Introduction

Rheumatoid arthritis is an autoimmune disease of unknown etiology that leads to chronic inflammation in the joints and subsequent destruction of the cartilage and erosion of the bone in the affected joint ***(Pattison et al., 2004).***

In spite of great advances that have been made in the development of medications and other conventional therapies, such as physical therapy treatment for rheumatoid arthritis such therapies remain far from ideal for many patients, leading to a search for other approaches that might improve outcomes ***(Bernatsky et al., 2011).***

Complementary and alternative medicine (CAM) has been defined by the National Center for Complementary and Alternative Medicine as "a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine ***(Oliver and Sliman, 2006).***

Arthritis is one of the foremost diseases for which patients seek CAM therapy ***(Brune, 2004).*** Its use by rheumatoid patients is higher than its use in the general population, ranging between 28% and 90% ***(Soeken et al., 2013)***, although patients often do not volunteer information about CAM use to their physicians. Reports have shown that

more than 70% of patients using CAM modalities never mention these products to their physicians ***(Astin, 2009)***.

Thus, an invisible parallel "mainstream" of alternative care exists in the United States, and little is known by physicians about its prevalence, safety, efficacy, and mechanism of action. Therefore; physicians may think of rheumatoid arthritis (RA) patients who utilize CAM as a uniform group of severely affected patients, with chronic intractable pain, multiple co- morbidities and partial or no response to main stream therapies, who may even have lost faith in traditional medicine. Choice of CAM therapy reflects each individual patient's personal and cultural beliefs and is not necessarily associated with specific demographic or disease characteristics ***(Soeken et al., 2013)***.

CAM treatment has traditionally been thought of as an "alternative" treatment, instead of mainstream treatments- used together with conventional medical treatment- and is often used in chronic diseases as a "last resort"; after all other measures have proved unsuccessful or had unacceptable side effects ***(Zanette Sde et al., 2010)***.

Given the lack of a consistent definition of CAM, some have tried to bring clarity to the situation by proposing classification systems that can be used to organize the field. One of the most widely used classification structures,

developed by (National Center for Complementary and Alternative Medicine (NCCAM), divides CAM modalities into five categories:

Alternative medical systems, mind-body interventions, biologically based treatments, manipulative and body-based methods, and energy therapies.

As the name implies, alternative medical systems is a category that extends beyond a single modality, and refers to an entire system of theory and practice that developed separately from conventional medicine. Examples of these systems include traditional Chinese medicine, ayurvedic medicine, homeopathy, and naturopathy ***(Cutolo et al., 2009).***

The second category in the NCCAM classification scheme is mind-body interventions, which include practices that are based on the human mind, but that have an effect on the human body and physical health, such as meditation, prayer, and mental healing.

The third category, biologically based therapies, includes specialized diets, herbal products, and other natural products such as minerals, hormones, and biologicals. A few of the well-known herbals for which there is evidence of effectiveness include St. John's wort for the treatment of mild to moderate depression and *Ginkgo biloba* for the treatment of mild

cognitive impairment. An example of a nonherbal natural product is fish oil for the treatment of cardiovascular conditions ***(Hufford, 2012).***

The fourth category, manipulative and body-based methods, includes therapies that involve movement or manipulation of the body. Chiropractic is the best known in this category, and chiropractors are licensed to practice in every U.S. state. A defining feature of chiropractic treatment is spinal manipulation, also known as spinal adjustment, to correct spinal joint abnormalities. Massage therapy is another example of a body-based therapy ***(Hufford, 2012).***

The final category described by NCCAM is energy therapies which include the manipulation and application of energy fields to the body. In addition to electromagnetic fields outside of the body, it is hypothesized that energy fields exist within the body. The existence of these biofields has not been experimentally proven; however, a number of therapies include them, such as qi gong, Reiki, and therapeutic touch ***(Hufford, 2012).***

A different approach to classifying CAM modalities is a descriptive taxonomy that groups therapies according to their philosophical and theoretical identities. Practices are divided into two groups. The first group appeals to the general public and has become popularly known as CAM.

This group includes professionalized or distinct medical systems (e.g., chiropratic, acupuncture, homeopathy), popular health reform (e.g., dietary supplement use and specialized diets), New Age healing (e.g., qi gong, Reiki, magnets), psychological interventions, and nonnormative scientific enterprises (conventional therapies used in unconventional ways or unconventional therapies used by conventionally trained medical or scientific professionals). The second group includes practices that are more relevant to specific populations, such as ethnic or religious groups (e.g., Native American traditional medicine, Puerto Rican spiritis, folk medicine, and religious healing) ***(Jonas, 2013).***

Aim of the Study

This study aimed at review the role of complementary and alternative medicine in the treatment of rheumatoid arthritis to detect its efficacy "if any" and to select the beneficial alternative agents for the treatment of rheumatoid arthritis.

