

Rheumatoid Arthritis
Beneficial Roles of Citrus
Executive Summary
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Arthritis refers to a disease of the joints, which can often result in joint pain, swelling, stiffness or loss of function over time. Some forms of arthritis can be accompanied by problems of muscles, tendons and ligaments surrounding a joint or, more rarely, the skin or internal organs. The two most common types of arthritis are: **osteoarthritis** (this form of arthritis is often called degenerative or wear-and-tear arthritis) and **rheumatoid arthritis (RA)**, a chronic disease, mainly characterized by inflammation of the lining (synovium), which is supposed to protect and lubricate the joints.

Due to the recent interest in the possible benefits of citrus or its components relating to RA, this paper will mainly focus on this type of arthritis. RA can lead to long-term joint damage, resulting in chronic pain, loss of function and disability. Unlike osteoarthritis, rheumatoid arthritis is considered an autoimmune disease, meaning the immune system attacks part of your body. In the case of rheumatoid arthritis, the immune system primarily attacks joint linings. RA is the most common form of inflammatory polyarthritis (IP). IP is inflammation in more than 4 joints (Mayo Clinic Health Letter, 2005).

Rheumatoid arthritis is a debilitating disease that is associated with increased risk of cardiovascular disease and osteoporosis. Some drug therapies prescribed to alleviate RA symptoms may increase the requirement for some nutrients due to their reduced absorption.

There is evidence that some antioxidants obtained from foods, such as the carotenoids β -cryptoxanthin and zeaxanthin, as well as vitamin C, may be protective against the development of rheumatoid arthritis.

Methotrexate, one of the most widely used disease-modifying anti-rheumatic drugs, is a known folate antagonist. Having a folate deficiency may predispose an individual to methotrexate toxicity, which remains an important reason for the discontinuation of MTX.

In addition, there are certain medications used in the treatment of arthritis that reduce potassium levels while retaining sodium.

Citrus juices are good sources of vitamin C, potassium and folate. Orange juice is also a source of β -cryptoxanthin. There is a growing body of evidence that β -cryptoxanthin, as well as vitamin C, may be protective against development of rheumatoid arthritis.

For a more detailed and referenced review of this topic, please continued reading below

Rheumatoid Arthritis
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Literature Review
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1- Introduction:

Arthritis occurs in more than 100 forms with varying signs and symptoms. Generally, arthritis refers to a disease of the joints, which can often result in joint pain, swelling, stiffness or loss of function over time. Some forms of arthritis can be accompanied by problems of muscles, tendons and ligaments surrounding a joint or, more rarely, the skin or internal organs. Common types of arthritis and the population affected by each form of the disease in the U.S are listed below (Mayo Clinic Health Letter, 2005):

- *Osteoarthritis*, affects 21 million people.
- *Rheumatoid arthritis (RA)*, affects 2.1 million people.
- *Gout and pseudogout*, affects 2.1 million people.
- *Inflammatory spine arthritis or Spondyloarthropathies*, affects 380,000 people.
- *Polymyalgia rheumatica*, affects 670,000 people.
- *Systemic lupus erythematosus*, affects 1.4 million people.
- *Infectious arthritis*, 15,000 to 25,000 cases a year.

The two most common types of arthritis are:

- *Osteoarthritis:*

This form of arthritis is often called degenerative or wear-and-tear arthritis. Osteoarthritis usually first appears after age 40 or 50 and develops slowly. Severe trauma to a joint can sometimes cause more rapid development of osteoarthritis. It is caused by the wearing out of a joint through use or overuse. The main signs and symptoms are pain, stiffness and, occasionally swelling in a joint. These typically come on slowly, with periods of relative calm alternating with flare-ups. Osteoarthritis can occur in essentially any joint, but usually affects only a few joints on one or both sides of the body. It commonly occurs in the knees and hips, the fingers, the joint at the base of the thumb, the joint at the base of the big toe, and in the spine. Although it is not known

exactly what causes osteoarthritis, cartilage damage appears to be a key factor. This can be caused by a previous joint injury. Other risk factors include aging, lack of exercise, excessive weight and certain genetic conditions (Mayo Clinic Health Letter, 2005).

