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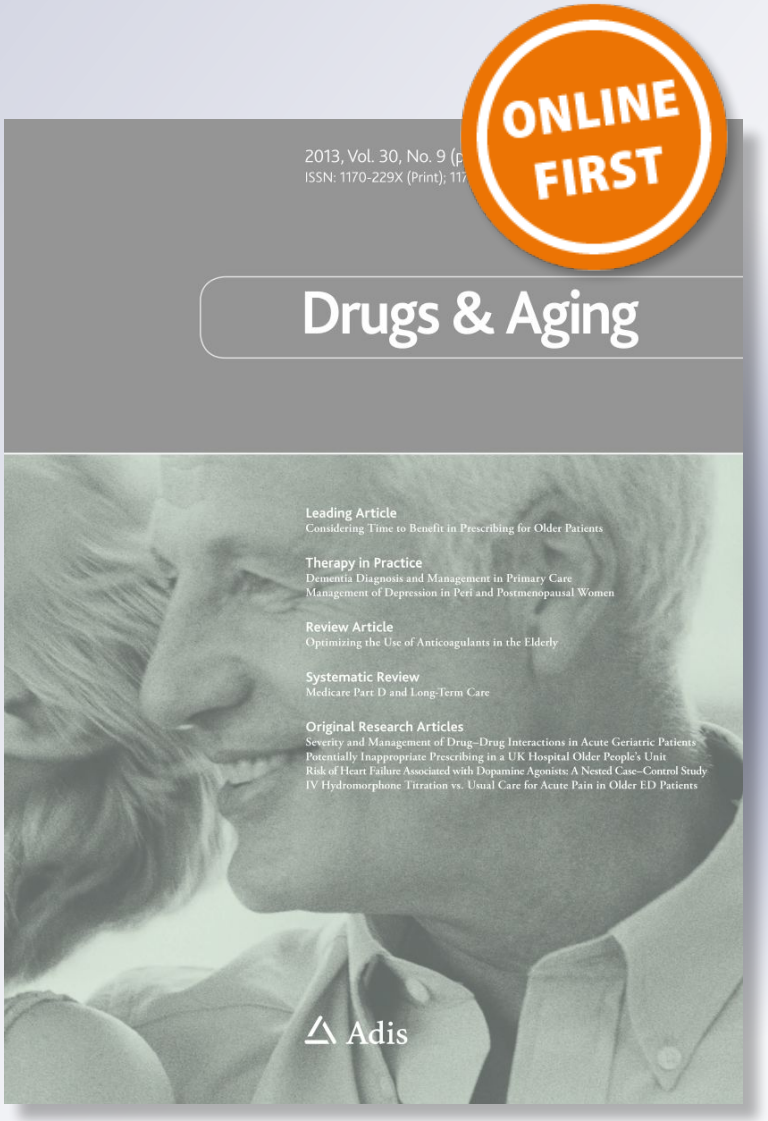

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REVIEW ARTICLE

Complementary and Alternative Medicine Use in Rheumatoid Arthritis: Considerations for the Pharmacological Management of Elderly Patients

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Abstract Complementary and alternative medicines (CAMs) are widely used by patients with rheumatoid arthritis (RA); however, a significant proportion of these patients 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; therefore, physicians should engage patients in dialogues regarding CAM usage. This review introduces common CAMs used by RA patients, such as herbal remedies, supplements, and fish and plant oils, and their potential impact on conventional therapy. Efficacy of these treatments are not reviewed in detail 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 CAMs, 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 on CAMs with patients. Common CAM therapies covered in this review include fish and plant oils, herbs and traditional Chinese medicine, and various supplements and diet regimes.

Elderly patients often take multiple pharmaceuticals for comorbidities and are therefore at risk of side effects and interactions when using CAMs in addition to pharmaceuticals.

