Thermotherapy is a tool for management of flacherie disease in silkworm *Bombyx mori* L.

Kalpana P. V[1], Jothimani, P[2], Shanmugam, R[3], Venu, V. S[4], Mohanraj, P [5]

[1]Department of Sericulture, Forest College and Research Institute, Mettupalayam - 641 301, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, (India)

[2]Asst. Professor (Environmental science), Forest College and Research Institute, Mettupalayam - 641 301, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, (India)

[3]Asst. Professor (Sericulture), Forest College and Research Institute, Mettupalayam - 641 301, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, (India)

[4]Department of Sericulture, Forest College and Research Institute, Mettupalayam - 641 301, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, (India)

[5]Teaching assistant (Sericulture), Forest College and Research Institute, Mettupalayam - 641 301, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, (India)

Abstract- *The silkworm is the larva of the domestic silk moth, Bombyx mori L. It is an economically important insect, being a primary producer of silk. The success of sericulture industry mainly depends on proper disease management. Microsporidia, bacteria, fungi and viruses cause an estimated crop loss of about 27-35% (Selvakumar et al., 2002). The bacterial disease is also as called flacherie diseases because the corpses of silkworms die, later becomes soften and rot.*

Thermotherapy consists of application of heat for the purpose of changing the cutaneous, intra articular and core temperature of soft tissue with the intention of improving the symptoms of certain conditions. Thermotherapy is to alter tissue temperature in a targeted region over time for the purpose of inducing a desired biological response. The majority of thermo-therapies are designed to deliver the thermal therapy to a target tissue volume with minimal impact on intervening or surrounding tissues. Late age silkworms held at higher temperature had lower incidence of infectious flacherie.

In this review, the importance of thermotherapy, management of flacherie disease in silkworm will be discussed.

Keywords- Silkworm, thermotherapy, BmIFV, BmDNV

I. INTRODUCTION

The silkworm, *Bombyx mori* is an insect with a high socio-economic and cultural value.The success of sericulture depends upon proper management and protection of silkworm crop from diseases**.** The average silkworm crop loss in India due to diseases is to the tune of 15 – 47 per cent, while it is 10 – 15 per cent in other countries like China and Japan. The major diseases affecting silkworm are flacherie, grasserie, muscardine and pebrine. Among these four diseases, flacherie is more prevalent causing cocoon crop loss to the tune of 33.88 per cent in India (Tayal and Chauhan, 2017).

II. SILKWORM FLACHERIE

Flacherie (literally: "flaccidness") is a disease of silkworms, caused by silkworms eating infected or contaminated mulberry leaves. Louis Pasteur, who began his studies on silkworm diseases in 1865, was the first one able to recognize that mortality due to viral flacherie was caused by infection. Bacteria as an etiological agent of silkworm flacherie. The flacherie in silkworms is by virus or by bacteria alone, or it can also caused by the combined infection of viruses and bacteria.

2.1 Causative agents of flacherie in silkworms:

a. Virus: Infectious Flacherie virus (*Bm*IFV)
Densonucleosis virus (*Bm*DNV)

Cypovirus-1(*Bm*CPV-1) – Occluded

b. Bacteria:*Streptococcus* sp.,*Staphylococcus*sp., *Bacills*sp., *Serratiamarcscence, Psuedomonas*sp., *Proteous*sp.

Occurrence:

- The disease is common during summer and rainy seasons.

Source of infection:

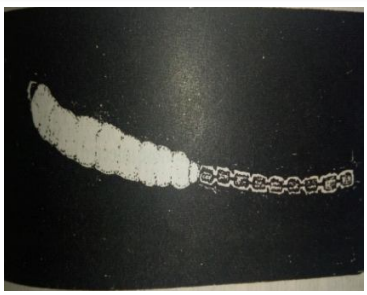
- ✓ Silkworm gets infected by eating contaminated mulberry leaf.
- ✓ Dead diseased silkworm, its faecal matter, gut juice, body fluid are the sources of pathogen contamination.
- ✓ The infection can also takes place through injuries / cuts / wounds.

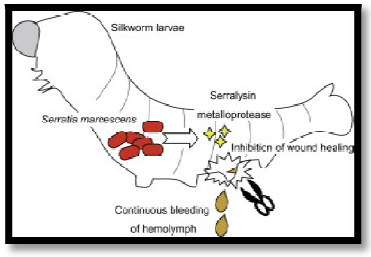
Predisposing factors:

- Fluctuation in temperature, high humidity and poor quality of leaves.

