Introduction
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Musculoskeletal disease is one of the most common and persistent suffering of mankind. It remains as the main cause of physical disability in ageing population. Musculoskeletal diseases are the conditions causing pain in bones, joints and in “soft tissues” like muscle, tendon and ligaments. These conditions are seen in many forms of arthritis. The commonest of the inflammatory arthritis is Rheumatoid arthritis. Rheumatoid arthritis includes the myriad of condition presenting in the so called ‘soft tissue rheumatism’ for which a diagnosis and underlying pathology is often difficult to identify. The common features of RA are pain and inflammation (Sweetman, 2003).

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by steep increase in erosive synovitis with extraarticular involvement (Harris, 1990). It is clear that the variation in the RA symptoms has hindered attempts to discover the causes of the disease such as RA. Several different genetic traits may predispose to RA but none is
present in all patients. There is no definite epidemiologic association to connect a single human pathogen and RA. It is a well known fact that RA is the outcome of an interplay between genetic risk factors, environmental pollutions and a random change in the immune system that occur with advancing age.

In this juncture, recent evidences indicate that RA susceptibility and severity are controlled differently. The onset of RA is insidious with a wide range of presentations and most of the patient experiences progressive joint destruction, deformity, disability and even premature death (Hochberg, 1981; Lee and Weinblatt, 2001).

RA is a systemic inflammatory disease, affecting about 1.0% of the population worldwide (Sweetman, 2003). The prevalence is relatively constant across the globe, regardless of geographic location and race with some exceptions (Harris et al., 2005). It affects women two to three times as often as men with a peak onset between the ages of 40 and 60. The progressive joint destruction and flaring of inflammation often lead to major disability responsible for severe limitations in quality of life, work capacity, family involvement and social activities (Rat and Bossier, 2004).

The causative factor of RA may be due to genetic and environmental factors. It is generally know that RA is genetic in nature and lively silently in many people across the world. It is clear that, about 50% to 60% of the susceptibility, severity, and phenotype of RA may be due to genetic factors (MacGregor et al., 1995; Deighton et al., 1989). On the other
hand, exposure to bacteria, viruses, lifestyle with smoking and diet contribute to environmental factors responsible for RA (Reckner, 2001).

The human immune system comprises an interactive network of lymphoid organs and immune cells and plays an important function as host defense (Delves and Roitt, 2000; Parkin and Cohen, 2001). Interaction between the various components of the immune system during activation is realized by multiple signaling molecules. These molecules, which can be released in response to tissue injury or exogenous pathogens, signal danger to the host and are necessary for initiating primary immune responses as well as for controlling the course and resolution of the concomitant inflammatory processes (Nathan, 2002; Skoberne et al., 2004) (Figure1).

Once the inciting agent enters, the immune system is triggered which results in activation of various pathways leading to joint destruction. Further it leads to bone, cartilage damage inflammation of many other tissues in the body (Peter, 2006).

In this connection macrophages are the key participants in many inflammatory response and they further activate T cells through antigen presentation and co-stimulatory molecules. In arthritis, macrophages accumulate in the synovial membrane and at the cartilage-pannus junction. The number of macrophages in the synovial lining and sublining layers correlates with radiographic outcome and disease progression in patients with RA (Mulherin et al., 1996). This can be activated by several factors expressed in arthritic joint (Hu et al., 2002). The activation can also result from direct
Figure 1

Schematic representation of Early and Developed arthrits
Figure 2

Schematic presentation of pathways showing cartilage and bone destruction
activated state predominate in synovial fluid in patients with active RA (Pillinger, et al., 1995).

The enzyme which is responsible for tissue degradation is matrix metalloproteinases (MMP). MMP's are synthesized as latent proenzymes that require activation in order to degrade cartilage extracellular matrix proteins (Malemud et al., 2003). Interlukins and tumour necrosis factor alpha are the main inflammatory cytokines which help in activating these enzymes during tissue degradation. In this reaction, three types of enzymes such as collagenases, stromelysin, and gelatinases are believed to regulate the turnover of extracellular matrix proteins.

