**Complementary and alternative medicine use in rheumatoid arthritis: Considerations for the pharmacological management of elderly patients**

Running title: Complementary and alternative medicine in rheumatoid arthritis

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**Abstract**

Complementary and alternative medicines (CAM) are widely used by patients with rheumatoid arthritis (RA). A significant proportion of them do not inform their physicians. This has many potential implications in a group of predominantly elderly patients with altered pharmacokinetics, comorbidities and polypharmacy of potentially toxic drugs. CAM usage may affect compliance and pharmacokinetics of conventional therapy for RA and comorbidities. Physicians should engage patients in dialogues regarding CAM usage. This review introduces common CAMs used by RA patients, such as herbal remedies, supplements, fish and plant oils, and their potential impact on conventional therapy. Efficacy of these treatments are not reviewed but references for reviews and trials are provided for further reading. Fish oils and vitamin D supplementation may generally be recommended while thunder god vine should be avoided. Patients should also be made aware of the risks of contamination and adulteration of less reputable sources of CAM, and directed to evidence-based sources of information. Physicians should acknowledge the limitations of scientific evidence and not be prejudiced or dogmatic. However they should remain resolute against therapies that are known to be ineffective or unsafe.

**Key points:**

* Complementary and alternative medicines are increasingly popular among patients with rheumatoid arthritis.
* Physicians should be well informed and comfortable in discussing and advising CAM with patients. Common CAM therapies are covered in this review.
* Elderly patients often take multiple pharmaceuticals for comorbidities and are therefore at risk of side-effects and interactions when using CAM in addition.
1. **Introduction**

Complementary and alternative medicines (CAM) include diverse medical practices and products that are not currently considered to be part of conventional medicine [[1](#_ENREF_1)]. CAM users are more often female and suffering from chronic conditions [[2](#_ENREF_2)]. Moreover, patients with pain-associated or mobility-limiting conditions were more likely to seek CAM [[3](#_ENREF_3)]. It is therefore unsurprising that CAM is widely used in rheumatic diseases. The lifetime prevalence of CAM usage among those with arthritis in England is 38% [[4](#_ENREF_4)]. In the US, up to 94% of patients with rheumatic diseases use CAM at significant health expenditure [[5](#_ENREF_5)].

Rheumatoid arthritis (RA) is one of the most common rheumatic diseases affecting up to 1% of the population [[6](#_ENREF_6)]. It is a chronic, systemic, auto-inflammatory condition which predominantly affects the joints, leading directly to disability, and also indirectly through associated comorbidities [[7](#_ENREF_7)]. The management of RA has continued to improve globally, where early use of conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) have dramatically improved patient outcomes. However a sizeable proportion of patients do not respond adequately to treatment [[8](#_ENREF_8), [9](#_ENREF_9)]. In addition, these powerful drugs are often associated with unpleasant side-effects and occasionally serious adverse events [[8](#_ENREF_8)]. Furthermore, the high cost of biologic drugs has implications for their accessibility [[10](#_ENREF_10)]. For these and many other reasons, RA patients are increasingly seeking CAM, which are often (mis)perceived as “natural” and safe with fewer side-effects [[11](#_ENREF_11)].

Half of CAM users with rheumatic diseases do not inform their physicians. Most commonly cited reasons by patients were that they were not asked or that they forgot to tell the physician, and rarely due to fear of disapproval [[12](#_ENREF_12), [13](#_ENREF_13)]. Patients primarily rely on their social network for information on CAM, and are willing to try therapies without support of scientific evidence or their physicians’ approval [[13](#_ENREF_13)]. This has many potentially important consequences in RA patients who often have multiple comorbidities, polypharmacy of potentially toxic drugs, and altered pharmacokinetics as a result of increased age. It is therefore important for physicians to be aware of commonly available CAM therapies. The gold-standard scientific method of randomized clinical trials for CAM is often limited by unstandardized ingredients and research design. In the age of greater patient awareness, physicians should not be overly dogmatic but still be firm against CAMs that are known to be unsafe or ineffective.