1 Introduction

Complementary and alternative medicines (CAMs) include diverse medical practices and products that are not currently considered to be part of conventional medicine [1]. CAM users are more often female and suffering from chronic conditions [2]. Moreover, patients with pain-associated or mobility-limiting conditions were more likely to seek CAMs [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]. Worldwide, the prevalence of CAM usage in rheumatoid arthritis (RA) patients is estimated to be 20–86% [5].

RA is one of the most common rheumatic diseases, affecting up to 1% of the population [6]. It is a chronic,

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systemic, autoinflammatory condition that predominantly affects the joints, leading directly to disability, and also indirectly through associated comorbidities [7]. The management of RA has continued to improve globally, where early use of conventional and biologic disease-modifying antirheumatic drugs (DMARDs) have dramatically improved patient outcomes; however, a sizeable proportion of patients do not respond adequately to treatment [8, 9]. In addition, these powerful drugs are often associated with unpleasant side effects and occasionally serious adverse events [8]. Furthermore, the high cost of biologic drugs has implications for their accessibility [10]. For these and many other reasons, RA patients are increasingly seeking CAMs, which are often (mis)perceived as 'natural' and safe with fewer side effects [11].

Half of CAM users with rheumatic diseases do not inform their physicians. The 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, 13]. Patients primarily rely on their social network for information on CAMs, and are willing to try therapies without the support of scientific evidence or their physicians' approval [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 CAMs 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 used 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.

2 Types of Complementary and Alternative Medicine (CAM) Therapies Used in Rheumatoid Arthritis

This section will focus on common complementary and alternative *per os* pharmacological therapies. Table 1 in Appendix offers some suggested references for further reading on efficacy. Surveys of patients with arthritis showed that they most commonly used ingestible CAMs [14]; however, it is also important to be well-informed of the many non-pharmacological modalities that 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 CAMs in RA, with 19% of patients reporting its use [15]. Oils are extracted from either whole fish (e.g. herring, sardines, mackerel) or fish liver (e.g. cod). They are rich in long-chain, omega-3 (n-3) polyunsaturated fatty acids (PUFAs), mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [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] and may have non-steroidal anti-inflammatory drug (NSAID)-sparing effects [18]. RA is associated with increased cardiovascular mortality and increased prevalence of cardiovascular risk factors such as dyslipidemia [19]. Oils rich in n-3 have been shown to reduce cardiovascular risk factors in RA [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, with the most common include fishy odour and gastrointestinal disturbances such as flatulence and diarrhoea [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].

Western diets tend to be rich in omega-6 (n-6) PUFAs but lacking in n-3 [20]. Both n-3 and n-6 are essential fatty acids and cannot be synthesized by the body or interconverted. n-6 PUFAs are converted to arachidonic acid (AA), which is metabolized by cyclooxygenase (COX) to inflammatory eicosanoids such as prostaglandin-2 series and leukotriene-4 series. EPAs are metabolized to less inflammatory eicosanoids and are thought to be competitive substrates for COX (Fig. 1). n-3 PUFAs also form anti-inflammatory mediators such as resolvins and protectins [16, 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]. 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]. Patients taking flaxseed oils may therefore benefit from fish oils instead. Flaxseed oil also contains lignans, which have additional anti-inflammatory properties [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,