2.2 Symptoms:

- At the early stage of infection, symptoms are not clear and difficult to identify.
- The larvae become soft and flaccid, the growth of affected larvae retards, become inactive and vomit gut juice.
- The faeces become soft with high moisture content. Sometimes chain type of excreta is observed. Often, rectal protrusion is also observed.
- Cephalothoracic region becomes translucent.
- When infected with *Bacillus thuringiensis*, symptoms of toxicity such as paralysis and sudden death are observed. After death larvae turn black in colour and give foul smell.
- Sometimesthe dead larvae turn red when infected with *Serratiamarcescence*during injury.





2.3 Management of flacherie disease:

- ❖ Disinfection of rearing house, its surroundings and equipments with recommended disinfectants.
- ❖ Pick up diseased larvae and dispose them by burning.
- ❖ Provide good quality leaf grown under good sunlight and recommended inputs. Do not provide over matured/over stored /dirty leaf to the silkworms.
- ❖ Avoid starvation, overcrowding and accumulation of faeces in the rearing bed.
- ❖ Rear silkworms under optimum temperature and humidity.
- ❖ Avoid injury to the larvae.
- ❖ Apply recommended bed disinfectant as per schedule and quantity.
- ❖ Feed Amruth as per schedule to control flacherie disease.

2.4 Role temperature on silkworm growth:

Temperature plays a vital role on the growth of the silkworms. As silkworms are cold-blooded animals, temperature will have a direct effect on various physiological activities. The optimum temperature for normal growth of silkworms is between 20 °C and 28 °C and the desirable temperature for maximum productivity ranges from 23 °C to 28 °C. Temperature above 30 °C directly affects the health of the worm. If the temperature is below 20 °C all the physiological activities are retarded, especially in early instars as a result, worms become too weak and susceptible to various diseases.

2.5 High temperature treatment in sericulture:

- Ingrainges for early emergence, mother moths are treated at 32-33 °C which accelerates the development of pupae and moth emerges early.
- To develop thermo tolerant breeds of silkworms.
- Management of infectious diseases of silkworm.

III. THERMO THERAPY

Heat therapy, also called **thermotherapy**, is the use of heat in therapy.Modern research in thermal medicine aims to understand molecular, cellular and physiological effects of temperature manipulation and the “stress” response, as well as to develop effective and safe equipment for clinical application and temperature monitoring.As a result, today

there are a growing number of clinical applications of thermal therapy that benefit patients with a variety of diseases. The goal of thermo therapy is to alter tissue temperature over time for the purpose of inducing a desired biological response in an organism.

3.1 Effect of high temperature on the resistance of insects to infectious diseases:

Plants and animals, when reared at high temperatures, are able to resist the infections by certain microorganisms. This phenomenon has been applied in heat therapy or thermal therapy. In insects, high temperatures may increase their resistance to protozoan and virus infections by Tanada, (1967). The first insect virus that was subjected to heat therapy was the sigma virus of *Drosophila* sp., by Lheritier & Sigot in 1946.The first study with an insect virus possessing an inclusion body was conducted with the granulosis virus of the imported cabbageworm, *Pierisrapa*e L. by Tanada in1953.

3.2 Th
ermo therapy in silkworm disease management:

High temperature is known to increase the resistance or cause disappearance of viral infections in plants and higher animals. This is also true to the silkworm. The virus infected larvae reared at an elevated temperature of 36 – 37 ºC survive from virus infection (Aruga *et al.*, 1963).

The silkworms of fourth and fifth instar larvae immediately after each ecdysis are used for per oral inoculation with cytoplasmic polyhedrosis virus. Before the inoculation larvae are reared at room temperature for first to third or for the fourth instars. All larvae administered with virus are reared at 25 °C for 24 hours and shifted high temperature 36 ºC for 24 hours. The larvae are able to survive from cytoplasmic polyhedrosis virus infection reared at 36 °C for 24 hours (Watanabe, 1964).

Effect of high temperature on the development of nuclear polyhedrosis and nuclear polyhedrosis virus (NPV) studied by employing pupae and isolated pupal abdomens of the silkworm, *Bombyx mori,* revealed that pupae inoculated with NPV and incubated at 35 °C survived longer than those incubated at 25 ºC. At lower dosages of virus, pupae at 35 °C escaped death from NPV(Kobayashi *et al.,* 1981).