This review aims to inform the reader of commonly use CAM treatments among RA patients. It will focus particularly on the pharmacological implications in the elderly. This review does not intend to review literature on the efficacy of CAM treatments, but does provide suggestions for further reading.

1. **Types of CAM therapies used in rheumatoid arthritis**

This section will focus on common complementary and alternative *per os* pharmacological therapies. Table 1 offers some suggested references for further reading on efficacy. Surveys of patients with arthritis showed that these patients most commonly used ingestible CAMs [[14](#_ENREF_14)]. However, it is also important to be well informed of the many non-pharmacological modalities which are mentioned briefly at the end with references for further reading.

2.1 Fish and plant oils

Fish oils are perhaps the most commonly used CAM in RA with 19% of patients reporting its use [[15](#_ENREF_15)]. Oils are extracted from either whole fish (eg. herring, sardines, mackerel) or fish liver (eg. cod). They are rich in long-chain, omega-3 (n-3) polyunsaturated fatty acids (PUFA), mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [[16](#_ENREF_16)]. Fish oils are also rich in vitamin D which is discussed separately under the supplements section.

Fish oils have been shown to improve the number of tender joints and morning stiffness in RA [[17](#_ENREF_17)] and may have non-steroidal anti-inflammatory drug (NSAID) sparing effects [[18](#_ENREF_18)]. RA is associated with increased cardiovascular mortality, and increased prevalence of cardiovascular risk factors such as dyslipidemia [[19](#_ENREF_19)]. Oils rich in n-3 have been shown to reduce cardiovascular risk factors in RA [[20](#_ENREF_20)]. Fish oils, and a diet rich in oily fish, should therefore be positively recommended in the management of RA for its many potential benefits. Side-effects are uncommon and usually minor. The most common include fishy odor and gastrointestinal disturbances such as flatulence and diarrhea [[20](#_ENREF_20)].

The New Zealand green-lipped mussel (*Perna canaliculus*) is also sometimes used by RA patients and is thought to exert its beneficial effects through n-3 PUFA content [[21](#_ENREF_21)].

Western diets tend to be rich in omega-6 (n-6) PUFA but lacking in n-3 [[20](#_ENREF_20)]. Both n-3 and n-6 are essential fatty acids and cannot be synthesized by the body or interconverted. n-6 PUFA are converted to arachidonic acid (AA), which is metabolized by cyclooxygenase (COX) to inflammatory eicosanoids such as prostaglandin 2-series and leukotriene 4-series. EPA are metabolized to less inflammatory eicosanoids, and are thought to be competitive substrates for COX (figure 1). n-3 PUFA also form anti-inflammatory mediators such as resolvins and protectins [[16](#_ENREF_16), [22](#_ENREF_22)]. An increase in the n-3 to n-6 ratio is therefore thought to have an anti-inflammatory effect.

Several plant seed oils also contain various concentrations of n-3 and/or n-6 PUFAs. Flaxseed (also known as linseed) oil, of the plant *Linum usitatissimum*, is a source of alpha-linolenic acid (ALA) and is a popular vegan source of n-3 [[23](#_ENREF_23)]. This short-chain n-3 PUFA is converted into long-chain EPA/DHA. However studies showed that it did not increase EPA/DHA levels or have significant benefits in RA [[23](#_ENREF_23)]. Patients taking flaxseed oils may therefore benefit from fish oils instead. Flaxseed oil also contains lignans, which have additional anti-inflammatory properties [[24](#_ENREF_24)].

Oils produced from blackcurrant seed (*Ribes nigrum*) borage seed (*Borago officinalis*) and evening primrose (*Oenothera biennis*) contain high levels of the n-6 PUFAs, gamma-linolenic acid (GLA) and linolenic acid (which is converted to GLA) [[25-27](#_ENREF_25)]. GLA is converted to dihomo-GLA (DGLA) which is then converted to less inflammatory prostaglandin 1-series. DGLA is also thought to inhibit conversion of AA (figure 1). Studies have demonstrated some benefit of GLA in RA, especially for pain and disability [[28](#_ENREF_28)]. GLA are also converted to prostaglandin 1-series which are thought to be anti-inflammatory [[29](#_ENREF_29)]. These seed oils are also well tolerated with minor gastrointestinal side-effects as with fish oils [[28](#_ENREF_28)].

