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Title of the thesis : Study of the Effects of Potential Therapeutic Agents on the Inflammatory Process Associated with Rheumatoid Arthritis

Abstract

Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disorder affecting primarily the synovial joints with their concomitant damage. Males are almost 2.5 times less affected than females. The etiology of RA is not yet fully understood. Cytokines such as TNF-α and other interleukins have critical role in the pathogenesis of RA and they significantly contribute to the degeneration of joints. Macrophage activation results in the infiltration of numerous polymorphonuclear cells (PMNs) towards the synovial tissue. The systemic and local inflammatory responses play a role in the induction and activation of ROS generating enzymes viz. xanthine oxidase, myeloperoxidase, NADPH oxidase and others. These enzymes also produce reactive nitrogen species (RNS) such as NO which may contribute in the heightened pathogenesis through alteration of antioxidant enzymes, depletion of glutathione and lipid peroxidation. It may be inferred that with suppression of such oxidative stress and inflammatory mediators the pathogenesis and implications of RA can be controlled. Use of herbal drugs have been considered as effective and safe in the reduction of chronic pain associated with RA.

The present thesis is aimed towards the study of various anti-inflammatory agents for their potential anti-arthritic therapeutic properties.

To begin with, “Introduction” is presented as **Chapter 1** which also encompasses the review regarding the interplay between arthritis, inflammation, cytokines and oxidative stress.

The **second chapter** "Aims and Objectives" briefly describes the background, rationale and the purpose of this study, which is to search for potential therapeutic alternatives to the current drug regimen as the patients of RA very often become tachyphylactic to conventional drugs, and alternative therapy may have to be instituted as time goes on.

Third chapter comprises of the “materials and methods” which discusses about various reagents and experimental procedures included in the study for the accomplishment of objectives.

The results and discussions of the experiments pertaining to the use of medicinal plants in the treatment of the animal models of arthritis have been reported in the **Chapter 4** which is again subdivided into three sections, namely 4A, 4B and 4C. In these chapters, the use of medicinal plant *Centella asiatica, Arnica montana* and *Quassia amara* has been evaluated as an anti-arthritic agent. All three plant extracts or fractions reduced progression in CIA pathogenesis by inhibiting oxidative stress, inflammatory cytokines and that too without toxicity. These outcomes provide a strong basis for the application of these herbal agents for treatment of RA in future.

Chapter 5 highlights the efficacy of the plant derived compounds, viz., coumarin compounds namely 7-hydroxy coumarin (7-HC) and 7-methoxy coumarin (7-MC) and a polyhydroxyphenolic compound gallic acid were found to be anti-inflammatory using both AIA and CIA models of arthritis. For the first time, as far as we are aware, this work has demonstrated the anti-arthritic properties of these three compounds on autoimmunity using both models of arthritis and a wide range of *in vivo* biological assays. Arthritic scores were reduced significantly while the arthritis related weight loss was recovered with the treatments of all the mentioned plant compounds indicating their low or no toxicity at the given doses. Administration of these compounds significantly reduced the nitrite and cytokines concentration of plasma and joints of the immunized rats. Treatment with indomethacin also yielded similar results ($p<0.0001$). Activities of plasma, liver, kidney and joints antioxidant enzymes like catalase, glutathione peroxidase, superoxide dismutase, glutathione S-transferase and glutathione reductase were significantly elevated. Gene expression studies revealed a significant inhibition of TNF-α, iNOS and COX-2 in the PBMC of rats from the treatment groups - coumarin compounds and gallic acid.

These findings demonstrate novel drug features of all the three compounds administered that are of considerable biological and clinical interest in the treatment of RA and other inflammatory diseases. Further studies are necessary to understand the pharmacokinetics, pharmacodynamics, and toxicity at molecular levels, as well as to investigate the clinical efficacy of the compounds.

Chapter 6 briefly describes the work done in the thesis as summary and conclusion. **Bibliography** covers all the literature cited in the text which has been given as a list of references.