6.1 Summary.
A number of factors like poor diet, steroids, environmental pollution and stressful conditions can affect the immune system function and disturb the Th1/Th2 homeostasis. Of these factors, chronic stress is more deleterious and leads to a dysfunctional immune system that opens the door to many health hazards. Stress inhibits many aspects of immune response, including innate immunity (e.g. natural killer cell lysis), T-cell responses and antibody production, both in vivo and in vitro, (Rabin et al., 1996) and therefore makes the organism susceptible to opportunistic infections. Currently, the importance of natural products in achieving T-cell homeostasis by selectively augmenting Th1 or Th2 responses is increasingly recognized and many modern drugs have their origin in traditional medicine and ethnopharmacology. The present study entitled “Plant Based Immunomodulators as Antistress Agents” was an effort in this direction wherein an effort was made to study the stress busting potential two plants namely, *Cicer microphyllum* and *Taraxacum officinale* having traditional medicinal uses and to pen down their underlying mechanism of action. This study was carried out in two major steps. First, the immunomodulatory potential of both of these plants was evaluated using both in-vitro and in-vivo methods. Our results showed TO -10 (*Taraxacum officinale*, aerial part aqueous extract) and, I^3M/38/A001 (*Cicer microphyllum*, alcoholic extract) having considerable immune stimulatory activity with specific Th1 upregulation. Second, both these extracts were hen subjected to antistress activity where their capability to restore altered immunological/biochemical and behavioural response was evaluated.

The study can be summarized as follows:

- Both *Cicer microphyllum* (alcoholic extract, I^3M/38/A001) and *Taraxacum officinale* (TO-10) are potent immunestimulators with selective Th1 upregulatory potential.
- I^3M/38/A001 as well as TO-10 has the ability to restore immune response in chronically stressed mice by normalizing HPA axis and regulating Th1/Th2 homeostasis. The impact of chronic stress on T cell function as well as Th1/Th2 pathway is reversed by the administration of TO-10 as well as I^3M/38/A001.
Ethyl acetate, CM-3a and aqueous alcoholic CM-6a fraction of \( 1\text{M/38/A001} \)
were found to be the most active candidates as they significantly enhanced the
immune response in SRBCs immunized mice but none of these fractions could
significantly restore the suppressed immune response in chronically stressed mice
in comparison to parent extract.

There was also no significant normalizing effect of these fractions on raised
corticosterone levels in stressed mice which is a marker of stress response.

This can be attributed to the fact that the antistress activity exhibited by the parent
extract was perhaps, due to additive response of the various molecules present in
the parent extract. Fractionation resulted in the distribution of these molecules in
different fractions, thus resulting in the non-responsiveness of the fractions in
chronically stressed conditions.

On the other hand, Chloroform fraction (C.F) of TO-10 was found to be the
active fraction showing significant immunestimulatory as well as antistress
potential which on further processing yields two main constituent molecules,
chicoric acid (CA) and chlorogenic acid (CGA).

Further experiments carried out with CA revealed that this molecule, the main
constituent of TO-10, is the key principle responsible for the antistress activity
of the TO-10 and it restores immune response affecting the expression of co-
stimulatory molecules particularly CD28/CTLA-4 pathway that are necessary for
the activation/inhibition of T cells and also by also augmenting the expression of
Th1 cytokines, IL-12, IFN-gamma, that have a function central to the initiation
and regulation of cellular immune responses.

The significant stress busting potential possessed by the CA enables it to exhibit
protection against chronic stress induced biochemical and behavioral alterations.

Finally, CA significantly reversed the chronic stress induced delay in wound
healing which can again be attributed to its Th1 immune stimulatory potential
along with its regulatory effect on HPA axis.
6.2 Conclusion.

In conclusion, our study clearly indicates that the *Taraxacum officinale* (TO-10) regulates stress induced disturbances in the body’s normal regulation of the neuroendocrine, metabolic, behavioral, and immunologic systems. The study also reports that the antistress activity exhibited by TO-10 can be attributed to the presence of CA, which is the main constituent of TO-10 and is the active principle of the extract. The significant antistress potential of CA enables it to exhibit protection against chronic stress induced deterioration of the endocrine functions, melancholic depression and delay in wound healing. This suggests the therapeutic use of the CA, a herbal molecule, in the treatment of stress and related disorders where T-cell function restoration and Th1 modulation is required as a reaction to chronic stress. Further studies would be required for this novel moiety to translate to human health care.