- *Rheumatoid arthritis (RA)*

Rheumatoid arthritis is a chronic disease, mainly characterized by inflammation of the lining (synovium), which is supposed to protect and lubricate the joints. Due to the recent interest in the possible benefits of citrus or its components relating to RA, this paper will mainly focus on this type of arthritis. RA can lead to long-term joint damage, resulting in chronic pain, loss of function and disability. It progresses in three stages. The first stage is the swelling of the synovial lining, causing pain, warmth, stiffness, redness and swelling around the joint. Second is the rapid division and growth of cells, or pannus, which causes the synovium to thicken. In the third stage, the inflamed cells release enzymes that may digest bone and cartilage, often causing the involved joint to lose its shape and alignment, more pain, and loss of movement (Arthritis Foundation Website <http://www.arthritis.org>). It usually begins between the ages of 25 and 50, often developing within weeks or months. Unlike osteoarthritis, rheumatoid arthritis is considered an autoimmune disease, meaning the immune system attacks part of your body. In the case of rheumatoid arthritis, the immune system primarily attacks joint linings. The disease can come on suddenly or gradually. In addition to joint discomfort, the individual may also have a general feeling of muscle aching and fatigue. Flare-ups may occur unpredictably. RA is the most common form of inflammatory polyarthritis (IP). IP is inflammation in more than 4 joints (Mayo Clinic Health Letter, 2005).

Rheumatoid arthritis affects women more commonly than men by a ratio of 3:1, although the peak age of onset in women is in the sixties, it can occur at any age. Its course varies considerably from a mild variant to a severe chronic deforming condition. Severe disability or marked functional loss can be a problem even in the early stages of the disease. Young et al. (2000) reported that approximately 10% of patients with RA of less than 2 years duration and prior to any second-line drug treatment had marked functional loss at recruitment.

RA is associated with an increase in mortality from both complications of the disease and its treatment, and also from CVD (cardiovascular disease), with a reported reduced life expectancy of between 3 and 10 years (Pattison et al., 2004).

Cardiovascular disease and RA share very similar inflammatory and immunological responses, with increased production of reactive free oxygen radicals, and proinflammatory cytokines. Products of free radical oxidation have in fact been identified in the synovial fluid of inflamed rheumatoid joints, which supports the theory that inflammation is mediated by free radical activity (Pattison et al., 2004b).

Overall, RA results in enormous personal, social and economic cost to patients and the community (Pattison et al., 2004).

The two most common types of arthritis are shown in Figure 1:

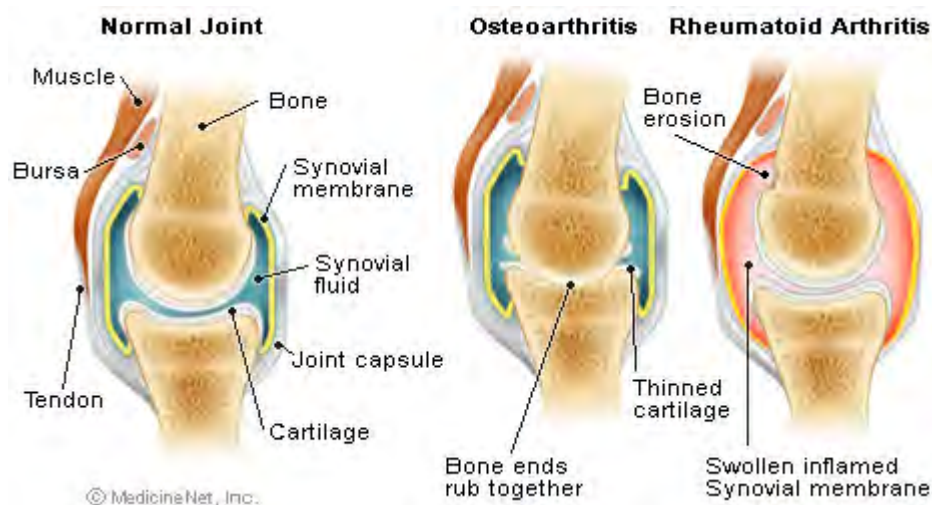


Figure 1 - Normal and arthritic joints
(from: http://www.medicinenet.com/rheumatoid_arthritis/article.htm).

1.1 – Etiology of Rheumatoid Arthritis:

The cause of RA remains uncertain, but genetic factors are known to be involved. Which genetic factors play a part in susceptibility to, rather than the severity of, RA remain controversial. It has been suggested that genetic susceptibility explains $\leq 40\%$ of the risk of developing RA (Silman et al, 1993).