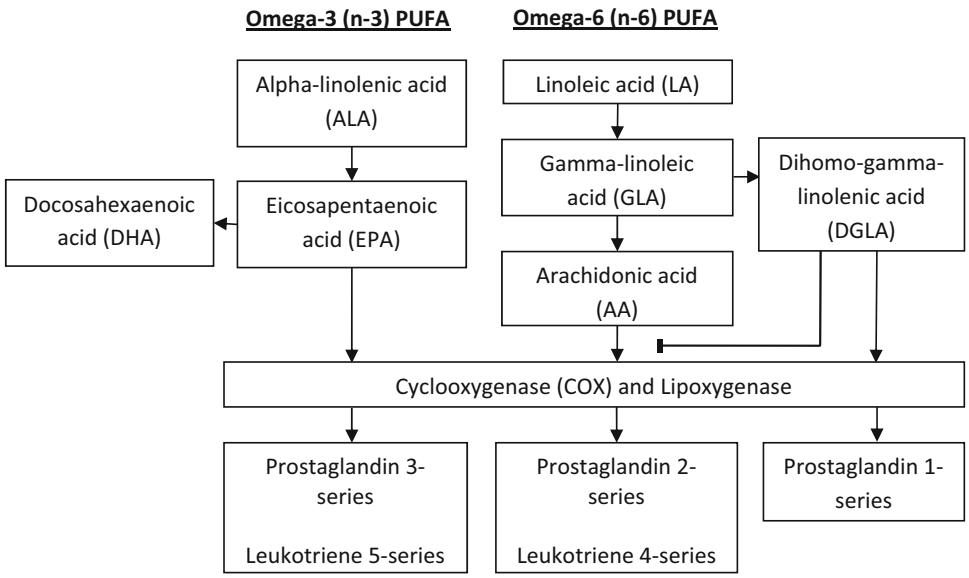

Fig. 1 Metabolism of omega-3 and -6 PUFAs. ALA (from flaxseed) is metabolized into EPA (fish oils) which, via COX and lipoxygenases, are converted to less inflammatory eicosanoids, PG-3 series and LT-5 series. GLA (borage, evening primrose, blackcurrant seed oils) can be converted to both AA and DGLA.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

gamma-linolenic acid (GLA) and linolenic acid (which is converted to GLA) [25–27]. GLA is converted to dihomo-GLA (DGLA), which is then converted to the less inflammatory prostaglandin-1 series. DGLA is also thought to inhibit conversion of AA (Fig. 1). Studies have demonstrated some benefit of GLA in RA, especially for pain and disability [28]. GLA is also converted to prostaglandin-1 series, which are thought to be anti-inflammatory [29]. These seed oils are also well-tolerated with minor gastrointestinal side effects, as with fish oils [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 [30]. The theory of TCM is based around five solid organs and six hollow viscera that are connected by conduits and vessels with 'qi' (energy) [31]. 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 that has been used for inflammatory swelling in TCM [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 [32]. A review of four studies in RA showed improvements in some outcomes [28]; however, it is important to note that thunder god vine has been associated with serious adverse events such as aplastic anemia and respiratory tract infections [33]. Side effects are not uncommon and include nausea, diarrhoea, hair loss, amenorrhoea and rash [33]. Given the unfavourable risk-benefit profile, thunder god vine should not be recommended for use in RA. Indeed, several agencies have issued warnings against its use [34].

Uncaria tomentosa and *Uncaria guianensis* are species of vine that have a long Peruvian tradition as a remedy for rheumatic diseases. Because of their curved thorns, they are 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 [35]. 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, seeds and shells of a species of wild rose (*Rosa canina*). It is reportedly rich in antioxidants [36], such as polyphenols and vitamin C, and also a galactolipid similar to GLA [37, 38]. Free radicals from oxidation are produced by, and can further amplify, the inflammatory processes [39]. Rose hip has been shown to improve measures of disease activity [37]. Side effects are mild and uncommon [40, 41].

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 [42].

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 [43], but only poor evidence is available in RA [44]. Turmeric is the rhizome of another plant (*Curcuma domestica*) belonging to the ginger family, and is a widely used dietary pigment and spice. The main constituent is curcumin, which has reported anti-inflammatory and analgesic properties in osteoarthritis [45]. It has been trialed with an NSAID in RA but does not have substantial evidence [46]. 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, is metabolized to salicylic acid in vivo and has been claimed to have anti-inflammatory and analgesic properties similar to aspirin [47]. 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 [48]. 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 [49]. It is available as glucosamine sulphate and glucosamine hydrochloride. In animal models, glucosamine sulphate has been shown to repair damaged cartilage and reduce inflammation. Trials of some glucosamine preparations in osteoarthritis show modest benefits [49]. However, in RA, glucosamine has no effect on disease activity but may improve pain [50, 51]. Side effects are rare and mild.