Rheumatoid Arthritis

Epidemiology

Rheumatoid arthritis is the most common autoimmune disease that affects the joints. Worldwide, approximately 1% of the population is affected, with higher prevalence in persons of European or Asian ancestry ***(Helmick et al., 2008).***

Rheumatoid arthritis can develop in persons of any age, with the typical age at onset of about 20-40 years. The prevalence of rheumatoid arthritis increases considerably with age, affecting approximately 6% of the white population older than 65 years. In the United States, the lifetime risk of developing rheumatoid arthritis is 3.6% in women and 1.7% in men. There is some indication that the risk of developing rheumatoid arthritis has increased somewhat in recent years, at least in women ***(crowson et al., 2011).***

Predisposing factors:

The cause of RA is still unknown. Multiple environmental factors including hormones, dietary factors, infections and exposure to tobacco smoke as well as gene-environment interactions have been associated with increased risk for rheumatoid arthritis (RA). Importantly, the growing understanding of the prolonged period prior to the first onset of symptoms of RA suggests that these environmental and

genetic factors are likely acting to drive the development of RA-related autoimmunity long before the appearance of the first joint symptoms and clinical findings that are characteristic of RA ***(Firestein et al., 2010).***

The concordance of RA in identical twins is reported as 15% to 30%, suggesting that nongenetic factors have a predominant impact on disease expression (However, the association of HLA-DR with RA is well established. There is an increased relative risk of RA of about 4 to 5% in patients with this allele ***(Stastny et al., 2009).***

Whether shared alleles contribute to disease severity is controversial. More data are needed to establish the precise role of genetic factors ***(Silman et al., 2008).***

Infectious agents have long been suspected as potential triggers of RA. Although investigations have failed to identify any one organism in synovial tissue or fluid, polymerase chain reaction techniques have detected bacterial nucleotide sequences in synovial tissues in RA patients. Viral pathogens are also under study, with the Epstein-Barr virus (EBV) targeted for several reasons. RA patients have been found to have higher levels of virus-infected B cells and higher levels of EBV antibody titers than the general population. In addition, the ability of the virus to activate B

cells to produce RF has generated interest in this virus as a potential trigger ***(Depper et al., 2008).***

Other viruses of interest include parvovirus B19 and the retroviruses, but conclusive data definitely identifying any viral pathogen as a causative agent are lacking. In fact, bacterial and viral antigenic particles may be carried to sites of inflammation by gut-associated macrophages ***(Brandtzaeg et al., 2007).*** Exposure to silica mineral and chronic periodontal disease all increases the risk of developing rheumatoid arthritis. There are theories about different gut bacteria (microbes that inhabit the lining of the bowels) that might trigger the onset of rheumatoid arthritis in genetically susceptible individuals ***(Brandtzaeg et al., 2007).***

Studies have found that people with RA have more GI issues than people who do not have RA. Higher levels of inflammation and impaired immunity due to the disease likely play a significant role.

Another factor is fibromyalgia. About 20-30 percent of people with RA develop fibromyalgia as well. Among fibro's many symptoms are: abdominal pain, bloating and alternating constipation and diarrhea (called irritable bowel syndrome or spastic colon).

Additionally, medications used to treat RA – including nonsteroidal anti-inflammatory drugs (NSAIDs), cortico-steroids and most disease-modifying antirheumatic drugs (DMARDs) – list GI problems as a common side effect ***(Firestein, 2011).***

Upper-GI events (occurring between the mouth and the end of the stomach) include bleeding, GI perforation (a hole in the wall of the stomach), ulcers, obstruction and esophagitis (inflammation, irritation or swelling of the esophagus). Lower-GI events (affecting the large and small intestines) include bleeding, perforation, ulcers, obstruction, diverticulitis (infection or inflammation of the small sacs in the lining of the intestine) and colitis (swelling of the large intestine) ***(Firestein, 2011).***

Pathogenesis:

Rheumatoid factor, an immunoglobulin (Ig) M antiglobulin against the Fc portion of human IgG, is detected in about 70% of patients with RA. Evidence suggests its participation in disease pathogenesis. The presence of RF in RA is associated with extra-articular manifestations of disease, and its absence is generally associated with milder disease. Its proposed mechanisms include enhanced presentation of immune-complexed antigens, cross-linkage and stabilization of low-avidity IgG antibodies, and cryoprecipitation ***(Silman et al., 2010).***RF is not specific for

RA, despite its name, and it may be found in other conditions including bacterial infection, lymphoproliferative disorders, liver disease, and other autoimmune disorders.