Rearing of *Bm*IFV infected silkworm at high temperature of 37 ºC for 6 – 12 h in each instar after moult, prolonged the larval duration and also mortality due to *Bm*IFV reduced drastically (Savithri, 2006).

IV. THERMO THERAPY ON SILKWORM FLACHERIE

4.1 Number of fluorescent cells in a 6 µ section larva. Group (A) held at 27 °C. Group (B) was held at 27 °C for 96 hr after inoculation of virus, and then moved to 37 ± 1 °C.

The infected third instar larvae were reared at 27 °C until 96 hour, and then a group of larvae was moved to 37± 1 °C (Group B) and the rest kept at 27 °C (Group A).At 24hr intervals after the treatments, six µvertical sections were obtained from the midguts of the larvae of both groups. The fluorescent cell number and the intensity of fluorescence were examined.

The number of fluorescent cells observed in the larvae. In the larvae of Group A which were reared at 27 ºC, many fluorescent cells, 650 to 726 in number, were observed in a six µ section. On the other hand, in the larvae, which were reared at 27 °C until 96 hour after infection and then transferred at 37 ±1°C, the number of fluorescent cells was smaller than that of Group A and also the number decreased with the lapse of time. At 168 hour, many cells and small light bodies glittered in the larvae of Group A, but only small light bodies appeared in those of Group B. In addition, fluorescence of small light bodies observed in Group B was fainter than that in Group A **(Inoue and Ayuzawa, 1972)**.

4.2 Infectivity of the inoculated larvae at various time at two temperatures. Group (A') was held at 27 ° C. Group (B') was held at 27 ° C until 120 hr, and then moved to 37 ± 1 °C.

The infected fourth instar larvae were reared at 27 °C until 120 hour and afterwards some of the larvae were placed at 37± l °C (Group B') and the rest at 27 ºC (Group A').The result is as presented in Fig, 2. Group A' maintained high LD_{50} but Group B' gave low LD_{50} values with time, and a thousand time discrepancy in infectivity was recognized between the two groups at 72 hour after the treatment **(Inoue and Ayuzawa, 1972)**.

4.3 Portion of a goblet cell of larva (J 124 x C 124) kept at 27 °C for 6 days post-virus infection.

A silkworm strain, J124 x C124, which is highly susceptible to the flacherie virus, was used as the test insect. The larvae were reared at 27°C. On the fifth day of post infection, when the larvae were in the fifth instar just after ecdysis, half of them were transferred to 37 °C. At l-day intervals, the larvae in both groups were dissected, and the anterior portions of the midguts were fixed in 2.5%

glutaraldehyde for 1 hr and post fixed in 1per cent osmium tetroxide for 1 hr. After dehydration in a graded ethanol series, the specimens were embedded in Epon 812. The sections were stained with uranyl acetate and lead citrate.

The majority of the goblet cells in the infected larval midgut showed similar pathology when exposed to the virus for 6-8 days at 27°C. Portions of the cytoplasmic wall surrounding the lumen of the goblet cell were thick, and there were very few microvilli. Virus particles and "specific vesicles" occurred in the thickened portions of the cytoplasm, and there were few or no ribosomes. Virus particles were also found in several microvilli **(Inoue and Tanada, 1977)**.

4.4 Virus – infected goblet cells of larva (J124 x C124) kept at 27 °c for 6 days post-virus infection

The goblet cells shrunk in size and were discharged into the midgut lumen. Some of the goblet cells, however, were enclosed within adjacent columnar cells and were presumably phagocytized. They were discharged into the midgut lumen when the columnar cells degenerated. A few goblet cells showed no morphological changes, but virus particles and specific vesicles were observed in parts of the cytoplasm **(Inoue and Tanada, 1977).**

4.5 A goblet cell from a larva (J124 x C124) infected 5 days earlier and then reared at 37 °C for 1 day. The cell appears normal and not contains any virus particles.

The cytopathology of midguts of larvae reared at 27°C for 5 days and then transferred to 37°C for 1 day differed from those maintained for 6 days at 27" C. The majority of the goblet cells appeared normal and contained no virus particles or specific vesicles . A few goblet cells, however, had many specific vesicles and virus particles in their cytoplasms and microvilli. Several columnar cells contained goblet cells. There were no signs of the dissolution of the virus particles in the cells. On the other hand, none of the larvae kept at 37°C for 2-3 days had goblet cells which contained virus particles and specific vesicles **(Inoue and Tanada, 1977)**.