2.2 Herbs and traditional Chinese medicine

Traditional Chinese medicine (TCM) has evolved over thousands of years and encompasses many practices including herbal mixtures (sometimes combined with non-botanical substances) and acupuncture. The theory of TCM is based around five solid organs and six hollow viscera that are connected by conduits and vessels with 'qi' (energy) [[30](#_ENREF_30)]. Of the CAM therapies used in rheumatic diseases, most were TCM [[12](#_ENREF_12)]. Examples of popular ingredients used in TCM and herbs across the world that have emerged for use in RA are reviewed below.

Thunder god vine or 'Lei Gong Teng' (*Tripterygium wilfordii* Hook F*)* is a perennial vine native to China. It has been used for inflammatory swelling In TCM [[28](#_ENREF_28)]. Extracts are prepared from skinned root of the vine, while other parts of the plant are poisonous. The active ingredient is unclear. Diterpenoids such as triptolide have demonstrated immunosuppressive and anti-inflammatory properties [[31](#_ENREF_31)]. Review of four studies in RA showed improvements in some outcomes [[28](#_ENREF_28)]. It is however important to note that thunder god vine has been associated with serious adverse events such as aplastic anemia and respiratory tract infections [[32](#_ENREF_32)]. Side-effects are not uncommon with nausea, diarrhea, hair loss, amenorrhea and rash [[32](#_ENREF_32)]. Given the unfavorable risk-benefit profile, thunder god vine should not be recommended for use in RA. Indeed, several agencies have issued warnings against its use [[33](#_ENREF_33)].

*Uncaria tomentosa* and *U. guianensis* are species of vine that have a long Peruvian tradition as a remedy for rheumatic diseases. Because of their curved thorns it is also known as cat’s claw. The active chemical is thought to be pentacyclic oxindole alkaloids, but they also contain other antioxidants. Extracts have immunomodulatory properties *in vitro* and some benefit in RA when used with other DMARDs [[34](#_ENREF_34)]. It is generally well tolerated with some minor gastrointestinal side-effects and high quality extracts are relatively safe.

Rose hip is made from the fruits of a species of wild rose (*Rosa canina*). It is reportedly rich in antioxidants such as polyphenols and vitamin C, and also a galactolipid similar to GLA [[35](#_ENREF_35)]. Free radicals from oxidation are produced by, and can further amplify, the inflammatory processes [[36](#_ENREF_36)]. Rose hip has been shown to improve measures of disease activity [[35](#_ENREF_35)]. Side-effects are mild and uncommon.

*Andrographis paniculata* is a shrub used in TCM for a variety of conditions. Andrographolide is thought to be the main active ingredient with anti-inflammatory properties *in vitro*. In RA it has demonstrated some beneficial effects with rare side-effects such as pruritus [[37](#_ENREF_37)].

Ginger, the rhizome of *Zingiber officinale,* is a common dietary constituent worldwide and is claimed to possess antioxidant and anti-inflammatory properties. In TCM, ginger has been used for thousands of years to treat inflammatory diseases. The major constituents of ginger include gingerol, linoleic acid and salicylates (see willow bark below). Extracts have been reported to reduce pain in osteoarthritis [[38](#_ENREF_38)], but only poor evidence is available in RA [[39](#_ENREF_39)]. Turmeric is the rhizome of another plant (*Curcuma domestica*) belonging to the ginger family. It is a widely used dietary pigment and spice. The main constituent is curcumin, which has reported anti-inflammatory and analgesic properties in osteoarthritis [[40](#_ENREF_40)]. It was trialed with an NSAID in RA and therefore does not have substantial evidence [[41](#_ENREF_41)]. Both are safe for consumption with rare and mild side-effects.

Willow trees (*Salix* species) were the origin from which aspirin was developed. Its medicinal properties have been known for centuries. The active ingredient, salicin, are metabolised to salicylic acid *in vivo* and has been claimed to have anti-inflammatory and analgesic properties similar to aspirin [[42](#_ENREF_42)]. However therapeutic doses of willow bark extracts do not sufficiently raise serum salicylate levels to explain the alleged analgesic effects and had no significant effects in RA [[43](#_ENREF_43)]. It is difficult to justify willow bark when aspirin is not a preferred NSAID in RA and when modern COX inhibitors have proven efficacy.