Collagenases (MMP-1 and -13), Stromelysin (MMP-3) and Gelatinases (MMP-2) are responsible for degradation of native collagen fibers, denatured collagen, fibronectin and proteoglycans during cartilage destruction respectively (Wu et al., 1991; Flannery et al., 1992; Goupille et al., 1998; Aida et al., 2005).

RA is accompanied by three types of bone loss such as i) focal articular bone erosion ii) juxta-articular osteopenia and iii) systemic osteoporosis (Goldring, 2000). The bone loss is attributed to fundamental alterations in bone remodeling (Ng, 1997). Therefore, the types of bone loss are probably mediated by a common cellular mechanism involving osteoclasts.

Bone erosions are a radiological feature of RA and reflect a poor forecast (Bongi, 2004; Kaarela, 198; Arnett 1987). They occur within weeks
or months of disease onset. Their severity is an indication of cumulative disease activity. A ‘bi-directional attack’ on the joint occurs whereby pannus drives ‘outside-in’ erosions and osteoclast cutting cones arising in the bone marrow erupt through the subchondral bone to cause ‘inside-out’ erosions (Bromley 1984;1985).

It is well known fact that there is a drastic need to educate the patients about the disease through various programs which will help the patient combat the disease emotionally. Physical therapy and occupational therapy may help the patient who is compromised in activities of daily living. Regular participation in dynamic and even aerobic conditioning exercise programs improves joint mobility, muscle strength, aerobic fitness and psychological well being without increasing fatigue or joint symptoms (Bell, 1998).

In this connection various drugs are used in the treatment of RA such as Non –steroidal antinflammatory drugs (NSAIDs), corticosteroids and Disease modifying antirheumatoid drugs (DMARD).

The initial drug to cure RA is NSAID’s and salicylates. These agents have analgesic and anti-inflammatory properties but do not alter the course of the disease or prevent joint destruction. Thus, they should not be used as the sole treatment for RA. Choice of available agents is based on considerations of efficacy, safety, convenience, and cost. Thus some salicylates and NSAIDs inhibit the production of prostaglandins by inhibiting one or both of the cyclooxygenase enzyme isoforms (COX-1 and COX-2).
COX-1 is produced constitutively and is present in many cells, including platelets, cells of the gastric and intestinal mucosa, and endothelial cells. On the other hand, the production of COX-2 can be increased many times over, particularly by cells at sites of inflammation. Although selective COX-2 inhibitors have a significantly lower risk of serious adverse gastrointestinal (GI) effects than do nonselective NSAIDs (Hickling et al., 1995, Kirwan et al., 1998).

Corticosteroids provide symptomatic relief for patients with RA, but systemic use is controversial due to short-term, the potential for disease flare on cessation, and concerns over adverse effects. Continued corticosteroid treatment exacerbates the local and systemic osteopenia that accompanies active and chronic RA (Kirwan, 1995 and Hickling, 1998).

Disease modifying antirheumatoid drugs (DMARDs) are agents have been classified according to their reported benefit (as disease-modifying or remission-inducing), their onset or duration of action (slow-acting or long-acting). These drug probably block the release of cytokines and are selected based on their efficacy and toxicity. The DMARD's are methotrexate (Jackson, 1998) D-Pencillamine, Gold compounds, sulphasalazine, etc. Sulfasalazine and methotrexate are usually prescribed first line. Sulfasalazine is preferred in mild to moderately severe disease in view of its reasonable efficacy and low rates of serious adverse effects.

