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Rishi Raj

JRF Student MBAC, Agwanpur,
Saharsa, Bihar, India

Kumari Shyam Lata

PG Student, MLT Collage,
Saharsa, Bihar, India

Vishakha Raj

Bsc. Nursing Student, IGIMS,
Patna, Bihar, India

Dr. Mukul Kumar

Assistant Professor-Cum-JR.
Scientist, Department of
Biochemistry and Crop
Physiology. MBAC, Agwanpur,
BAU, Sabour, Bihar, India

Corresponding Author:

Dr. Mukul Kumar

Assistant Professor-Cum-JR.
Scientist, Department of
Biochemistry and Crop
Physiology. MBAC, Agwanpur,
BAU, Sabour, Bihar, India

Phytochemicals and its application

Rishi Raj, Kumari Shyam Lata, Vishakha Raj and Dr. Mukul Kumar

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Abstract

The paper confers the use of phytochemicals in resisting of several diseases caused by different microbes/pathogen. In the current scenario, there is a high demand for proven plant therapies, herbal drugs, and other natural products, as well as their therapeutic application, which are often found to be more effective than synthetic pharmaceuticals in chronic diseases. In many cases, plant extracts, herbal formulations, and phytochemicals perfectly supplement the typical therapy and at the same time do not cause side effects for example skin irritation, gastrointestinal problems. It is an urgent demand to find out complete therapeutic potential and adverse effects, of these phytochemical compounds because of the continued rise of drug- resistant bacterial infections.

Keywords: Phytochemicals, dentistry, rheumatoid arthritis (RA), herbal therapies, pharmaceuticals

Introduction

Phytochemicals are the chemicals compound derived from the plants [1]. These chemicals are classified based on their role in plant metabolism, as primary or secondary constituents [2, 3]. Primary constituents include the common sugars, amino acids, proteins, purines, and pyrimidines of nucleic acids, chlorophylls, etc. Secondary constituents are the remaining plant chemicals such as alkaloids (derived from amino acids), terpenes (a group of lipids), and phenolics (derived from carbohydrates) [3]. It helps plant host in its biological activity, also play role in plant growth or defense against predators, competitors, pathogens [2]. Phytochemical, mainly Herbal products have been used since ancient times in folk medicine, and pharmaceutical companies trying something new way to explore plants as sources for new Phytotherapeutic agents with proven efficacy, safety, and quality [4]. Many plants with biological and antimicrobial properties have been studied since there has been a relevant increase in the incidence of antibiotic overuse and misuse, which lead to multi-drug-resistant bacteria [5, 6, 7]. Consumption of natural, fresh plant products rich in phytochemicals and antioxidants has been reported to overcome some of the degenerative diseases that affect humans. Given the advantage of using dietary components with relatively low toxicity, an abundance of materials, and low cost; nutritional therapy provides an important strategy for preventing and treating numerous diseases and contributing to the welfare of individuals [8, 9]. The protective effects of these phytochemicals were found in many human diseases [10, 11, 12]. The aim of review, to discuss the use of herbal drugs and other natural products in different disease like dentistry, and Rheumatoid arthritis (RA).

Dentistry

A large variety of herbal and antimicrobial products are added to dentifrice and mouth rinsing solutions with the aim of preventing biofilm formation [14, 15]. Today's, the herbal products like Parodontax ® (GlaxoSmithKline, Middlesex) available in the market, which is widely used in dentistry. Phyto medicine has been used as an anti-inflammatory, antibiotic, analgesic, sedative agents, and also as endodontic irrigants.

Antimicrobial activity

Antimicrobial agents play an important role in oral microbes, especially those who make sub- and supra-gingival biofilm formation.

sodium fluoride and sodium bicarbonate, composed of the following herbal products:

1. *Echinacea purpurea* (Asteraceae) stimulates immune response;
2. *Matricaria chamomilla* (Asteraceae) has anti-inflammatory properties that reduce gingival

- inflammation;
3. *Salvia officinalis*
(Lamiaceae) has
antihemorrhagic
properties;

4. *Commiphora myrrha* (Burseraceae) has natural antiseptic properties and *Mentha piperita* (Lamiaceae) has analgesic, antiseptic and anti-inflammatory properties.

Parodontax® could reduce gingivitis significantly but not a plaque [15]. Parodontax® and a triclosan dentifrice were as effective in reducing plaque and gingival indexes [16].