2.3 Supplements

Glucosamine is an amino sugar found naturally in the body. It is a precursor for many components of cartilage, and has been widely studied and used in osteoarthritis [[44](#_ENREF_44)]. It is available as glucosamine sulphate and glucosamine hydrochloride. Glucosamine sulphate has been shown, in animal models, to repair damaged cartilage and reduce inflammation. Trials of some glucosamine preparations in OA do show modest benefits [[44](#_ENREF_44)]. In RA, however, glucosamine has no effect on disease activity but may improve pain [[45](#_ENREF_45), [46](#_ENREF_46)]. Side-effects are rare and mild.

Vitamins are essential for health and should be promoted through a balanced diet. Vitamin D is however predominantly produced via ultraviolet exposure and consequently deficiency is common in Northern countries such as the UK. Vitamin D is important for calcium and bone metabolism, which is relevant in RA as it is associated with osteoporosis, falls, and fractures [[47](#_ENREF_47)]. Vitamin D deficiency should therefore be identified and treated by physicians using licensed preparations in sufficient doses. It is important to note that supplementary doses are unlikely to be sufficient to treat deficiency. In addition to its role in bone metabolism, immunomodulating properties of vitamin D have gained much attention in recent years. Vitamin D intake and levels have been associated with RA incidence and activity, however trials have not found significant benefits [[48](#_ENREF_48)]. Vitamin D can rarely cause hypercalcemia, especially in those with subclinical hyperparathyroidism [[49](#_ENREF_49)].

Vitamin B6 are enzyme cofactors and important regulators of protein metabolism. Total B6 includes pyridoxine (which occurs in plants), pyridoxal and pyridoxamine (in animal tissues). They are converted to pyridoxal-5-phosphate (PLP) which is the metabolically active form. Many studies have demonstrated lower B6 levels in RA compared to healthy controls. Levels have also been associated with increased cytokine production, such as tumor necrosis factor (TNF) [[50](#_ENREF_50), [51](#_ENREF_51)]. Impaired vitamin B6 status could be a result of inflammation, and these patients may have higher demand for vitamin B6. Trials of high-dose B6 have reported improvements in inflammatory profiles but not disease activity [[52](#_ENREF_52)]. Low-dose had no appreciable effect [[51](#_ENREF_51)]. Tolerance to supplementation is good, but over-dosing is associated with adverse effects [[53](#_ENREF_53)].

Free radicals are intimately associated with the inflammatory process and consequent damage. Antioxidants, such as vitamins C, E and selenium, have been used in many inflammatory conditions including RA. Vitamin E is group of compounds that can be found in plant oils such as sunflower and corn oil. It is the most investigated antioxidant in RA where some studies have reported reduction in pain. However most trials have been poor quality [[54](#_ENREF_54)]. Vitamin C acts as an antioxidant as well as a cofactor for several enzymatic processes, including collagen synthesis. It was reported to reduce pain in one study of osteoarthritis but no evidence exists for RA [[54](#_ENREF_54)]. Selenium is an essential trace element nutrient. It is a cofactor of antioxidant enzymes such as glutathione peroxidase. Selenium levels have been found to be reduced in RA patients compared to healthy controls. However supplementation trials have not demonstrated efficacy [[54](#_ENREF_54)]. Selenium is toxic in large doses but is otherwise well tolerated.

2.3 Diets and other CAM therapies

There are many other CAM therapies used by RA patients, predominantly used to reduce pain. They include acupuncture and electro-acupuncture [[55](#_ENREF_55)], laser therapy [[56](#_ENREF_56)], electrical stimulation [[57](#_ENREF_57)], mind-body techniques [[58](#_ENREF_58)], and massage therapies [[59](#_ENREF_59)]. Many variations of physical exercise should be generally encouraged.