The patients affected with RA develop nutritional disorders due to the intake of various medicines and this may be due to interference with the
normal absorption, metabolism and excretion of nutrients. Thus, there is considerable shift seen in patients with RA in their energy, protein, fat and vitamin levels in their body. The mechanism of food sensitivity involved in RA is still a mystery and patients with sensitivity develop episodic arthritis and progress to true RA. Rheumatoid Arthritis victims however requires special attention to certain nutrients, such as the proper essential fatty acids, vitamin, mineral supplements and various antioxidants.

Extra articular features of RA are neither clinical curiosities nor just complications of RA but rather very important process that occur during RA progression. Patients with RA die slowly by degrees, often with multiple problems, making it difficult to determine the final cause of death. A wide array of nonspecific changes is seen in patients with RA and the various extraarticular features are listed below.

I. Essential systemic rheumatoid disease

1. Serositis
2. Vasculitis
3. Granulomata (nodules)

II. Features related to chronic immune stimulation

1. Anemia
2. Lymphadenopathy
3. Felty’s syndrome

III. Associated syndromes occurring in RA

1. Sicca syndrome
2. Fibrosing alveolitis

IV. Complications of Rheumatoid arthritis

1. Amyloidosis
2. Osteopenia

V. Drug-induced complications

1. Osteoporosis
2. Peptic ulcer
3. Anemia

Subcutaneous nodules are commonly found in patients with RA and occur as classic rheumatoid nodules and rheumatoid nodulosis. Rheumatoid nodules are frequent in males than females (Ball, 1952; Gall, 1988). Further the histological features of rheumatoid nodules consist of a central region of necrosis, with palisading histiocytes, fibroblasts, and a mixed inflammatory infiltrate (Ziff, 1990). Nodules are skin colored, can be solitary or multiple, and range from 5 mm to many centimeters in diameter. They lie deeply adhering to underlying periosteum, tendons, or bursae (Kaye, 1984).

The other common complications of RA are rheumatoid vasculitis (RV) and Felty syndrome. RV occur in seropositive RA and they manifest neuropathy, rash, skin ulcers, gangrene, and abnormalities in visceral organs (Mongan, 1969) whereas the Felty syndrome is accompanied by leucopenia and spleenomegaly (Goldberg, 1980). The mortality rate is high in
Felty syndrome and is due to splenic dysfunction. The patients affected with Felty syndrome are more prone to lymphomas and leukemia (Mellemkjaer, 1998; Gridley 1994).

Inadequate knowledge of the aetiology and pathogenesis of rheumatoid arthritis affecting human remains still a fizzy and so it is necessary and need to model out similar conditions in experimental animal to gain in depth knowledge about the disease and new therapies (Billingham, 1983).

Animal models of RA serve as valuable tools to investigate the underlying mechanisms at early, intermediate and late stages of RA. With the recent advances in molecular biology, immunology, bioinformatics, and drug designing techniques, the possibility of developing novel therapies for RA and other inflammatory diseases is all the more promising. Animal models of RA are most common, due to cost, homogeneity of the genetic background and in mice (Kannan et al., 2005).

Generally, chronic inflammatory polysynovitis can be readily induced in three different in vivo models such as Adjuvant induced arthritis, Streptococcal cell wall induced arthritis and Type II collagen induced arthritis (David, 1987). An ideal model of RA should mimic the complexity of the human disease in being polygenic and dependent on environmental factors.

Adjuvant-induced arthritis (AIA) in rats is an established model to study the physiological, biochemical and pharmacological aspects of inflammation. Paw swelling, bone lesions and internal biochemical responses
are widely used for screening the anti-inflammatory properties of the compounds and the model shares many such characteristics with human rheumatoid arthritis (Lalenti et al., 1993).

Rheumatoid arthritis, cancer, emphysema, cirrhosis and atherosclerosis have all been correlated with oxidative damage. The role of reactive oxygen and free radicals in tissue damage are increasingly recognized in such diseases (Halliwell and Gutteridge, 1985).