4.6 Effect of high temperature on the production of cocoons by silkworm larvae exposed to the flacherie virus.

The result of the effect of high temperatures on the resistance of the larvae to virus infection is given in Table 1. Twenty-five percent of the larvae reared at 27 °C after exposure to the virus died eighth day, and the remained are died on the ninth day. On the other hand, all of the larvae maintained at 37°C for 1 day, 95% of the larvae held at 37°C for 2 days, and 75% of the larvae held at 37°C for 3 days produced cocoons. The larvae which did not form cocoons apparently died from the adverse effects of high temperature on their growth and metabolism. The spinning of the cocoons in larvae held at 37°C for 1, 2, and 3 days were delayed for 0.5-1, l-2, and 224 days, respectively. The sizes and weights of the cocoons, nonetheless, were the same as those produced by the non-infected control larvae **(Inoue and Tanada, 1977)**.

4.7 Effect of super optimal temperature on the accumulation of viral polypeptides in the midgut of the silkworm larvae infected with *Bm*DNV-2.

The larvae inoculated with *Bombyx*DNV-2 for 24 hr at 25 °C were reared at 25 °C or 35°C. At daily intervals until 8 days post inoculation, midgut polypeptides were resolved by SDS-PAGE and subjected to the immunoblot analysis using anti-*Bombyx* DNV-2 serum. As shown in Plate 4A, one strong and one or two weak bands were detected from 2 days post inoculation onward when the infected larvae were reared continuously at 25°C.These polypeptides had approximate molecular weights of 53,000 (53K), 51K, and49K, respectively, and corresponded to three of six *Bombyx*DNV-2 structural polypeptides identified on Coomassie brilliant blue-stained SDS-poly acryl amide gels. The relative intensities of these three bands on the immunoblots, however, differed strikingly between the infected midgut and the purified virions (Plate. 1A). In contrast, none of such polypeptides were detectable in the midgut at 35 °C (Plate. 1B), suggesting that production and/or accumulation of viral polypeptides was inhibited at a high temperature **(Kobayashi and Choi, 1990).**

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4.8 Disappearance of viral polypeptides preexisting in the midgut upon temperature shift of the infected larvae from 25 °C to 35 °C. then reared for 24 hr at 25°C were shifted to 35 °C. At daily intervals until 8 days post I infection, midgut polypeptides were analyzed

Temperature on the viral polypeptides preexisting in the infected midgut, infected larvae reared at 25°C for 48 hour were shifted to 35°C. viral polypeptides accumulated in the midgut during the incubation at 25°C decreased from 2 to 3 of days post infection and became undetectable thereafter until 8 days of post infection **(Kobayashi and Choi, 1990)**.

4.9 Effect of a super optimal temperature on the viral polypeptides in the feces. Larvae inoculated with the virus for 24 hr at 25°C and then reared for another 24 hr at 25°C were either reared continuously at 25°C (A) or shifted to 35°C (B). Feces produced by the infected larvae during each 24-hr period at 25 and 35°C were collected and stored at -20°C. Thawed feces were extracted with 100 m MTris-HCI, pH 9, and the resultant extracts were

subjected to the immunoblot analysis. Each lane contains extract from 100 mg of feces.

To give a better understanding of the mechanism involved in the disappearance of viral polypeptides preexisting in the midgut at 25°C polypeptides in the feces were subjected to the immunoblot analysis. Larvae inoculated with the virus for 24 hr at25°C and reared for an additional 24 hr at25°C were either shifted to 35°C or reared continuously at 25°C. In the feces from the larvae at 25°C two viral polypeptides with approximate molecular weights of 53K and46.5K were first detected at 4 days post I infection, increased at 5 and 6 days post infection, and then decreased to 8 days post infection. In the feces at 35 °C, although these viral polypeptides were also detected at 4 days pi at a level comparable to that at 25 °C, they decreased strikingly at 5 days post infection and were undetectable from 6 days post infection onward **(Kobayashi and Choi, 1990).**

4.10 Accumulation of viral polypeptides in the *Bm*DNV – 2 infected midgut following the temperature shift from 35 °C to 25 °C. Larvae inoculated with the virus for 24 hr at 25°C and then reared for 24 hr at 25°C were shifted to 35°C. After being reared at 35°C for 72 hr, the larvae were reversed to 25°C. At daily intervals, midgut polypeptides were subjected to the immunoblot analysis