Environmental and non-genetic constitutional factors must therefore account for the main risks. Several putative antigens have been proposed (Table 1), the most likely being an infectious agent, but the evidence is inconclusive. It is likely that there are more than one potential environmental triggers of RA and these factors may interact, resulting in additive effects (e.g. smoking plus infection) (Pattison, et al., 2004).

Table 1 – Main risks of rheumatoid arthritis (Symmons & Harrison, 2000)

Risk
Genetic, human leucocyte-associated antigen DRB 4
Viral infection e.g. Epstein-Barr virus, <i>Proteus</i> , rubella, parvovirus
Immunization, e.g. rubella, tetanus, influenza
Hormonal and reproductive factors, e.g. prolactin production during lactation
Smoking
Previous blood transfusion
Obesity
Stress or physical trauma

1.2 – Mechanism of inflammation:

Inflammation is the body's reaction of invasion by an infectious agent, antigen or physical damage (Cancalon, 2005). Antigen exposure triggers the immune response, resulting in a cascade of cellular activity and an inflammatory response in the end organ.

In rheumatoid arthritis, the immune response is not switched off, the inflammatory response continues in articular tissue, as though in response to a persistent stimulus leading in time to irreversible damage to tendons and joints. Although a greater understanding of the mechanisms of inflammation and tissue destruction in RA has evolved over the past 10 years (Arend, 2001), there is still little understanding as to why inflammation persists.

1.3 – Treatments:

Treatment for arthritis comes in many forms. Although pain-relieving medications are usually the mainstay of arthritis pain relieve, several non-medication techniques may also be helpful. These include application of cold and heat, topical creams, gels or sprays, transcutaneous electrical nerve stimulations (TENS), visco-supplementation, physical and occupational therapies and psychological therapies.

Various drug regiments are likely to be recommended by doctors in order to help reduce pain, and in some cases, reduce inflammation. With rheumatoid arthritis, a group of medications called disease-modifying antirheumatic drugs (DMARDs) are typically used to slow or stop the disease’s progress and to save joints and other tissues from permanent damage.

Other drugs include anti-inflammatories, such as traditional nonsteroidal anti-inflammatory drugs (NSAIDs, i.e. ibuprofen, naproxen, ketoprofen); COX-2 inhibitors (i.e. celecoxib); aspirin and corticosteroid injection into the affected joint.

Two of the better-studied alternative therapies for arthritis are glucosamine and chondroitin sulfate.

Eating a healthy diet can help one control their weight, and feel more energetic and healthy, all factors that may play a role in the degree to which arthritis may affect an individual. However, there is no special “arthritis diet” (Mayo Clinic Health Letter, 2005).

2- Specific role of eating patterns:

“Does diet affect arthritis?” Recently scientific data are emerging that serve to illuminate the dietary link to rheumatic disorders. Because diet is an unavoidable universal exposure for people, even a small effect that can be achieved by dietary manipulation may produce a large impact on the population’s health (Choi, 2005).

Fruit and vegetable consumption has been shown to have an important role in the etiology of other chronic diseases, such as cardiovascular disease and some cancers. As cardiovascular disease shares similar inflammatory and immunologic pathways with those observed in RA, it is reasonable to hypothesize that a higher intake of fruit and vegetables may influence the etiology of inflammatory joint disease (Pattison et al., 2004a).

Pattison et al. (2004a) systematically reviewed studies with comparison groups that examined dietary intake or biological markers prior to the onset of RA. Four electronic databases were searched to identify relevant reports and fourteen reports were included in the review. Higher intakes of fruit, cooked (but not raw) vegetables, and cruciferous vegetables were associated with a lower risk of developing RA in three studies. In two of these studies, β -cryptoxanthin, a carotenoid found in fruits and vegetables, and vitamin C were also found to be protective against developing RA.

Pattison et al. (2004b) also conducted their own prospective, population based, nested case-control study to investigate whether there is an association between the consumption of fruits and vegetables and dietary antioxidants and the risk of developing inflammatory polyarthritis (IP).