Reactive oxygen species contribute to the decline in function of the immune system (Kyoung et al., 2003). Free radicals have long been implicated as mediators of tissue damage in RA patients. Correspondingly, it has been shown that RA bloodstream neutrophils and monocytes are, as a rule, characterized by the overproduction of oxygen and nitrogen reactive species (Vanderoost et al., 2003).

The close relationship between the generation of ROS including superoxide (O$_2^-$), by phagocytic cells in inflammatory processes and tumor promotion is generally accepted. Among the inflammatory cells, polymorphonuclear leukocytes (PMNs) are particularly adept at generating and releasing ROS including, O$_2^-$, hydrogen peroxide (H$_2$O$_2$), hypochloric acid (HOCl), singlet oxygen (¹O$_2$) and hydroxyl radicals (•OH) The generation of O$_2^-$ by PMNs is attributable to the activation of a plasma-membrane enzyme, NADPH oxidase. Utilization of O$_2^-$ derived H$_2$O$_2$ by myeloperoxidase (MPO) results in the formation of HOCl, further reaction of which with H$_2$O$_2$ generates ¹O$_2$. In addition, •OH has been demonstrated to be
generated from the interaction of HOCl with O$_2^-$, and this can randomly react with biological components such as lipids or DNA bases intracellularly (Yoshimasa et al, 2000). As a result of ROS production there is further activation of cells of the synovium, which produce pro-inflammatory cytokines and matrix-degrading enzymes, which maintain the inflammation and lead to permanent joint damage.

Herbs are used extensively in various traditional medicine systems around the world. Botanicals are main source that directly provides ~25% of currently used herbal drugs, with another 25% derived from chemically altered natural products (Huxtable, 1992). Various traditional medicine systems around the world, including ancient Indian, Chinese and Amazonian ethnomedicine, rely heavily on herbs for health preservation and healing.

The health promotive, disease preventive and rejuvenation approach available in the Indian system of medicine like “Ayurveda” is gaining importance in many regions of the world. The disease preventive and health promotive approach of ‘Ayurveda’, which takes into consideration the whole body, mind and spirit while dealing with the maintenance of health, promotion of health and treating ailments is holistic approach and finds increasing acceptability in many regions of the world. The Ancient Ayurvedic physicians understood the delicate mechanism and the functional efficacy of the body tissues and they developed various formulations as supplements in the diet, therapeutic measures to normalize the whole functional dynamics of
the body organs. This revitalization / rejuvenation is known as the “Rasayana Chiktisa” (Govindarajan et al., 2005).

“Ayurveda” classifies medicinal plants into different groups according to their actions. One of these is the ‘Rasayana’ group. The word ‘Rasayana’ literally means the path that ‘Rasa’ takes (‘Rasa’: plasma; Ayana: path). It is believed, in Ayurveda that the qualities of the ‘Rasadhatu’ influence the health of other dhatus (tissues) of the body. Hence any medicine that improves the quality of ‘Rasa’(‘Rasayana’) should strengthen or promote the health of all tissues of the body. ‘Rasayana’ drugs act inside the human body by modulating the neuro-endocrino-immune systems and have been found to be a rich source of antioxidants (Brahma and Debnath, 2003).

The Rasayana plants are said to possess the following properties viz: a) they prevent ageing b) re-establish youth c) strengthen life, brain power and d) prevent diseases (Ghanekar, 1981; Sharma, 1983).

Rejuvenation therapy mainly deals with promotion and maintenance of health by revitalizing the metabolism and enhancing immunity. ‘Rasayana’ is not a drug therapy, but is a specialized procedure practiced in the form of rejuvenation recipes, dietary regimen and special health.

Rasayana’ treatment for rejuvenation is done after the system is thoroughly cleansed by ‘Panchakarma’ therapy and these therapies are used for treating broad category of conditions like arthritis, rheumatism, neurological, muscular skeletal disorders and also degenerative conditions
like infertility, menstrual problems, obesity, respiratory disorders, gastrointestinal disorders, etc (Joshi, 1998). Rasayana drugs are very rich in powerful antioxidants and a number of workers have studied on the plants used as Rasyana drugs in order to reason out to the modern world (Puri (1970a, b, 1971, 1972, 2003).