An herbal-based mouth rinse containing *S. officinalis*, could be used daily in patients with periodontal diseases as an adjunctive procedure to reduce gingival inflammation [17].

Aloe vera: containing in mouth rinse was found to reduce gingival inflammation and gingival bleeding [18] moreover in decreasing the number of the anaerobic microbe and anaerobic bacteria [19].

Salvadora persica: (Salvadoraceae), effective in controlling dental plaque, having great antimicrobial activity against *Streptococcus fecal* [20, 21].

Punica granatum: (Punicaceae) And *Centella Asiatica* (Apiaceae) function in promoting tissue healing.

Azadirachta indica: (Phytoseiidae) mouth rinse has antibacterial activity against *S. mutans*, reducing incipient carious lesions [22]. Extracts of *Mikania glomerata* (Asteraceae) and *Mikania laevigata* (Compositae) have also shown inhibitory activity against mutans streptococci [23].

Extracts of green and black tea

Both originating from *Camellia sinensis* (Theaceae), revealed inhibitory activity against microorganisms such as *E. coli*, *S. salivarius* and *S. mutans* [24]. Moreover, black and green tea were observed to inhibit salivary amylase activity.

Eucalyptus oil and orange oil were reported as being as effective as chloroform and xylene to dissolve or soften gutta-percha [25].

A polyphenol identified in the oolong tea (*C. sinensis*) showed strong antiglycosyl transferase activity and could inhibit dental caries in rats infected with mutants streptococci [26].

Aqueous extracts of both *Allium sativum*: (Liliaceae) and *Allium cepa* (Liliaceae) have shown good antimicrobial activity against Gram-positive and Gram-negative bacterial species and fungi [27, 28], and with the *A. sativum* (garlic) extract showing better results [29].

Antiinflammatory activity

Guaco (*Mikania* – Asteraceae), commonly used in Brazil, has antimicrobial, antiinflammatory and analgesic properties [30]. Decoctions of dried leaves and stems of *M. laevigata* and *M. involucreata* were found to inhibit edema formation after sub plantar injection with carrageenin and pleurisy in rats [31].

***Kalanchoe brasiliensis*:** (Crassulaceae) extracts isolated from leaves especially before blooming also showed a good anti-inflammatory effect on carrageenin-induced rat paw oedema [32].

***Plumeria acuminata*:** (Apocynaceae) extracts showed potential anti-inflammatory activity in both acute and chronic experimental animal models [33]. Anti-inflammatory activity

for one of the most commonly consumed herbals teas, chamomile tea – *M. chamomilla* [34].

Sedative and anxiolytic activities

Many herbal compounds are sedative properties, extracted form of *Melissa officinalis* (Lamiaceae), *Valeriana officinalis* (Valerianaceae), *Passiflora incarnate* (Passifloraceae) and *Piper methysticum* (Piperaceae).

Dentists have developed several techniques to treat patients presenting with high levels of anxiety or fear of dental treatment. Currently, orally administered benzodiazepines and nitrous oxide-oxygen inhalation have been used for sedation in dentistry [35]. Studies on herbal drugs used to control dental anxiety or fear are scarce in the literature.

Valerenic acid: was found to inhibit the enzyme system causing a breakdown of GABA in the brain, Which then increases in GABA levels is associated with sedation and a decrease in CNS activity.

V. officinalis relaxant effect might be associated with its volatile oils and valepotriates. Valepotriates are classified as tranquilizers rather than sedatives nature [36].

Lemon balm: (*M. officinalis*), derived from dried leaves, contains volatile oils citronellal, geranial, and neral responsible for its mild sedative, anxiolytic and hypnotic effects.

Rheumatoid Arthritis: RA

Rheumatoid arthritis (RA), chronic, autoimmune, and systemic inflammatory disorder which mainly affects the diarthrodial joint disease which targets synovial joints [37]. About 2.5–3% in adults and mainly after the age of 50. Efforts are being made to understand the cellular and molecular mechanism for the pathogenesis of RA.

Changes at the molecular scale in RA

Pro-inflammatory cytokines such as interleukin (IL)-1 β , tumor necrosis factor- α (TNF- α), and IL-6 are important players to cause RA. Then there is a free radical generation, which intensifies the disease and subsequent damage of cartilage and bone. T cells, also contribute their role in the progress of the disease. Inflamed synovium is central to the pathophysiology of RA. The synovial tissue of patients with RA is characterized by mononuclear cell infiltration, neovascularisation, and proliferation of synovial fibroblasts [38]. Persistent inflammation cause the production of pro-inflammatory cytokines [8]. Inflammatory cytokines IL-1 β and TNF- α are the principal mediators of tissue destruction in RA. These two cytokines induce, in synergy, the production of high levels of matrix metalloproteinases by synovial cells and chondrocytes [39].

