Conclusion
The present investigations were carried out with the prime objective of developing new, non-toxic and inexpensive drug(s) against indomethacin-induced gastropathy. The detailed objectives of the present investigations have been outlined in the first chapter. For a comprehensive view of the outcome of the project, the results are summarized below.

1. Considering the fact that NSAIDs induced gastropathy remains a major clinical burden in developed country like India, search for a novel antiulcerogenic agent becomes the need of the hour.

2. The NSAID, indomethacin was found to cause acute gastric ulceration in mice by producing oxidative stress as revealed by reduced plasma TAS, increased mucosal neutrophil infiltration and MPO activity. Indomethacin also inhibited ulcer healing by reducing angiogenesis by suppressing the expressions of key modulatory growth factors (VEGF, PGDF and bFGF) and their receptors at the gastric tissue and also reducing the concentrations of some of these.

3. Expectedly, the NSAID reduced both the isoforms of COX, thereby reducing PGE$_2$ synthesis that explains the observed angiogenesis.

4. In addition, indomethacin shifted the balance of arginase/iNOS activities by increasing the Th$_1$/Th$_2$ cytokines ratio. The cytokines imbalance also reduced the eNOS/iNOS ratio markedly, causing oxidative stress through peroxynitrite.

5. The leukocyte-endothelial cell adhesion that is responsible for the pathogenesis of a variety of inflammatory diseases including gastric ulcers was also significantly augmented by the NSAID. This was established from the increased levels of soluble L-, P- and E-selectins as well as ICAM-1 and VCAM-1.

6. The antioxidant-rich fraction (K-7) of the methanol extract of *P. kurroa* and the phenolic constituent (mal C), obtained from the ethanol extract of *M. malabarica* could effectively heal the ulceration.

7. Three-day treatment with mal C (10 mg/kg) and K-7 (15 mg/kg) provided considerably faster healing against acute ulceration than that observed without any treatment. Between the two drugs, mal C showed comparable efficacy as that of the commercial drug, Omez (3 mg/kg), while K-7 was only marginally inferior. The healing observed by the treatment under the optimized treatment regime was better, compared to even seven days of autohealing.
8. The test samples acted as efficient *in vivo* antioxidants and reversed the above-mentioned biochemical adverse effects, induced by indomethacin. These include augmentation of TAS, PGE\(_2\), and the designated growth factors and reduction of the MPO activity, neutrophil infiltration and NO generation. However, K-7 was not evaluated for its ability to improve angiogenesis.

9. The cytokines imbalance of was also alleviated by K-7 and mal C, improving the arginase/NOS ratio. This facilitated quicker recovery by augmenting the polyamine pathway in lieu of NO generation. Consistent with this, the eNOS/iNOS balance was also significantly restored by the test samples.

10. Importantly, mal C also reduced the inflammatory modulators (selectins and CAMS) blocking the leukocyte-endothelial cell interaction. This suggested mal C as a potentially novel anti-inflammatory agent.

11. True to the expectation, mal C (10 mg/kg) offered protection against LPS-induced inflammation in mice that equalled to those of Omez (5 mg/kg) and dexamethasone (50 mg/kg). This was also confirmed using LPS (200 ng/ml)-induced RAW 264.7 macrophage cell model, when mal C was effective at 10 \(\mu\)M concentration.

12. The anti-inflammatory action of mal C was mediated by blocking the MyD88-dependent pathway of TLR 4 signalling. This led to reduced activation of NF\(\kappa\)B and MAPK pathways, eventually reducing different inflammatory modulators (iNOS/NO, COX/PG, cytokines).

13. None of the test samples showed any acute toxicity to the mice even at a substantially higher dose (500 mg/kg) than used in the ulceration experiments.

14. These results, taken together suggested K-7 and mal C as potent anti-ulcer agents for further evaluation. In addition, mal C was also a very effective anti-inflammatory agent.