To examine whether or not the inhibition of viral polypeptide accumulation at 35°C is also reversible, the infected larvae reared at25°C for 48 hour were shifted to 35°C. After being incubated at 35°C for 3 days, these larvae were reversed to 25°C and midgut polypeptides were subjected to the immunoblot analysis using anti-*Bombyx* DNV-2serum., viral polypeptides were clearly detected as early as 1 day after the temperature shift from 35 to 25°Cindicating that translation of viral polypeptides resumed quickly upon temperature shift to 25°C **(Kobayashi and Choi, 1990).**

4.11 Effect of Thermo therapy on mortality (%) of silkworm rearing to infectious flacherie.

CSR2 × CSR4 layings were brushed and reared. The second instar silkworm larvae were inoculated with *Bm*IFV at 10^{-8}dilution/ml and allowed for 24h. The larvae were then held at 25, 27, 30, 32, 35, 37 and 40ºC for 6, 12 and 24h durations. The infected larval batch at 25ºC served as inoculated control. An un-infected control batch was also maintained. Mortality was recorded in three replications of 100 silkworms each. The mortality at 25 – 27ºC was 24.3 - 46.0% as against 21.0 - 42.6% at high temperature range of 30 –37ºC. The mortality was least (21%) in 12h at 37ºC and highest (94.6%) at 40ºC for 24h in all instars. The per cent mortality was within this range in other treatments **(Selvakumar and Savithri., 2012).**

4.12 Effect of thermo therapy on reduction of infectious flacherie in silkworm

The low temperature treatment of 25 and 27ºC failed to check infectious flacherie as high temperature treatments (30, 32, 35 and 37ºC) (Table 3). The temperature treatment when given in all instars from second instar is more effective than when it is given to second instar only. The durations of 6 and 12h in each instar reduced flacherie incidence by 54.3 – 67.6% as against 30.2 – 57.9% in 24 h **(Selvakumar and Savithri., 2012).**

4.13 Efficacy of thermo therapy on silkworm larval weight (g) inoculated with infectious flacherie

The change in the larval weight of less than of 40ºC as in the range of 7.0 to 8.7g / 10 larvae as against 6.6 and 8.9g in inoculated and un-inoculated controls (15 days PI) respectively. The larval weights ranged from 7.0 to 8.7g in treated larvae at 25 – 37ºC and 5.0 – 7.6g at 40ºC. Highest larval weight (8.7g) was observed in treated larvae at 37ºC for 6h in second instar and lowest at 40ºC for 24 h in each instar **(Selvakumar and Savithri., 2012)**.

4.14 Total protein content in haemolymph collected from silkworm inoculated with *Bm*IFV at different temperature treatments

The total protein content in haemolymph had shown difference among different temperature treatments, inoculated control and normal control. The total protein content was less in the haemolymph of silkworm larvae inoculated with *Bm*IFV (4.45 mg / ml) compared to normal control (7.56 mg / ml). in different temperature treatments, the total protein content ranged from 4.52 mg / ml to 7.51 mg / ml, which was higher than the inoculated control. Between different temperature treatments, the lowest protein content (4.52 to 6.91 mg / ml) was observed in the highest temperature treatment of 40 ºC. Among other temperature treatments, the high temperature treatment of 37 °C had shown high protein content (7.05 – 7.51 mg / ml) compared to the other temperature treatments (6.06 – 7.10 mg / ml) **(Selvakumar and Savithri., 2013).**

4.15 Protein profile of haemolymph of silkworm collected from different durations of 37 °C temperature treatment, BmIFV inoculated control and normal control

The protein profiles of haemolymph in silkworm infected with infectious flacherie and under different periods of effective temperature treatment (37 °C)as thermo therapy

against infectious flacherie was analysed through 10 per cent SDS-PAGE and show in plate 10. In the haemolymph of all the silkworms od\f all the batches, 68 and 29.0 kD protein are observed. The haemolymph of healthy silkworm had another two distinct protein bands (16.01 and 17.44 kD) between 14.3 – 20.0 kD. These bands are not observed in inoculated control and 6 hour temperature treatment. However, these bands started appearing in treatment of 6 hour every instar and in all other treatments (37 °C) with increased intensity. There is an increase in the intensity of protein bands between 29 to 43 kD in all the treated batches when compared to inoculated control **(Selvakumar and Savithri., 2013).**

4.16 Effect of thermo therapy on mortality (%) of late age silkworm (CSR2 x CSR4) rearing to infectious flacherie.

Layings of CSR2 x CSR4 are brushed and reared till they come out of third moult. The fourth instar larvae are divided into different batches and inoculated with *Bm*IFV at 10^{-4} dilution / ml. Then the inoculated larvae are left for 24 hours and treated to temperature of 25, 27, 30, 32, 35, 37 and 40 °C conditions for 6, 12 and 24 hours duration.