Vitamins are essential for health and should be promoted through a balanced diet. However, vitamin D is 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 [52]. Vitamin D deficiency should therefore be identified and treated by physicians using licensed preparations in sufficient doses. It is important to note that supplement 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 [53]. Vitamin D can rarely cause hypercalcemia, especially in those with subclinical hyperparathyroidism [54].

Vitamin B6 is an enzyme cofactor and important regulator 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 with healthy controls, and levels have also been associated with increased cytokine production, such as tumor necrosis factor (TNF) [55, 56]. 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 [57], whereas low-dose had no appreciable effect [56]. Tolerance to supplementation is good but overdosing is associated with adverse effects [58].

Free radicals are intimately associated with the inflammatory process and consequent damage. Antioxidants, such as vitamins C and E and selenium, have been used in many inflammatory conditions, including RA. Vitamin E is a group of compounds that can be found in plant oils such as sunflower and corn oil. It is the most investigated antioxidant in RA and some studies have reported reduction in pain; however, most trials have been poor quality [59]. 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 [59]. Selenium is an essential trace element nutrient and is a cofactor of antioxidant enzymes such as glutathione peroxidase. Selenium levels have been found to be reduced in RA patients compared with healthy controls; however, supplementation trials have not demonstrated efficacy [59]. Selenium is toxic in large doses but is otherwise well-tolerated.

2.4 Diets and Other CAM Therapies

There are many other CAM therapies used by RA patients, predominantly to reduce pain, including acupuncture and electro-acupuncture [60], laser therapy [61], electrical stimulation [62], mind–body techniques [63], and massage therapies [64]. Many variations of physical exercise should be generally encouraged.

Homeopathy uses ingredients that, when administered 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 [65]. Such mechanisms are difficult to fit into traditional scientific understanding. Homeopathic effects and side effects are negligible [65].

One important non-pharmacological CAM with relevance to conventional RA therapy is dietary modification. Common regimes include fasting, vegetarian-type and Mediterranean diets [66]. In general, these diets are rich in antioxidants and lower in saturated fats. For example, the Mediterranean diet is high in fruit, vegetables, and 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 [66]. 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.

3 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 [67]. With increasing age comes altered pharmacokinetics, increased number of comorbidities and associated polypharmacy [68], which are important considerations for conventional RA therapy. The prevalence of CAM usage also increases with age [69]. Furthermore, studies have demonstrated associations between CAM use and increasing number of comorbidities [2]. It is therefore essential that physicians engage in dialogues with patients regarding the use of CAMs, and to consider the 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 [68]. 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 have been reviewed in detail by Diaz-Borjon [67]. The recurring theme is that reduced renal function increases the 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 [70].

Active ingredients and therapeutic doses of CAMs 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 CAMs [71, 72]. These events are sporadic and unpredictable, and none are specific to CAMs used in RA. Nevertheless contaminants, adulteration and misidentification remain serious concerns across the herbal CAMs industry. Patients should always be advised to avoid obtaining herbal CAMs from unregulated sources. Even better regulated CAMs, for example fish oils, can be contaminated with environmental chemicals such as methylmercury and polychlorinated biphenyls (PCBs) [73].

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 [68].

The extent of polypharmacy is proportionately associated with reduced compliance with medication, which is of particular concern when adherence to conventional RA therapy is already low [74]. Many DMARDs cause gastrointestinal side effects [67], as do CAM treatments [75]. Patients may choose to take CAMs in preference to and instead of DMARDs, or misattribute side effects to, and therefore stop, DMARDs. The importance of taking conventional therapy over CAM therapy should be highlighted to patients.

The most common comorbidity in RA is reported to be depression [76]. 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 [77], is known to decrease activity of ciclosporin, and may have interactions with methotrexate [78, 79]. Depression in RA has a significant impact on quality of life and should be identified and treated appropriately with the help of licensed antidepressants.