Homeopathy uses ingredients which, when given in high concentrations, produce symptoms similar to the ailment. These ingredients undergo repeated serial dilution until no or few molecules of the starting substance could be present. The claim is that medicinal properties are imprinted into water and retained [[60](#_ENREF_60)]. Such mechanisms are difficult to fit into traditional scientific understanding. Homeopathic effects and side-effects are negligible [[60](#_ENREF_60)].

One important non-pharmacological CAM with relevance to conventional RA therapy is dietary modification. Common regimes include fasting, vegetarian-type and Mediterranean diets [[61](#_ENREF_61)]. In general, these diets are rich in antioxidants and lower in saturated fats. For example, the Mediterranean diet is high in fruit, vegetables, fish and olive oils and low in red meat. Trials have demonstrated some benefits with regard to pain, but not other aspects of disease activity. It is important to note the significant attrition rates in these studies. These diets were also associated with significant weight loss [[61](#_ENREF_61)]. While many components of these regimes should be promoted as part of a balanced diet, strict dietary alterations are often difficult to adhere to. Furthermore, they may have implications on nutrition needs, and conventional treatment which will be discussed below.

1. **Pharmacological considerations in elderly patients**

RA is predominantly a disease of the elderly, with approximately one-third of patients experiencing first symptoms after the age of 60 years [[62](#_ENREF_62)]. With increasing age comes altered pharmacokinetics, increased number of comorbidities and associated polypharmacy [[63](#_ENREF_63)]. These are important considerations for conventional RA therapy. Prevalence of CAM usage also increases with age [[64](#_ENREF_64)]. Furthermore, studies have demonstrated associations between CAM use and increasing number of comorbidities [[2](#_ENREF_2)]. It is therefore essential that physicians engage in dialogues with patients regarding use of CAM, and to consider effects on conventional therapy. This is especially relevant in RA patients who use potentially toxic drugs and often have multiple comorbidities.

3.1 Altered pharmacokinetics

Many physiological changes of aging have important effects on pharmacokinetics [[63](#_ENREF_63)]. Absorption is reduced due to changes in gastric pH, motility and blood flow. Sudden or sporadic dietary alterations such as fasting or changing to low-fat diets may further affect absorption of conventional RA therapies.

Age-related alterations in hepatic metabolism and decline in glomerular filtration rate markedly reduce drug clearance. Several specific considerations for aging and pharmacokinetics of DMARDs are reviewed in detail in [[62](#_ENREF_62)]. The recurring theme is that reduced renal function increases risk of toxicity in the elderly. For example, discontinuation of therapy due to toxicity rather than lack of efficacy is a major issue with the cornerstone DMARD, methotrexate [[65](#_ENREF_65)].

Active ingredients and therapeutic doses of CAM are often uncertain. This not only hampers study of their efficacy, but also limits understanding of their pharmacokinetic and pharmacodynamics. CAM treatments described above are not reported to have specific effects on pharmacokinetics of conventional treatments. Most documented serious adverse events, such as liver and renal failure, have been attributed to contaminants and impurities in herbal CAM [[66](#_ENREF_66), [67](#_ENREF_67)]. These events are sporadic and unpredictable, and none are specific to CAM used in RA. Nevertheless contaminants, adulteration and misidentification remain serious concerns across the herbal CAM industry. Patients should always be advised to avoid obtaining herbal CAM from unregulated sources. Even better regulated CAM, for example fish oils, can be contaminated with environmental chemicals such as methylmercury and polychlorinated biphenyls (PCBs) [[68](#_ENREF_68)].

3.2 Polypharmacy and comorbidity

There is a well-established relationship between adverse drug reactions and increasing age, which has been suggested to be a marker for polypharmacy and comorbidities [[63](#_ENREF_63)].

The extent of polypharmacy is proportionately associated with reduced compliance with medication. This is of particular concern when adherence to conventional RA therapy is already low [[69](#_ENREF_69)]. Many DMARDs cause gastro-intestinal side-effects [[62](#_ENREF_62)] as do CAM treatments [[70](#_ENREF_70)]. Patients may choose to take CAM in preference and instead of DMARDs, or misattribute side-effects to, and therefore stop, DMARDs. It should be highlighted to patients the importance of taking conventional over CAM therapy.

