krause et al. 2013). Studies demonstrated that the NO plays a role in regulating maternal delivery of nutrients and oxygen to the fetus and assist angiogenic (Ang) factors and vascular endothelial growth factor (VEGF) in regulating placental angiogenesis (Krause et al. 2013).

Dietary NCG supplementation can influence the content of NO in plasma and the expression of endothelial NOS (eNOS) mRNA and protein in uterine tissue of pregnant sows (Liu et al. 2012; Zhang et al. 2014), thereby allowing sows to deliver more nutrients and oxygen to the fetus. In addition, the increased concentrations and gene expression of Ang-1, Ang-2, VEGF-A, and placental growth factor (PLGF) by NCG supplementation also contribute to reproductive performance by regulat-

Table 1. Effects of NCG and Arg on reproductive performance of breeding pigs and possible mechanisms

Breed	Parity	Dose added	Period of addition	Results	Reference
Arg supplementation					
Landrace × Large-White sows	3 or 4	10.0 g/kg feed	pregnancy day 90 to end	Litter birth weight of born alive piglets increased by 15%; serum growth hormone increased by 40%, while VEGF and eNOS decreased by 11% or 17%, respectively.	Liu et al. (2012)
PIC 1040 Boars	–	6.0, 8.0, or 10.0 g/kg feed	84 days were added to the 407.65 days of age	Supplementation with 10.0 g/kg Arg increased the sexual desire of breeding boar under heat stress, including an 8% increase in ejaculate volume, and increased the levels of Estradiol 17β and Testosterone.	Chen et al. (2018)
NCG supplementation					
Landrace × Large-White sows	3 or 4	1.0 g/kg feed	pregnancy days 90 to end	Litter birth weight of piglets increased by 14%; serum growth hormone increased by 39%, while estradiol, VEGF and eNOS decreased by 50%, 10% or 23%, respectively; the gene expression level of VEGFA increased, while and the expression level of eNOS decreased in the umbilical vein.	Liu et al. (2012)
Yorkshire × Landrace × Duroc sows	1	0.5 g/kg	pregnancy days 0 to 28	Number of births of piglets increased by 11%; mean litter weight increased by 17%; placental weight increased by 10%; plasma arginine content increased by 38%.	Zhu et al. (2015)

Arg = arginine; eNOS = endothelial nitric oxide synthase; NCG = *N*-carbamylglutamate; PIC = Pig Improvement Company; VEGF = vascular endothelial growth factor; VEGFA = vascular endothelial growth factor A

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ing angiogenesis and nutrient supply between the uterus and placenta (Zhang et al. 2014). When using ovarian granular cells and porcine placental trophoblast cells as the experimental materials, it is found that NCG can influence the production concentration of progesterone, estradiol and steroids, and inhibit the apoptosis to regulate ovarian function (Wei et al. 2020).

NCG can improve antioxidant and immune function. Oxidative stress is one of the important factors affecting pig production efficiency. NCG, as a functional amino acid, plays a role in improving antioxidant and immune function in young animals (Hu et al. 2023). Studies have found that dietary NCG can improve the antioxidant capacity of the body by regulating nuclear factor erythroid 2-related factor 2 (Nrf2) (Hu et al. 2023). Nrf2 is a key regulator of enzymatic antioxidation in the body. It can up-regulate the transcription of antioxidant enzyme genes and promote catalase (CAT) and glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and other genes expression.

In addition, Xiao et al. (2016) found that the accumulation of intestinal reactive oxygen species (ROS) and MDA was significantly negatively correlated with the intake of Arg, indicating that Arg could participate in the reaction process of scavenging intestinal ROS. For young piglets, the activity of NAG in the intestine is low, which leads to the inhibition of the expression of P5CS, the rate-limiting enzyme of Arg synthesis, and accordingly limits the efficiency of intestinal Arg synthesis (Geng et al. 2011).

However, NCG possesses a metabolic pathway similar to NAG and can activate P5CS in the intestine, thereby promoting stable Arg synthesis. Arg is a basic amino acid, and its lone electron pair is located in the guanidinium group, when combined with ROS, it can affect the REDOX state of the body (Chacher et al. 2014). In addition, guanidinyl group can also bind to the cysteine sulfhydryl group of Kelch-like epichlorohydrin-related protein 1 (Keap1), competitively inhibit the binding of Nrf2 to Keap1, and accordingly up-regulate the expression of antioxidant related enzymes and phase II detoxification enzymes.