The study included men and women aged 45 to 74 years, recruited between 1993 and 1997, through general practice age-sex registers to the Norfolk arm of the European Prospective Investigation of Cancer (EPIC-Norfolk). Dietary intake was assessed at baseline using 7-day diet diaries. Seventy-three participants who developed IP between 1993 and 2001, and were registered by the Norfolk Arthritis Register (NOAR), were identified. Incident cases of IP fulfilled the criteria of two or more swollen joints that persisted for a minimum of 4 weeks. Each case of IP was matched for age and sex with two controls free of IP. Results showed that lower intakes of fruits

and vegetables and vitamin C were associated with an increase risk of developing IP. Those in the lowest category of vitamin C intake, compared with the highest, increased their risk of developing IP more than threefold. For those with an intake of vitamin C below 40 mg/day (UK RNI – UK reference nutrient intake for vitamin C), the risk of developing IP was nearly four times greater than those with intakes above 40 mg/day. There was a significant difference between cases and controls in the dietary intake of vitamin C but not for other antioxidants.

An eight-ounce glass of 100 percent orange juice contains approximately 72 milligrams of vitamin C, and an eight-ounce glass of 100 percent grapefruit juice contains approximately 60 milligrams of vitamin C (<http://www.floridajuice.com>).

Cerhan et al. (2003) investigated the association of vitamin C and E, carotenoids and trace elements from foods and supplements with the risk of rheumatoid arthritis, using a prospective cohort study of 29,368 women who were aged 55 to 65 years at baseline in 1986. Through 1997, 152 cases of rheumatoid arthritis were identified.

There were inverse associations between intakes of vitamin C (total, food and supplemental), vitamin E (total and supplemental), and carotenoids (supplemental only) and risk of rheumatoid arthritis, however, they were statistically non-significant. There was no association between intake of vitamin E or carotenoids obtained from food and risk of rheumatoid arthritis. The authors found that there was a statistically significant inverse association of β -cryptoxanthin intake with rheumatoid arthritis risk that remained virtually unchanged after adjustment for other arthritis risk factors. Compared with women consuming less than 40 $\mu\text{g}/\text{day}$ of β -cryptoxanthin, women consuming 40 to 86.9 $\mu\text{g}/\text{day}$ and women consuming greater than 86.9 $\mu\text{g}/\text{day}$ were at lower risk of developing RA. When supplemental vitamins C and E and β -cryptoxanthin were included in the same model, only β -cryptoxanthin was significantly associated with the risk of RA, while the initially suggestive associations with other variables were attenuated (Cerhan et al., 2003).

Analyses focusing on fruits that provide the major dietary sources of antioxidants showed an inverse association between risk of rheumatoid arthritis and greater intake of fruits. Nonetheless, this association was attenuated after adjustment for other rheumatoid arthritis risk factors.

Table 2 depicts the relative risk of rheumatoid arthritis according to intake of all fruits and selected citrus fruits from the participants in the Iowa Women Health Study (1986-1997). As shown in the afore mentioned table, citrus fruits, an important source of β -cryptoxanthin, showed a weak inverse association with rheumatoid arthritis that was not statistically significant. Of the food items contributing to the citrus fruit category, only consumption of oranges showed a significant inverse association with rheumatoid arthritis (Cerhan et al., 2003).

Table 2 - Relative risk of rheumatoid arthritis according to intake of all fruits and selected citrus fruits, Iowa Women Health Study, 1986-1997.

Fruit (servings per month)	No of cases	Person-years of followup	Model adjusting for age and energy intake			Model also adjusting for other rheumatoid arthritis risk factors*		
			RR†	95% CI†	<i>p</i> -trend	RR	95% CI	<i>p</i> -trend
All fruits								
<52	61	98,306	1.00‡			1.00		
52-83	48	108,149	0.70	0.47, 1.02		0.75	0.50, 1.13	
>83	43	107,726	0.63	0.42, 0.96	0.03	0.72	0.46, 1.12	0.13
Citrus Fruits								
<16	57	99,751	1.00			1.00		
16-32	43	101,941	0.74	0.50, 1.10		0.80	0.53, 1.21	
>32	52	112,489	0.80	0.55, 1.18	0.26	0.84	0.56, 1.27	0.40
Oranges								
0	42	70,669	1.00			1.00		
1-4	67	131,430	0.88	0.59, 1.29		0.96	0.64, 1.45	
>4	43	112,082	0.66	0.43, 1.02	0.06	0.69	0.43, 1.10	0.10
Orange juice								
0	37	72,907	1.00			1.00		
1-12	64	137,822	0.92	0.61, 1.38		1.05	0.68, 1.63	
>12	51	103,452	0.97	0.63, 1.49	0.92	1.11	0.70, 1.77	0.64
Grapefruit								
0	54	117,919	1.00			1.00		
1-3	38	65,398	1.30	0.86, 1.97		1.46	0.94, 2.27	
>3	60	130,864	1.03	0.71, 1.50	0.90	1.12	0.75, 1.66	0.62
Grapefruit juice								
0	126	249,044	1.00			1.00		
>0	26	65,137	0.76	0.50, 1.17	0.21	0.75	0.48, 1.18	0.21

