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Silkworm: A Novel Invertebrate Model for Drug Screening

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Invertebrates are used to determine the desired effect in the early stages of drug development/screening in pharmacology and toxicology studies like other laboratory animals. Silkworm (*Bombyx mori*) an invertebrate, is one of the best models having great agricultural and economic importance. It has numerous advantages in life science, such as low breeding cost, large progeny size, short generation time and clear genetic background and additionally its death does not involve any bioethical issues (Meng *et al.*, 2017). The importance of various stages of the silkworm *viz.*, eggs, larvae, pupae, moths and its products, byproducts and waste products as a potential medicinal source has been indicated (Singh and Jayasomu, 2002). In a silkworm model, the lethal doses of cytotoxic compounds were highly correlated with that in rat model, suggesting that silkworms are a suitable model for evaluation of the acute phase toxicity of cytotoxic compounds (Hamamoto *et al.*, 2009). Studies found that silkworm was highly sensitive to human pathogenic microorganisms, pathogenic fungi, virus, antibiotics and organ toxicity. Silkworm models for bacterial infection, fungal infection, virus infection, and diabetic model were established. Thus, the use of silkworm as a model organism for studying of various disease and drug development/screening has become a current research focus.

Silkworms killed by injecting hemolymph with bacteria that are pathogenic to humans such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* were reported (Kaito *et al.*, 2002). Results revealed that the doses of *S. aureus* and *S. maltophilia* were killed 90% of the silkworms without antibiotic administration. All tested antibiotics increased the number of surviving silkworms, depending on the dose. The ED_{50} in the silkworm model and mouse model were similar. This suggests that the therapeutic efficacy of antibiotics can be evaluated using a silkworm model of bacterial infection (Hamamoto *et al.*, 2004). Lysocin E was screened for its therapeutic activity in a silkworm model of bacterial infection. So, it is the advantages of using a silkworm model of bacterial infection to identify and develop therapeutically efficacious antimicrobials (Hamamoto and Sekimizu, 2016).

A major sugar in hemolymph of the silkworm is trehalose, which is composed with two molecules of glucose. Increase of total sugar level in hemolymph of silkworm fed a diet containing 10% glucose also accumulation of sugar in various organs of silkworm. Based on these findings, they expected that they would be able to establish diabetes models with silkworms, where evaluation of anti-diabetes drugs would be possible. Silkworm has bombyxin, a peptide hormone homologous to mammalian insulin. Decrease of total sugar level in hemolymph of hyperglycemic silkworm by injection of human insulin. Diabetic silkworms are useful for evaluation of hypoglycemic effects of type II diabetes (Matsumoto *et al.*, 2015). Extract of *Rehmanniae Radix*, a hypoglycemic effect was shown in the study conducted by using hyperglycemic silkworm model (Garip and Temamogullari, 2021)

Ganciclovir, foscarnet, vidarabine and ribavirin, are used to treat viral infections in humans that also, inhibited the proliferation of a baculovirus in BmN4 cells, a cultured silkworm cell line. These antiviral agents inhibited the proliferation of baculovirus in silkworm body

fluid and had therapeutic effects. These all results suggest that the silkworm–baculovirus infection model is useful for screening antiviral agents that are effective for treating humans infected with DNA viruses (Orihara *et al.*, 2008).

Silkworm infection models have been established for *Arthroderma vanbreuseghemii* and *Cryptococcus neoformans* fungal infections. Administration of terbinafine to silkworms injected with A. *vanbreuseghemii* suppresses hyphal formation in their organs and the infected silkworms administrated with terbinafine live longer than those that do not received terbinafine (Ishii *et al.*, 2017). Silkworm infection model is useful for distinguishing between weakly pathogenic and highly pathogenic strains of *C. neoformans* (Matsumoto *et al.*, 2012).

Injection of various hepatotoxic chemicals also leads to elevated alanine aminotransferase (ALT) activity in the hemolymph of silkworms. Furthermore, transparent transgenic silkworms expressing GFP (Green Fluorescent Protein) have been produced to facilitate continuous analysis without the need to collect hemolymph. These results suggest that the silkworms can serve as alternative animal model for evaluation of drug-induced tissue injury (Inagaki *et al.*, 2016).

Silkworm as an important economic insect, has numerous advantages as model organism. Silkworm were useful in various research areas, including human disease, screening of antimicrobial agents, antidiabetic drugs, antiviral drugs, antifungal drugs as well as used as model for evaluation of hepatotoxicity. More research on silkworm as a model organism should be invited and encouraged in drug development/ screening as an alternate to mammals in the future.

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