Association of Free Radicals (ROS) with RA

reactive products of oxygen and nitrogen termed as free radicals are also one of the main players to cause RA and also agents of other degenerative diseases [40, 41, 42]. ROS such as superoxide radicals, hydroxyl radicals, and hypochlorous acid contribute significantly to tissue injury in RA [43]. generation and action of ROS in the joint of RA patient, including increased pressure in the synovium cavity, reduced capillary density, vascular changes, and increased metabolic rate of synovial tissue [44]. Normal equilibrium between ROS production and the antioxidant system of the cell is disturbed

due to oxidative stress, thus resulting in damage to vital cell components such as proteins, DNA, and membrane lipids [45]. Significant decrease in the activities of catalase, glutathione reductase, and the levels of thioredoxins, which is a marker of oxidative stress, are significantly higher in synovial fluid of RA patients [46]. production of nitric oxide (NO) is also upregulated in arthritic tissue [47, 48].

Previous Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs), effects by inhibiting cyclooxygenase activity and blocking the downstream production of prostanoids and eicosanoids. Effective therapy for treating RA. This may exacerbate the potential for hepatic enzyme disturbances. Additional side-effects include weight loss, diarrhea, skin rash, and alopecia [49].

Cytokine research has led to ideas for the use of anti-cytokine therapy for the treatment of RA. Etanercept (a recombinant form of the p75 TNFR-II) and Infliximab (a monoclonal antibody directed against TNF- α) were the first biological response modifiers approved for the treatment of RA in the year 1992 [50, 51]. Both drugs have been designed to bind with TNF- α and decrease its bioavailability.

Herbal Therapies

Most of the treatments are relatively free of side effects [52].

Ginger: (*Zingiber officinalis*, Zingiberaceae), an anti-inflammatory agent, inhibitors of prostaglandins. Another constituent of ginger, gingerol inhibited lipopolysaccharide (LPS) induced inducible nitric oxide synthase (iNOS) expression and production of NO *in vitro* [53]. Oral administration of ginger oil suppressed the induction of adjuvant-induced inflammation [54].

Pineapple

Bromelain, an extract of pineapple stem has anti-inflammatory properties. bromelain is a general name for a family of sulfhydryl proteolytic enzymes obtained from *Ananas comosus*. Active components of bromelain are peroxidase, acid phosphatase, several protease inhibitors. bromelain treated with RA patients, about 72% of total patients reported reduced swelling and pain [55].

Turmeric: (*Curcuma longa*), have curcumin which is an active anti-inflammatory component. The rhizome, the root, of *Curcuma* is used in medicinal and food preparations. Curcumin is the main active component of this herb and exhibits antioxidant properties, regular *Curcuma* consumption by RA patients have shown significant improvement in joint swelling [56].

Harshingar: (*Nyctanthes arbor tristis* Linn., NAT), used widely as a decoction for the treatment of arthritis. Arbutin, nictanthic acid, and crocetin is the main active principals of NAT. Water-soluble ethanolic extract of NAT leaves have been reported to reduce significantly the levels of inflammatory cytokines (IL-1, TNF- α) in experimental arthritis [57].

Chirayita: (*Swertia Chirayita*), a herb found mainly in the temperate regions of Himalayas, is commonly used for chronic fever, anemia, and asthma. Chirayita comprises of

swerchirin, swertanone and swertianin, as active components responsible for the anti-inflammatory activity. Chirayita reduce the elevated levels of IL-1 β , TNF- α , and IL-6 (Pro-inflammatory cytokines) in experimental arthritis as well as in asthmatic conditions [58].

Saffron: (*Crocus sativus*, Iridaceae), medicine for various purposes such as aphrodisiac, antispasmodic and expectorant. Saffron stigma possesses anti-inflammatory action due to the presence of crocetin and carotenoids. Aqueous and ethanolic extracts of saffron petals exhibit radical scavenging as well as anti-inflammatory effects in xylene and formalin-induced inflammation [59].