*Adjusted for age, total energy intake, marital status, smoking history, age at menopause, use of hormone replacement therapy, decaffeinated coffee consumption, and tea consumption.

†RR, relative risk; CI, confidence interval.

‡Reference category.

Pattison et al. (2005) investigated the hypotheses that some dietary carotenoids are associated with reduced risk of inflammatory polyarthritis (IP). Specifically, they looked at β -cryptoxanthin, zeaxanthin, lutein, β -carotene, lycopene and whether they were protective against the development of IP. The subjects were participants either of the EPIC-Norfolk or the NOAR studies. Dietary carotenoid intakes were computed from the diet diaries of these subjects. A nested,

case-control analysis was undertaken to compare carotenoid intake between case subjects and age- and sex-matched control subjects. Eighty-eight incident cases of IP that occurred in the population surveyed were ascertained via the Norfolk Arthritis Register. The mean daily intake of zeaxanthin was 20% lower in these cases than in the 176 controls (21.7 μg for cases and 27.2 μg for controls) and β -cryptoxanthin was 40% lower in these cases than in the 176 controls (87.0 μg for cases and 139.9 μg for controls). There were no significant differences in the intakes of either lutein or lycopene. The subjects in the top one-third of intake of zeaxanthin and β -cryptoxanthin were at lower risk of developing IP than the subjects in the lowest one-third. The association with β -cryptoxanthin was significant after adjustments were made for total energy, protein intakes and for cigarette smoking. These data are supported by the findings from the Iowa Women's Health Study of an inverse association between high β -cryptoxanthin intake and RA onset (Cerhan et al., 2003).

The findings from Pattison et al. (2005) add to a growing body of evidence that some dietary antioxidants, such as the carotenoids β -cryptoxanthin and zeaxanthin as well as vitamin C may be protective of the development of IP. On the basis of these findings, supplementation of diets with just one glass (8 oz.) of orange juice per day is sufficient to raise the intake of β -cryptoxanthin to the highest and most protective tertile of intake. Due to the inherent difficulty of a randomized trial and the rarity of the disease, it may be difficult to prove the contribution of diet to the primary prevention of RA. **However, there is perhaps sufficient evidence to suggest a trial to test whether an increase in the consumption of foods that are high in dietary carotenoids and other antioxidant nutrients during early inflammatory joint disease decreases the risk of persistent disease and possibly joint damage.**

The USDA-NCC carotenoid database (1998) states that mean β -cryptoxanthin concentrations varies from 15 (raw orange juice) to 324 (raw orange juice, hybrid varieties) micrograms per 100 grams.

Based on these values an eight-ounce glass of 100 percent orange and/or hybrids juice could provide from 37.5 to 810 micrograms of β -cryptoxanthin.

3- Additional benefits of orange juice consumption and arthritis:

Methotrexate (MTX) has become one of the most widely used disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (Whittle & Hughes, 2004). MTX acts relatively fast, has one of the best efficacies to toxicity ratios and is also low priced. Toxicity, however, remains an important reason for the discontinuation of MTX (van Ede et al., 2001).

Despite extensive research, the precise mechanism of action of MTX is still unknown. MTX, a folic acid antagonist, influences several metabolic pathways, including the homocysteine-methionine pathway. MTX inhibits dihydrofolate reductase, resulting in decreased availability of reduced folates.