The commonest comorbidity in RA is reported to be depression [[71](#_ENREF_71)]. While there are no notable interactions between CAM therapies discussed above and antidepressants, it is worth noting a herbal CAM often used for depression, St John’s wort. St John’s wort (*Hypericum perforatum*) affects the metabolism of up to half of all prescription drugs [[72](#_ENREF_72)]. It is known to decrease activity of ciclosporin, and may have interactions with methotrexate [[73](#_ENREF_73), [74](#_ENREF_74)]. Depression in RA has significant impact on quality of life and should be identified and treated with conventional antidepressants.

The next most common group of comorbidities is cardiovascular diseases, such as myocardial infarction and stroke [[71](#_ENREF_71)]. Several CAM treatments have proven or potential effects on coagulation and blood pressure. Fish oils have anticoagulant properties, possibly through prostaglandin alteration, platelet aggregation or vitamin K metabolism. It has been shown to increase international normalizing ratio (INR) when taken with warfarin [[75](#_ENREF_75)]. A theoretical risk also exists for omega-6 oils. Patients on warfarin should therefore be advised to monitor their clotting or avoid high-dose PUFA altogether. Glucosamine [[76](#_ENREF_76)] and ginger [[77](#_ENREF_77)] have also been reported to increase INR. Andrographis paniculata may interact with anticoagulants [[78](#_ENREF_78)] and anti-hypertensives [[79](#_ENREF_79)]. These warnings are particularly pertinent to patients taking leflunomide, which has well documented interactions with warfarin and effects on blood pressure [[80](#_ENREF_80)].

Insulin resistance is a common cardiovascular risk factor in RA and is exacerbated by steroid therapy [[71](#_ENREF_71)]. Glucosamine has been reported to affect glycemic control and should be avoided in those with poorly controlled diabetes [[81](#_ENREF_81)].

The effect of age on the risk of gastrointestinal hemorrhage or perforation is well documented [[82](#_ENREF_82)]. Many conventional therapies used by RA patients (bisphosphonates, NSAIDs, steroids and maybe IL6 inhibition) further increase these risks. Dietary modifications, particularly those involving fasting, may contribute additional risk; indeed bisphosphonates are advised to be taken with food.

Restrictive diets and fasting may have other implications. Rheumatoid cachexia is the loss of body cell mass despite normal nutritional intake, predominantly in skeletal muscle [[83](#_ENREF_83)]. Abnormal protein metabolism is implicated. Diets with reduced protein content may theoretically exacerbate catabolism. In addition, fasting has been demonstrated to cause decline in B6 levels in animal models. Lastly, vegetarian-type diets may also be lacking in vitamin D, although this does not appear to impact risk of osteoporosis and fractures [[84](#_ENREF_84)].

Epilepsy is not a specific comorbidity in RA. Nevertheless there have been concerns that evening primrose oil may lower seizure threshold [[85](#_ENREF_85)]. This has been contested. However given the limited benefit of this CAM, patients with poorly controlled epilepsy should avoid it and other sources of LA and GLA. This may be of particular relevance in those taking hydroxychloroquine, which has some evidence of reducing seizure threshold [[80](#_ENREF_80)]. Epileptics are also an often forgotten high-risk group for vitamin D deficiency and should be screened [[86](#_ENREF_86)].

Biologic DMARDs are large molecule protein based drugs. Many of these are monoclonal antibodies (mAb). Their pharmacokinetics are different to small molecules drugs in that renal and biliary elimination play a much smaller role. Biologics instead undergo fluid-phase or receptor-mediated intracellular catabolism [[87](#_ENREF_87)]. Therefore interactions with small molecule drugs or CAM are much less likely. The impact of CAM on adherence to synthetic DMARDs, however, may affect concomitant biologics. It is thought that synthetic DMARDs reduce formation of anti-drug antibodies, which can potentially neutralize mAb. Tocilizumab is an anti-interleukin-6 receptor antibody used in RA. Since up-regulation of IL-6 reduces the activity of cytochrome P450 (CYP) enzymes, Tocilizumab may reverse it [[88](#_ENREF_88)]. This may be of particular relevance in polypharmacy of other CYP inducers (such as St John’s wort) or inhibitors.

