**Abstract**

Protection of channel catfish against edwardsiellosis, one of the most significant problems affecting its industry, was the aim of this study. This was achieved by using live attenuated vaccines. *E. piscicida* C07-087, the recently identified cause of edwardsiellosis in fish farms, was used for constructing five mutants (*Ep*Δ*ssaV, Ep*Δ*esaM, Ep*Δ*yscR, Ep*ΔesaSand *Ep*Δ*escT*) by deleting five genes encoding structural proteins in the type III secretion system (T3SS) apparatus. The mutants were phenotypically characterized and their immune response, tissue persistence, virulence and efficacy as vaccines via immersion and intraperitoneal injection (i.p.) routes were evaluated. Three of the constructed mutants; *Ep*Δ*ssaV,* *Ep*Δ*yscR* and *Ep*ΔesaS were significantly attenuated. Vaccination by i.p. injection using two different doses of the constructed mutants was more significantly effective. Intraperitoneally vaccinated Channel catfish with high doses of *Ep*Δ*esaM, Ep*Δ*yscR* and *Ep*Δ*escT* showed zero mean percent mortality when challenged with *E. piscicida* WS. In addition, the cross-protection afforded by the previously prepared live attenuated *E. ictaluri* vaccine, ESC-NDKL1, against edwardsiellosis caused by *E. piscicida* C07-087 was investigated. Fish vaccinated with ESC-NDKL1 via immersion for one hour showed high level of antibodies and several *E. piscicida* immunogenic proteins were identified. In addition, all challenged fish with *E. piscicida* WS were protected opposite to 40% morality in non-vaccinated fish. In conclusion, ESC-NDKL1 vaccine is preferable as it protects channel catfish against edwardsiellosis and enteric septicemia of catfish and is easily applied.

**Keywords:** Edwardsiellosis,Channelcatfish, *Edwardsiella piscicida,* constructed mutants,type III secretion system, ESC-NDKL1 vaccine and live attenuated vaccines.