van Ede et al. (2001) studied the influence of methotrexate therapy on homocysteine and folate metabolism in patients with rheumatoid arthritis. The study involved 113 patients in a 48-week, multicenter, double blind, placebo-controlled, comparing the efficacy and toxicity of MTX treatment, with and without folic or folinic acid (a one carbon substituted, fully reduced folate) supplementation. Patients were randomized between 3 treatments modalities: MTX plus placebo, MTX plus 1.0 mg/day of folic acid and MTX plus 2.5 mg/week of folinic acid. The initial MTX dose was 7.5 mg/week and was increased to a maximum of 25 mg/week if necessary. The doses of folic and folinic acid were doubled when MTX dose reached 15 mg/week or more. After 48 weeks of MTX therapy, the mean homocysteine level showed an increase in the placebo group (+3.6 $\mu\text{mol/L}$). In contrast, a decrease was observed in the groups supplemented with folic or folinic acid (folic acid, -2.7 $\mu\text{mol/L}$; folinic acid, -1.6 $\mu\text{mol/L}$). The differences in the changes in plasma homocysteine level between the placebo group and each of the two folate-supplemented groups were statistically significant ($P < 0.0001$). The researchers concluded that MTX treatment leads to hyperhomocysteinemia that can be prevented by supplementation with folic acid or folinic acid.

A Cochrane review of seven trials reported the effects of folic and folinic acid in reducing mucosal and gastrointestinal side effects of low-dose MTX in patients with RA. A total of 147 patients received folate supplementation in the seven studies (80 with folinic acid and 67 with folic

acid), with folic acid, a 79% reduction in mucosal and gastrointestinal side effects was observed. For folinic acid a reduction of 43% was reported. The reviewers concluded that the results support the protective effect of low doses of folic acid supplementation (< 5 mg/week) in patients having RA treated with MTX. This exceeds the current recommended nutrient intake for folate (2.8 mg/week) and supplementation may be warranted in patients treated with MTX (Rennie et al., 2003).

An eight-ounce glass of 100 percent orange juice contains approximately 69 micrograms of folate. An eight-ounce glass of 100 percent grapefruit juice contains approximately 24 micrograms of folate (<http://www.floridajuice.com>).

Iron deficiency anemia that may develop as a result of chronic inflammation, gastrointestinal blood loss caused by RA medications, preferential uptake of iron by inflamed synovial tissue, as well as, poor dietary intake, is another health concern in RA patients (Rennie et al., 2003).

Ascorbic acid (vitamin C) is an enhancer of nonheme-iron absorption, increasing the absorption of native food iron and of iron fortificants, which dissolve in the gastric juice and enter the common iron pool (Hurrell, 2002). The enhancing effect appears to be due to both the reducing power and the chelating action of ascorbic acid (Conrad & Schade, 1968). Ascorbic acid has been shown to, at least partially, overcome the negative effect of all inhibitors of iron absorption, as recently reviewed by Hurrell (2002).

An eight-ounce glass of 100 percent orange juice contains approximately 72 milligrams of vitamin C, and an eight-ounce glass of 100 percent grapefruit juice contains approximately 60 milligrams of vitamin C (<http://www.floridajuice.com>).

According to the Arthritis Foundation Website (<http://www.arthritis.org>), certain medications used to treat arthritis (like glucocorticoids) can cause the body to lose potassium and retain sodium. Potassium is an important ion within the living cell, affecting almost every cellular function, and is also sodium's counter ion (Meneton et al., 2005).

An eight-ounce glass of 100 percent orange juice contains approximately 450 milligrams of potassium. An eight-ounce glass of 100 percent grapefruit juice contains approximately 300 milligrams of potassium (<http://www.floridajuce.com>).

4- CONCLUSIONS:

Rheumatoid arthritis is a debilitating disease that is associated with increased risk of cardiovascular disease and osteoporosis. Some drug therapies prescribed to alleviate RA symptoms may increase the requirement for some nutrients due to their reduced absorption.

A search of the literature on the subject of citrus and arthritis did not provide a substantial amount of information on the subject. However, there is a growing body of evidence that some dietary antioxidants, such as the carotenoids β -cryptoxanthin and zeaxanthin, as well as vitamin C, may be protective against the development of rheumatoid arthritis.

Methotrexate, one of the most widely used disease-modifying anti-rheumatic drugs, is a known folate antagonist. Having a folate deficiency may predispose an individual to methotrexate toxicity, which remains an important reason for the discontinuation of MTX.

In addition, there are certain medications used in the treatment of arthritis that reduce potassium levels while retaining sodium.

Florida citrus juices are good sources of vitamin C, potassium and folate. Orange juice is also a source of β -cryptoxanthin. There is a growing body of evidence that β -cryptoxanthin, as well as vitamin C, may be protective against development of rheumatoid arthritis.

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