Glutathione is an essential component of the non-enzymatic antioxidant system. It removes excessive reactive oxygen species in the body through the interconversion of reduced glutathione and oxidised glutathione, thereby alleviating oxidative stress in the organism (Liang et al. 2018). It has been found that NCG and Arg can up-regulate the expression of glutathione synthetase and promote the synthesis of reduced glutathione (Liang et al. 2018). Therefore, it is generally believed that NCG can regulate the REDOX state of the body by mediating the metabolism of Arg in the intestine of pigs.

NCG can promote the proliferation of immune cells and enhance the activity of macrophages by regulating the production of Arg, thus improving the immune function of the organism. At present, there are few studies on the immune mechanism of NCG in pigs. Liao et al. (2017) found that cupreous NCG chelate improved serum immunoglobulin G (IgG) content in weaned piglets. Liu et al. (2012) reported that NCG could increase the relative mRNA expression levels of transforming growth factor β1 (TGF-β1), IL-10, forkhead box protein P3 (FOXP3) and signal transducer and activator of transcription 5 (STAT5), as well as the protein abundance of FOXP3 in intestinal T cells of weaned piglets, and reduce the relative mRNA expression levels of pro-inflammatory factors (IL-1β, IL-6, IL-8 and tumour necrosis factor α). It was found that NCG could improve the immune function by regulating the differentiation of helper T cells and improving the function of regulatory T cells. Therefore, NCG plays an immunomodulatory function by regulating the proliferation and differentiation of immune cells in the body, and has a positive effect on regulating the body's immune function and improving the ability of autoimmune response.

THE APPLICATION OF NCG IN PIG PRODUCTION

NCG application in breeding pig production. The reproductive ability of breeding pigs is a basic guarantee for pig production. The level of Arg not only affects embryo growth and development but also affects the performance and health status of offspring piglets. Recent studies have shown that NCG has a positive effect on the reproductive performance of breeding pigs. Studies have shown that NCG supplementation at different gestational ages can improve the reproductive performance of sows, which is reflected in the increase in live litter number, placental weight, and litter weight of piglets (Liu et al. 2012; Zhang et al. 2014).

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During gestation in sows, several essential amino acids play important roles in the regulation of foetal development by participating in the synthesis of proteins and nucleotides. The addition of NCG promoted the synthesis of Arg through the ornithine cycle and enhanced the synthesis of amino acids, such as glutamine, glutamate, ornithine, proline, and citrulline, which play important roles in the placental nutrient supply, embryo implantation and foetal growth and development of sows (Kwon et al. 2003). Moreover, NCG supplementation during pregnancy increased live birth weight and upregulated the mRNA expression of VEGF-A, PLGF, and Ang-2 in the chorioallantoic sac, indicating that NCG might promote angiogenesis in the uterus and placenta to improve reproductive performance (Zhang et al. 2014).

Given the limited number of studies on NCG in stud boars, the results focused only on the effects of Arg and NO on semen quality (Chen et al. 2018).Arg supplementation in young boars increased spermatogonia and sperm counts, possibly by increasing the levels of NO in the serum and Arg in the semen, which in turn promoted testicular development (Chen et al. 2018). Dietary Arg supplementation also increased the libido and semen quality of boars (248.59 ± 3.84 kg b.w. and 407.65 ± 6.40 days of age), improved the antioxidant capacity of semen, and alleviated the decline in semen quality and the reduction in libido caused by high temperature in summer (Chen et al. 2018).

Due to the lack of sweat glands, the ability to regulate body temperature is poor, and this can easily lead to heat stress in sows during the late pregnancy and lactation periods. This may cause a reduction in feed intake and an insufficient supply of nutrients and oxygen to the uterus and placenta, which leads to a decline in reproductive performance in sows. Several studies have shown that NCG alleviates the decline in reproductive performance caused by heat stress by mediating Arg metabolism process. In animals, Arg synthesis is catalysed by NO synthase to produce NO, which is an important signalling molecule for maintaining the balance of body temperature. The NO content in the blood is involved in regulating the blood flow velocity in the uterus and placenta, thereby controlling the transfer efficiency of nutrients and oxygen to the fetus. Dietary supplementation with NCG was found to increase the plasma NO concentration in pregnant sows and significantly upregulate the related gene and protein expression levels of placental eNOS, which was proven to be a beneficial way to increase the placental blood flow rate and angiogenesis and relieve the heat stress response of sows (Zhang et al. 2014).