Late age silkworm held at higher temperature showed lower levels of 38.0 to 60.0 per cent of infectious flacherie against 79.3 per cent mortality in inoculated control. The mortality at 25 and 27 ºC ranged from 44.0 to 60.0 per cent while at 30 – 37ºC, it ranged from 38.0 to 56.3 per cent. The lowest mortality (38.0 – 49.3%) was observed at 37ºC against inoculated control (79.3%). At higher temperature of 40ºC, the mortality was 54.0 – 95.0 per cent. Among all the treatments, the treatment during 4th instar had shown lower mortality (38.0 – 49.6%) and in it the 12hour treatment yielded better results **(Selvakumar and Savithri., 2013).**

4.17 Efficacy of thermal therapy on reduction of infectious flacherie during late age silkworm rearing after inoculation with *Bm*IFV in 4th instar

Temperature treatments during late age silkworm rearing resulted in significant reduction in the incidence of infectious flacherie (24.3 – 52.1%). A gradual reduction of infectious flacherie was observed with the increase in the temperature treatments 24.3 – 44.5 per cent (25ºC), 26.4 – 42.8 per cent (27ºC), 28.9 – 46.6% (30ºC), 31.9 – 49.5% (32ºC), 34.4 – 51.6% (35ºC) and 37.8 – 52.1% (37ºC), respectively **(Selvakumar and Savithri., 2013).**

4.18 Effect of thermo therapy on larval weight of silkworm on 10th day of rearing after inoculation with *Bm*IFV in 4th instar

Ten silkworm larvae on 10th day after inoculation with *Bm*IFV weighed 36.3g against control of 41.6g (Table 8). The weight of 10 larvae ranged from 39.0g to 41.2g in different temperature schedules. Lowest weight of 34.1 – 39.2g was observed at 40ºC. Among other temperature treatments, at 37ºC resulted in more weight of 40.0 – 41.2g compared to other treatments (39.0 – 41.0g) **(Selvakumar and Savithri., 2013).**

4.19 Effect of heat shock on survival rate of *Galleria mellonella* larvae injected with *Bacillus thuriengenesis* cells.

G. mellonella larvae were exposed to heat shock (40 °C for 30 min) and further injected with *B. thuriengenesis.* As a control, the other group of larvae was not heat shocked before injection. As presented in fig 11, the larvae began to die of the infection after about 10 hour. In the non-heat shocked larval group, 50 per cent mortality was observed 19 hour after infection, while in the group of heat shocked larvae 50 per cent mortality was observed a few hours later. Finally, the number of survivors infected with *B. thuriengenesis* was two times higher in the group of the heat shock larval group in comparison to non-heat shocked larval group, 24 percent and 12 per cent respectively. These results show that the experience of heat shock by the host directly before infection increases its resistance to entomopathogenic bacteria. These results also show that requirement of high thermal inactivation point by bacterial organisms **(Iwona and Paulina, 2013).**

Limitations of thermotherapy:

- Thermo therapy may not work with all the infectious organisms.
- High temperature treatment affects on growth, development of silkworm larvae.
- Thermal inactivation points of the viruses are higher than the rearing temperature.
- The biological differences across the multiple species and strains of pathogens are much greater than the differences between normal cells, which suggest that a single unified model of thermal inactivation point is difficult.
- Inactivation of bacterial organisms requires greater temperatures for longer periods of time. This raises questions about the safety of thermal treatment without adverse effects on surrounding tissues and silkworm health.

V. CONCLUSION

Prevention of flacherie infection during silkworm rearing helps to increase the silk productivity, because if the diseases are controlled below the economic threshold level then there will be an increase in silk production. The goal of thermo therapy is to alter tissue temperature in a over time for the purpose of inducing a desired biological response. Silkworms being poikilothermic are prone to high temperature. Hence use of thermo therapy under proper precautionary condition is effective to manage flacherie disease in silkworms.

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