Although initiating factors have not yet identified, the presence and activity of a number of proinflammatory chemokines and cytokines have established roles in disease pathogenesis. The activation and infiltration of T cells and macrophages in the synovium result in production of interleukin-1, -2, -6, -8, -10, -17; tumor necrosis factor-α (TNF-α); platelet-derived growth factor; insulin-like growth factor; and transforming growth factor β ***(Kirkham et al., 2011).***These effector molecules are implicated in synovial tissue inflammation and proliferation, cartilage and bone destruction, and systemic effects ***(Sokka et al., 2010).***

B cells also infiltrate the synovium and differentiate into plasma cells, producing polyclonal immunoglobulin and RF. In addition, synovial fibroblasts are activated, releasing collagenases and activating metalloproteinase gene expression, which leads to destruction of matrix tissues. The net result of these activities is pannus formation with articular cartilage invasion, periarticular erosions and osteoporosis, and joint swelling with destruction of periarticular structures. Cigarette smoking increases the risk of developing RA and negatively influences disease course ***(Stolt et al., 2013).***

Arthritis in general and rheumatoid arthritis in particular, is a common cause of disability. More than a third of patients eventually experience work disability because of the disease ***(Allaire et al., 2008).***

Life expectancy is shortened by up to 3 to 5 years, especially in patients with extra-articular disease and those who develop serious treatment-related adverse effects including infections, tumors, and gastrointestinal toxicity from drugs used to treat rheumatoid arthritis ***(Turesson et al., 2012).***

In a radiographic study of 42 patients with early RA, 45% of patients experienced bone erosion of the joints within 4 months after diagnosis. Aside from causing joint damage that result in pain, disability, and work limitation, RA is a systemic disease that can continue to have manifestations even after the joint damage is controlled. A more consideration of the burden of RA must also include the comorbidities, psychosocial deficits, and impairment of health-related quality of life that accompany the extra-articular manifestations of RA ***(Hemminki et al., 2009).***

Systemic comorbidities associated with RA include cardiovascular manifestations, pulmonary manifestations, gastrointestinal manifestations, cancers, and psychiatric manifestations. Cardiovascular manifestations have attracted particular interest, as it appears to be an important source of mortality in RA. The results of a 2008 meta-analysis that

included more than 110,000 patients from 24 observational studies showed that patients with RA have a 50% increased risk of cardiovascular disease compared with the general population. Mortality risks for ischemic heart disease and cerebrovascular accident were increased by 59% and 52%, respectively ***(Stahl et al., 2010).***

RA is also associated with a heavy burden of psychosocial comorbidities, which have received considerably less attention than the other comorbidities. RA is associated with decreased health-related quality of life, increased fatigue and depression, and impaired cognitive function ***(Stahl et al., 2010).***

Considering that the focus in clinical trials of therapies for RA has typically been on joint related symptoms. The ability of currently available therapies for RA to address the psychosocial aspects of RA is unclear ***(Hemminki et al., 2009).***

Early treatment to avoid permanent joint damage is a key for preventing disability and progression of RA. Treatment for RA combines a variety of approaches and is aimed at relieving pain, reducing joint swelling, slowing or preventing joint damage, and improving physical function and well-being. Conventional medicines used for RA include:

Disease-modifying antirheumatic drugs (DMARDs) to slow the progress of the disease. Biological response

modifiers to reduce inflammation and structural damage to the joints. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to reduce inflammation ***(Aletaha et al., 2010).***

The goal of present-day therapy for rheumatoid arthritis is to control the underlying inflammatory disease. Attainment of this goal will alleviate pain, restore patients, quality of life, and ultimately, preserve their independence and ability to perform activities of daily living and vocational, avocational pursuits. Major long-term goals of treatment are to prevent joint destruction and prevent comorbidities of disease and treatment, including heart disease and osteoporosis ***(Smolen et al., 2011).***

The expectations for disease management have become more rigorous as the effects of the disease have become better understood and treatments have improved. Critical to these expectations has been a fundamental change in the mindset of rheumatologists and their patients, who now expect complete abrogation of disease activity and remission or near remission as treatment goals ***(Neogi et al., 2010).***

Remission may not be attainable in all patients; in particular those with established disease that has been refractory to many therapies. There is also uncertainty about the validity of the remission criteria in clinical practice in as

much as they were designed for use in clinical trials ***(O"Dell et al., 2011).***

Consideration of nonpharmacologic principles is crucial, in our opinion, to optimal management of rheumatoid arthritis. Education of patients about the pathophysiological characteristics of the disease, self-management skills, and principles of joint protection lead to improved health and physical function ***(Barsky et al., 2010).***

Role of GIT disorders in pathogenesis of RA:

GI disorders such as constipation (66 percent) or diarrhea (11 percent), possibly indicating an imbalance of intestinal bacteria, beyond the discomfort and disruption of symptoms like nausea and other digestive issues **(Chong and Wang, 2008)**. In particular, dyspepsia, abnormal bowel habits (hard/loose stool), and abdominal bloating have been reported by RA patients. Interestingly, such symptoms are also reported by patients with irritable bowel syndrome, in which they have been associated with an altered profile of intestinal microbiota and unbalanced fecal organic acid levels ***(Coulson et al., 2012).***

Upper-GI events (occurring between the mouth and the end of the stomach) include gum and periodontal diseases, bleeding, GI perforation (a hole in the wall of the stomach),