Karvi: (*Strobilanthes callosus*, Acanthaceae), another Indian medicinal herb, The Lupeol, and 19 α -H Lupeol isolated from the roots of *Strobilanthes callosus* have demonstrated the anti-inflammatory as well as anti-rheumatic activity in carrageenan-induced edema [60].

Trewia polycarpa Benth: (*Euphorbiaceae*) roots are also used in Indian Ayurvedic medicine for the treatment of rheumatism, arthritis, and gastritis [39]. after oral administration of the alcoholic extract at different doses to Wistar rats, also superoxide dismutase, glutathione peroxidase activities were found to be elevated thus indicating the free radical scavenging property [61].

Madimadi: a Korean folk medicine, Madimadi had inhibitory effects on pro-inflammatory cytokine, and dose-dependently inhibited TNF- α , IL-1 β , and IL-8 production in RA patients. Madimadi also downregulates the TNF- α and IL-1 β [61].

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References

1. Breslin A. The chemical composition of green plants. Sciencing, Leaf Group Ltd 2017, 76.
2. Molyneux RJ, Lee ST, Gardner DR, Panter KE, James LF. Phytochemicals: the good, the bad and the ugly? Photochemistry 2007;68(22-24):2973-2985.
3. Walton NJ, Mayer MJ, Narbad A. Vanillin. Photochemistry 2003;63(5):505-515.
4. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Brazilian Journal of medical and Biological research 2000;33(2):179-189.
5. Pannuti CS, Grinbaum RS. An overview of nosocomial infection control in Brazil. Infection Control & Hospital Epidemiology 1995;16(3):170-174.
6. Guzmán-Blanco M, Casellas JM, Sader HS. Bacterial resistance to antimicrobial agents in Latin America: The giant is awakening. Infectious Disease Clinics of North America 2000;14(1):67-81.
7. Cowan MM. Plant products as antimicrobial agents. Clinical microbiology reviews 1999;12(4):564-582.
8. Abrams P, Cardozo L, Khoury S, Wein AJ. eds., Incontinence: International Consultation on Urological Diseases 2013.
9. Tsao R, Deng Z. Separation procedures for naturally occurring antioxidant phytochemicals. Journal of chromatography B 2004;812(1-2):85-99.