Therefore it is of interest to investigate the evaluation of Operculina turpethum Linn. Silva Manso stem bark with special reference to anti-inflammatory, anti-arthritic, antiulcer and antioxidant activities in rats.

*Operculina turpethum* belongs to the family Convulvaceaea. It is a perennial climber and it exudates a milky juice (Kirtikar and Basu, 2000). The roots are long, slender, fleshy and much branched. Stem is very long, twining and much twisted, angled and winged. The leaves are ovate or oblong, rarely lobulate, subacute. Petioles are long and pubescent. There are few flowering cymes with white flowers. The root is bitter with sweet taste.

The plant is dense, bushy twiner on trees and fences. The branchlets are winged; leaves are simple, broadly ovate to cordate, apex subacute, margins entire, petiole 6cm long. Inflorescence is a lax cyme, corymbose, bract large and deciduous (Kirtikar and Basu, 2000).

**Synonyms are**

*Ipomoea turpethum* Linn.

*Convolvus turpethum* Linn. R.Br.

*Merremia turpethum* Linn.
Common names:

In English - Indian jalap (Source: Dict Rehm), transparent wood rose (Source: G. W. Staples, p.c.)

Chinese - he guo teng (Source: F ChinaEng)

In Hindi - Nisoth (Source: Dict Rehm) [India]

In Sanskrit - Trivrit

In Tamil - Sivadai

It grows throughout India up to an altitude of 900 m, Ceylon, Malaysia, Tropical America, Mauritius, Philippines, Tropical Africa and Australia.

The plant root contains a glycoside resin, which is mainly concentrated in the root bark. It contains an ether soluble glycoside, turpethin - a and turpethin - s. Stem of the plant contains triterpenes beutlin and lupeol and β - sitosterol (Jain et al., 1987; Kirtikar and Basu, 2000).

The plant is used in the treatment of ascites, leucoderma, itch, ulcers, constipation, inflammation, anemia, fevers, piles, tumors and jaundice (Ragunathan et al., 1982). It is also used in the treatment of neurological disorders like tremors of the body, diseases of the brain, paralysis, pains in the muscles, bronchitis, pains in the joints and is also used in the treatment of anemia associated with spleenomegaly (Asima et al., 1995).
Towards the end of the twentieth century many countries in the world started to give importance for their own traditional medicines and tribal medicines (Sivalokananthan et al., 2004;2005;2006 and Vidya et al., 2005;2006). These traditional medicines and tribal medicines are based mostly on herbs. In the present scenario the modern research is focused on herbal drugs, especially in the eastern countries like Japan, China, India, Korea etc.

Hence, in the present study an attempt has been made to evaluate the anti-inflammatory, anti-arthritic, anti-ulcer and antioxidant activities of stem bark of Operculina turpethum (Linn.) Silva Manso in experimental rats.

The aims and objectives of the present study are as follows

1. Pharmacognostical identification of the stem of Operculina turpethum.

2. Preliminary phytochemical screening of Hydro-alcoholic extract (HAOP) and Methanolic extract (MOP).

3. To evaluate the acute and chronic toxicity profile of HAOP and MOP.

4. To assess the anti-nociceptive, anti-inflammatory and antipyretic activities of HAOP and MOP.

5. To evaluate the anti-ulcer activity of HAOP and MOP.

6. To study the anti-arthritic and in vivo antioxidant activity of HAOP and MOP with reference to pharmacological, biochemical,
radiological and histopathological indices in adjuvant induced arthritis.

7. To study the *in vitro* antioxidant activity of HAOP and MOP like

- Scavenging of DPPH radical
- Scavenging of nitric oxide
- Scavenging of DNA adduct
- Determination of total antioxidant activity by FTC and TBA method.