NCG application to piglets. The growth potential of piglets can be influenced by regulating the level of nutrients that piglets ingest during lactation (Klindt 2003). When suckling is the main source of nutrition, the average daily gain of newborn piglets at 1–21 days of age is approximately 180–240 g. However, the growth potential of newborn piglets may exceed 400 g/d when fully fed with artificial powdered milk as the only nutrient source, suggesting that some nutritional composition of sow milk may limit the need for suckling piglets to achieve optimal growth rates (Kim et al. 2001). It was found that the content of Arg in sow milk accounted for only 40% of the requirement of suckling piglets, indicating that the insufficient supply of Arg may be one of the factors limiting piglets from achieving the maximum growth performance (Wilkinson et al. 2004).

Because the limited efficiency of endogenous Arg synthesis is influenced by the low content of NAG, dietary supplementation with NCG may alleviate the deficiency of NAG activity and promote Arg synthesis in suckling piglets. NCG supplementation was found to increase the serum concentrations of Arg, glutamate, citrulline, ornithine, and growth hormones in suckling piglets, leading to the promotion of skeletal muscle protein synthesis (Zeng et al. 2015).

Supplementation with NCG increased the serum immunoglobulin concentration and intestinal immunity in nursery pigs, which could protect the intestinal mucosa from pathogen infection. In addition, amino acids, such as Arg and glutamic acid, can increase the proliferation of beneficial bacteria, which play important roles in maintaining intestinal health and the normal balance of the intestinal microbiota (Dai et al. 2012). This study showed that the addition of NCG can increase the number of Lactobacillus and anaerobic bacteria in the cecum, thus promoting the synthesis and utilisation of Arg in the intestine as shown in Table 2 (Dai et al. 2012; Zeng et al. 2015).

At the weaning stage, piglets face drastic changes in nutritional, psychological, and environmental factors, which can easily induce weaning stress. Weaning stress often causes intestinal villus atrophy

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Table 2. Effects of NCG on performance of suckling or nursery pigs and possible mechanisms

Breed	Day age	Feeding methods and days	Dose added	Results	Reference
Suckling piglets					
Landrace × Yorkshire	1 day	oral/14 day	50.0 mg/kg and 100.0 mg/kg body weight per day	Serum levels of Arg, glutamic acid, citrulline and ornithine increased by 38%, 63%, 9% or 22%, respectively.	Zeng et al. (2015)
	4 day	oral/10 day	100.0 mg/kg body weight per day	Increased plasma Arg concentration and body weight gain.	Kim et al. (2001)
Nursery pigs					
Huanjiang mini pig	21 day	feed/35 day	1.0 g/kg feed	The ADG and ADFI increased by 64% or 8%, respectively, while plasma urea nitrogen content decreased by 13%; increased intestinal absorption capacity, growth rate and feed utilisation efficiency.	Yang et al. (2013)
Landrace × Yorkshire	21 day	feed/28 day	0.8 g/kg feed	The intestine weight increased by 28%, incidence of diarrhoea and the diarrhoea index decreased by 66% or 61%, respectively.	Wu et al. (2010)
Duroc × Landrace × Yorkshire	24 day	feed/28 day	0.5 g/kg feed	The ADG increased by 10%; the improvements observed in jejunal morphology, antioxidant capacity, as well as the gene expression of jejunal tight junction protein and amino acid transporters.	Hu et al. (2023)

ADFI = average daily feed intake; ADG = average daily gain; Arg = arginine; NCG = *N*-carbamylglutamate

and crypt hyperplasia in piglets, destroys intestinal barrier function and absorption ability, and leads to growth retardation in nursery pigs. These studies showed that Arg supplementation promoted intestinal cellular immunity and villus development and reduced the decline in the intestinal mucosa caused by pathogenic bacteria (Yao et al. 2011).

Correspondingly, several studies have indicated that NCG supplementation improved the performance of nursery pigs, promoted the proliferation of intestinal epithelial cells, upregulated the mRNA expression of jejunal amino acid transporters, and increased intestinal antioxidant capacity (Hu et al. 2023). The expression of intestinal heat shock protein 70 (HSP-70) was also enhanced at both the mRNA and protein levels after supplementation with 0.08% NCG in the diet, thereby alleviating intestinal dysfunction and weaning stress in nursery pigs (Wu et al. 2010). Another study revealed that dietary supplementation with 0.1% NCG significantly increased the plasma Arg concentration and the mRNA abundance of the jejunal amino acid transporters SLC6A19, SLC7A9, and SLC1A1 in Huanjiang mini pigs during the weaning period (Yang et al. 2013). These results suggest that NCG can be used as a functional feed additive to improve the performance, antioxidant capacity, immune function, and intestinal development of pigs at birth or after weaning. The NCG has been approved by the Ministry of Agriculture of China as a new feed additive in April 2014.