10. Barnes S. Role of phytochemicals in prevention and treatment of prostate cancer. *Epidemiologic reviews* 2001;23(1):102-105.
11. Chen MH, Bergman CJ. A rapid procedure for analysing rice bran tocopherol, tocotrienol and γ -oryzanol contents. *Journal of Food Composition and Analysis* 2005;18(2-3):139-151.
12. Schreiner M, Huyskens-Keil S. Phytochemicals in fruit and vegetables: health promotion and postharvest elicitors. *Critical reviews in plant sciences* 2006;25(3):267-278.
13. Pannuti CM, Lotufo RFM, Cai S, Saraiva MDC, Freitas NMD, Falsi D. Effect of a 0.5% chlorhexidine gel on dental plaque superinfecting microorganisms in mentally handicapped patients. *Pesquisa Odontológica Brasileira* 2003;17(3):228-233.
14. Pistorius A, Willershausen B, Marroquin BB. Effect of apical root- end filling materials on gingival fibroblasts. *International Endodontic Journal* 2003;36(9):610-615.
15. Pannuti CM, Lotufo RFM, Cai S, Saraiva MDC, Freitas NMD, Falsi D. Effect of a 0.5% chlorhexidine gel on dental plaque superinfecting microorganisms in mentally handicapped patients. *Pesquisa Odontológica Brasileira* 2003;17(3):228-233.
16. Ozaki F, Pannuti CM, Imbronito AV, Pessotti W, Saraiva L, Freitas NMD, *et al.* Efficacy of a herbal toothpaste on patients with established gingivitis: a randomized controlled trial. *Brazilian oral research* 2006;20(2):172-177.
17. Pistorius A, Willershausen B, Marroquin BB. Effect of apical root- end filling materials on gingival fibroblasts. *International Endodontic Journal* 2003;36(9):610-615.
18. Fani M, Kohanteb J. Inhibitory activity of Aloe vera gel on some clinically isolated cariogenic and periodontopathic bacteria. *Journal of Oral Science* 2012;54(1):15-21.
19. Kaim G, Dimroth P. Voltage- generated torque drives the motor of the ATP synthase. *The EMBO Journal* 1998;17(20):5887-5895.
20. Al Wassan KA, Almas K, Al Shethri SE, Al Qahtani M, Back & neck problems among dentists and dental auxiliaries. *J Contemp Dent Pract* 2001;2(3):17-30.
21. Al- Otaibi M, Al- Harthy M, Gustafsson A, Johansson A, Claesson R, Angmar- Månsson B. Subgingival plaque microbiota in Saudi Arabians after use of miswak chewing stick and toothbrush. *Journal of Clinical Periodontology* 2004;31(12):1048-1053.
22. Vanka A, Tandon S, Rao SR, Udupa N, Ramkumar P. The effect of indigenous Neem *Azadirachta indica* [correction of (*Adirachta indica*)] mouth wash on *Streptococcus mutans* and lactobacilli growth. *Indian journal of dental research: official publication of Indian Society for Dental Research* 2001;12(3):133-144.
23. Yatsuda R, Rosalen PL, Cury JA, Murata RM, Rehder VLG, Melo LV, *et al.* Effects of Mikania genus plants on growth and cell adherence of mutans streptococci. *Journal of ethnopharmacology* 2005;97(2):183-189.
24. Rasheed A, Haider M. Antibacterial activity of *Camellia sinensis* extracts against dental caries. *Archives of pharmacal research* 1998;21(3):348-352.
25. Hansen KH, Angelidaki I, Ahring BK. Anaerobic digestion of swine manure: inhibition by ammonia. *Water research* 1998;32(1):5-12.
26. Hamilton-Miller JMT. Anti-cariogenic properties of tea (*Camellia sinensis*). *Journal of Medical Microbiology* 2001;50(4):299-302.
27. Elnima EI, Ahmed SA, Mekkawi AG, Mossa JS. The antimicrobial activity of garlic and onion extracts. *Die Pharmazie* 1983;38(11):747-748.
28. Yang J, Liu X, Bhalla K, Kim CN, Ibrado AM, Cai J, *et al.* Prevention of apoptosis by Bcl-2: release of cytochrome c from mitochondria blocked. *Science*. 1997;275(5303):1129-1132.
29. Elnima EI, Ahmed SA, Mekkawi AG, Mossa JS. The antimicrobial activity of garlic and onion extracts. *Die Pharmazie* 1983;38(11):747-748.
30. Mourão RHV, Santos FO, Franzotti EM, Moreno MPN, Antonioli AR. Antiinflammatory activity and acute toxicity (LD50) of the juice of *Kalanchoe brasiliensis* (Comb.) leaves picked before and during blooming. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 1999;13(4):352-354.
31. Suyenaga ES, Reche E, Farias FM, Schapoval EES, Chaves CGM, Henriques AT. Antiinflammatory investigation of some species of Mikania. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 2002;16(6):519-523.
32. Mourão RHV, Santos FO, Franzotti EM, Moreno MPN, Antonioli AR. Antiinflammatory activity and acute toxicity (LD50) of the juice of *Kalanchoe brasiliensis* (Comb.) leaves picked before and during blooming. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 1999;13(4):352-354.
33. Gupta KC, Jabrail FH. Effects of degree of deacetylation and cross-linking on physical characteristics, swelling and release behavior of chitosan microspheres. *Carbohydrate Polymers* 2006;66(1):43-54.
34. McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (*Matricaria recutita* L.). *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 2006;20(7):519-530.
35. Ganzberg S, Pape RA, Beck FM., Remifentanyl for use during conscious sedation in outpatient oral surgery. *Journal of oral and maxillofacial surgery* 2002;60(3):244-250.
36. Cooper S, Erickson AL, Adams EJ, Kansopon J, Weiner AJ, Chien DY *et al.* Analysis of a successful immune response against hepatitis C virus. *Immunity* 1999;10(4):439-449.
37. Kontny E, Wojtecka-Łukasik E, Rell-Bakalarska K, Dziejczopolski W, Maśliński W, Maśliński S. Impaired generation of taurine chloramine by synovial fluid neutrophils of rheumatoid arthritis patients. *Amino Acids* 2002;23(4):415-418.
38. Hamilton JA. Hypothesis: *in vitro* evidence for the invasive and tumor-like properties of the rheumatoid pannus. *The Journal of rheumatology* 1983;10(6):845.
39. Arend WP, Dayer JM. Cytokines and cytokine inhibitors or antagonists in rheumatoid arthritis. *Arthritis and rheumatism* 1990;33(3):305.
40. Fang YZ, Yang S, Wu G. Free radicals, antioxidants, and nutrition. *Nutrition* 2002;18(10):872-879.
41. Goția S, Popovici I, Hermeziu B. Antioxidant enzymes