**4. Conclusions**

CAM usage is highly prevalent among RA patients and will likely increase. Many patients will often not volunteer CAM usage and therefore physicians need to make systematic enquiry in consultations. This should be of additional priority in elderly patients with comorbidities. Studies have repeatedly demonstrated that patients wish for improved dialogue [[13](#_ENREF_13)]. Physicians should be well informed and comfortable in discussing common CAM therapies, particularly with regard to their effects, side-effects and potential interactions with conventional RA therapies. Evidence-based educational material on CAMs should be made accessible to patients. However emphasis should be made on adherence to DMARDs. This review has explored common modalities and provided references for further reading on their evidence. Omega oils and vitamin D can be generally recommended whilst thunder god vine should be avoided. Physicians should acknowledge the limitations of scientific evidence and not be prejudiced or dogmatic. However they must remain firm when advising against therapies that are known to be ineffective or unsafe. Regulation of CAM and their advertising are lacking in many countries, while we await governmental intervention, patients should be advised against obtaining CAM from unreputable sources. Patients can be directed to evidence-based sources of information such as those provided by Arthritis Research UK or National Center For Complementary and Integrative Health [[89](#_ENREF_89), [90](#_ENREF_90)].

**Compliance with Ethical Standards**

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**Omega-3 (n-3) PUFA**

Alpha-linolenic acid (ALA)

Eicosapentaenoic acid (EPA)

Prostaglandin 3-series

Leukotriene 5 series

Docosahexaenoic acid (DHA)

**Omega-6 (n-6) PUFA**

Linoleic acid (LA)

Gamma-linoleic acid (GLA)

Prostaglandin 2-series

Leukotriene 4 series

Arachidonic acid (AA)

Cyclooxygenase (COX) and Lipoxygenase

Prostaglandin 1-series

Dihomo-gamma-linolenic acid (DGLA)

Figure 1. Metabolism of omega-3 and -6 polyunsaturated fatty acids (PUFAs). ALA (from flaxseed) is metabolized into EPA (fish oils) which, via COX and lipoxygenases, are converted to less inflammatory eicosanoids, PG 3-series and LT 5-series. GLA (borage, evening primrose, blackcurrant seed oils) can be converted both to AA and DGLA. AA is metabolized into pro-inflammatory eicosanoids, while DGLA converts into PG 1-series which is anti-inflammatory. DGLA also inhibits conversion of AA into its pro-inflammatory eicosanoids, PG 2-series and LT 4-series. PG, prostaglandin; LT, leukotriene.

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| Table 1. Recommended reading on clinical trials of different CAM. Where available, reviews and meta-analyses are provided instead of individual trials. |
| Fish and plant oils | Fish oils [[17](#_ENREF_17), [18](#_ENREF_18), [20](#_ENREF_20), [91](#_ENREF_91)] Cochrane review pendingGreen lipped mussel [[21](#_ENREF_21)]General GLA [[26](#_ENREF_26), [28](#_ENREF_28), [92](#_ENREF_92)]Black currant [[27](#_ENREF_27), [93](#_ENREF_93)] Evening primrose [[25](#_ENREF_25), [94](#_ENREF_94)]Flaxseed [[23](#_ENREF_23)] |
| Herbs and traditional Chinese medicine | Thunder god vine [[28](#_ENREF_28), [32](#_ENREF_32)]*Uncaria tomentosa*/cat’s claw [[34](#_ENREF_34)]Rosehip [[35](#_ENREF_35)]*Andrographis paniculata* [[37](#_ENREF_37)]Willow bark [[43](#_ENREF_43)] |
| Supplements and Diet regimes | Vitamin E and selenium [[54](#_ENREF_54)]Glucosamine [[45](#_ENREF_45), [46](#_ENREF_46)]Diet [[61](#_ENREF_61)] |
| General overviews | For physicians [[4](#_ENREF_4), [70](#_ENREF_70), [95](#_ENREF_95)]For patients [[89](#_ENREF_89), [90](#_ENREF_90)] |