Application of NCG in grow-finishing pigs. The grow-finishing period is the last growth stage before slaughter, during which individuals have a greater feed intake and a longer feeding duration. To reduce costs and reduce nutritional emissions of nitrogen, many people try to use a low-protein diet at this stage, but this approach also inevitably increases the frequency of decreasing meat quality.

After reducing the crude protein content in the diet, some studies have focused on the kinds and appropriate amounts of some special amino acids to improve the quality of meat without reducing the growth performance of grow-finishing pigs (Madrid et al. 2013) (Table 3). After 40 days of continuous feeding with 0.1% NCG in a low-protein diet (CP: 11.26%), the area of the longissimus dorsi muscle increased, and the backfat thickness decreased; however, growth performance was not affected by NCG supplementation (Ye et al. 2017). We also found

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Table 3. Effects of NCG on performance of growing-finishing pigs and possible mechanisms

Breed	Initial weight	Dose added	Results	Reference
Duroc × Yorkshire × Landrace	75.00 ± 5.18 kg	1.0 g/kg feed	Fat-free lean index and fat-free lean gain improved by 9% or 46%, respectively. Activation of mTOR signalling pathway increased protein synthesis in muscle and improved fatty acid composition of longissimus dorsi muscle.	Ye et al. (2017)
Chinese Ningxiang pigs	43.21 ± 0.57 kg	0.8 g/kg feed	The shear force of longissimus dorsi muscle reduced by 29%, and improved the fatty acid composition and meat quality.	Xing et al. (2020)
PIC	30.41 ± 3.24 kg	1.0 g/kg feed	The dressing percentage increased 2% compared with that of the control group; the weight of longissimus dorsi muscle improved..	Zhu et al. (2020)
Duroc × Landrace × Yorkshire	74.3 ± 3.8 kg	0.8 g/kg feed	Combination of non-protein nitrogen and NCG in low-protein diet increased ADG by increasing apparent nutrient digestibility.	Li et al. (2021)

ADG = average daily gain; mTOR = mechanistic target of rapamycin; NCG = *N*-carbamylglutamate; PIC = Pig Improvement Company

an increase in the serum Arg concentration and a decrease in the serum urea nitrogen concentration with the dietary addition of NCG (Zhu et al. 2020).

In addition, NCG increased the levels of Arg and leucine in the longissimus dorsi muscle of growing-finishing pigs, both of which could regulate mTOR activity in muscle to promote muscle protein synthesis, which might explain the increased dorsal longest muscle area of pigs (Ye et al. 2017). It has also been suggested that NCG improves meat quality and slaughter performance in growing-finishing pigs by regulating the expression of genes involved in myofibre development and intramuscular fat deposition (Zhu et al. 2020).

As a signal molecule, NO participates in the regulation of glucose, fatty acid, and amino acid synthesis in mammals (Jobgen et al. 2006). This study revealed that the addition of NCG reduced subcutaneous fat deposition and increased oleic acid and α-linolenic acid contents in the longest dorsal muscle of finishing pigs, suggesting that NCG might also mediate the NO metabolic pathway to regulate meat quality in finishing pigs (Xing et al. 2020). In addition, the combination of NCG and non-protein nitrogen added to the low-protein diet (CP: 11.14%) increased the apparent digestibility of nutrients and thus improved growth performance of finishing pigs (Li et al. 2021). Therefore, adding NCG can improve growth performance and meat quality, especially when a low-protein diet is used for growing-finishing pigs.

CONCLUSION

In conclusion, NCG can promote reproductive performance, growth, intestinal development, and meat quality in pigs. The mechanism of NCG may be related to the regulation of the synthesis and metabolism of endogenous Arg, such as its involvement in the metabolic processes of NO and polyamines. Compared with Arg, NCG was proven to have a longer half-life and was considered as a kind of potential alternative for Arg in pig diets in the recent years. However, most related studies have focused on the use of NCG involved in nursery or grow-finishing pigs, and limited information is available regarding the application evaluation in breeding pigs, especially for the boars. Therefore, it is necessary to carry out further research to provide reference for the application of NCG in the whole growth stage of pigs.

Conflict of interest

The authors declare no conflict of interest.

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Received: June 19, 2025
Accepted: June 10, 2026
Published online: July 23, 2026