- levels in children with juvenile rheumatoid arthritis. *Revista Medico-Chirurgicala A Societatii De Medici Si Naturalisti Din Iasi* 2001;105(3):499.
42. Mahdi AA. Free radicals and other antioxidants. A textbook of Biochemistry by SP Singh. CBS publishers and distributors. New Delhi 2002;545:555.
43. Bauerova K, Bezek S. Role of reactive oxygen and nitrogen species in etiopathogenesis of rheumatoid arthritis. *General physiology and biophysics* 2000;18:15-20.
44. Mapp PI, Grootveld MC, Blake DR. Hypoxia, oxidative stress and rheumatoid arthritis. *British medical bulletin* 1995;51(2):419-436.
45. Karatas F, Ozates I, Canatan H, Halifeoglu I, Karatepe M, Colak R. Antioxidant status & lipid peroxidation in patients with rheumatoid arthritis. *Indian Journal of Medical Research* 2003; 118:178-181.
46. Jaswal S, Mehta HC, Sood AK, Kaur J. Antioxidant status in rheumatoid arthritis and role of antioxidant therapy. *Clinica chimica acta* 2003;338(1-2):123-129.
47. McInnes IB, Leung BP, Field M, Wei XQ, Huang FP, Sturrock RD *et al.* Production of nitric oxide in the synovial membrane of rheumatoid and osteoarthritis patients. *Journal of Experimental Medicine* 1996;184(4):1519-1524.
48. McInnes IB, Al-Mughales J, Field M, Leung BP, Huang FP, Dixon R, *et al.* The role of interleukin-15 in T-cell migration and activation in rheumatoid arthritis. *Nature medicine* 1996; 2(2):175-182.
49. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL *et al.* Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *New England Journal of Medicine* 1997;337(3):141-147.
50. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, *et al.* Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Annals of internal medicine* 1999;130(6):478-486.
51. Moreland LW, Heck Jr, LW, Koopman WJ. Biologic agents for treating rheumatoid arthritis. Concepts and progress. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology* 1997;40(3):397-409.
52. Soeken KL, Miller SA, Ernst E. Herbal medicines for the treatment of rheumatoid arthritis: a systematic review. *Rheumatology* 2003;42(5):652-659.
53. Ueki Y, Miyake S, Tominaga Y, Eguchi K. Increased nitric oxide levels in patients with rheumatoid arthritis. *The Journal of rheumatology* 1996;23(2):230.
54. Sharma JN, Srivastava KC, Gan EK. Suppressive effects of eugenol and ginger oil on arthritic rats. *Pharmacology* 1994; 49(5):314-318.
55. Cohen A, Goldman J. Bromelains therapy in rheumatoid arthritis. *Pennsylvania Medical Journal* 1964;1928(67)27.
56. Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, *et al.* Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical Cancer Research* 2001;7(7):1894-1900.
57. Paul BN, Saxena AK. Depletion of tumor necrosis factor- α in mice by *Nyctanthes arbor-tristis*. *Journal of ethnopharmacology* 1997;56(2):153-158.
58. Sirish Kumar IVMLR, Paul BN, Asthana R, Saxena A, Mehrotra S, Rajan G. *Swertia chirayita* Mediated Modulation of Interleukin-1 β Interleukin-6, Interleukin-10, Interferon- γ , and Tumor Necrosis Factor- α in Arthritic Mice. *Immunopharmacology and immunotoxicology* 2003;25(4):573-583.
59. Hosseinzadeh H, Younesi HM. Antinociceptive and anti-inflammatory effects of *Crocus sativus* L. stigma and petal extracts in mice. *BMC pharmacology* 2002;2(1):7.
60. Chamundeeswari D, Vasantha J, Gopalakrishnan S, Sukumar E. Free radical scavenging activity of the alcoholic extract of *Trewia polycarpa* roots in arthritic rats. *Journal of ethnopharmacology* 2003;88(1):51-56.
61. Kim MS, Yi JM, Kim SH, Hong SH, Kim HM. Madimadi, Korean folk medicine, blocks TNF- α , IL-1 β , and IL-8 production by activated human immune cells. *Cytokine* 2004;25(4):179-186.