The next most common group of comorbidities is cardiovascular diseases, such as myocardial infarction and stroke [76]. 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. Fish oils have been shown to increase international normalized ratio (INR) when taken with warfarin [80]. A theoretical risk also exists for omega-6 oils. Patients receiving warfarin should therefore be advised to monitor their clotting or avoid high-dose PUFAs altogether. Glucosamine [81] and ginger [82] have also been reported to increase INR. Andrographis paniculata may interact with anticoagulants [83] and antihypertensives [84]. These warnings are particularly pertinent to patients taking leflunomide, which has well-documented interactions with warfarin and effects on blood pressure [85].

Insulin resistance is a common cardiovascular risk factor in RA and is exacerbated by corticosteroid therapy [76]. Glucosamine has been reported to affect glycemic control and should be avoided in those patients with poorly controlled diabetes [86].

The effect of age on the risk of gastrointestinal haemorrhage or perforation is well-documented [87]. Many conventional therapies used by RA patients (bisphosphonates, NSAIDs, corticosteroids and possibly interleukin [IL]-6 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 [88]. 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 on the risk of osteoporosis and fractures [89].

Epilepsy is not a specific comorbidity in RA. Nevertheless there have been concerns that evening primrose oil may lower seizure threshold [90]; however, this has been contested. Given the limited benefit of this CAM, patients with poorly controlled epilepsy should avoid it, as well as other sources of LA and GLA. This may be of particular relevance in those taking hydroxychloroquine, which has some evidence of reducing seizure threshold [85]. Epileptic patients are also an often forgotten high-risk group for vitamin D deficiency and should be screened [91].

Biologic DMARDs are large molecule monoclonal antibodies (mAbs) whose 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 [92]. Therefore, interactions with small molecule drugs or CAMs are much less likely. Nonetheless, the impact of CAMs on adherence to synthetic DMARDs may affect concomitant biologics. It is thought that synthetic DMARDs reduce the formation of antidrug antibodies, which can potentially neutralize mAbs. Tocilizumab is an anti-IL-6 receptor antibody used in RA. Although upregulation of IL-6 reduces the activity of cytochrome P450 (CYP) enzymes, tocilizumab may reverse it [93]. 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. Often, many patients will not volunteer CAM usage and therefore physicians need to make systematic enquiries in consultations. This should be of additional priority in elderly patients with comorbidities. Studies have repeatedly demonstrated that patients wish for improved dialogue [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 placed 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 generally be recommended, while 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 CAMs and their advertising are lacking in many countries. While we await governmental intervention, patients should be advised against obtaining CAMs from unreputable sources. They can be directed to evidence-based sources of information, such as those provided by Arthritis Research UK or the National Center for Complementary and Integrative Health [94, 95].

Author contributions Sizheng Zhao wrote the manuscript with substantial contributions from Fred Otieno, Asan Akpan and Robert J. Moots.

Compliance with Ethical Standards

Conflict of interest Sizheng Zhao, Fred Otieno, Asan Akpan and Robert J. Moots have no conflicts of interest to declare.

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Appendix

See Table 1.

Table 1 Recommended reading on clinical trials of different CAMs. Where available, reviews and meta-analyses are provided instead of individual trials

Fish and plant oils	Fish oils [17, 18, 20, 96], Cochrane review pending
	Green-lipped mussel [21]
	General gamma-linolenic acid (GLA) [26, 28, 97]
	Blackcurrant [27, 98]
	Evening primrose [25, 99]
	Flaxseed [23]
Herbs and traditional Chinese medicine	Thunder god vine [28, 33]
	Uncaria tomentosa/cat's claw [35]
	Rosehip [37]
	Andrographis paniculata [42]
	Willow bark [48]
Supplements and diet regimes	Vitamin E and selenium [59]
	Glucosamine [50, 51]
	Diet [66]
General overviews	For physicians [4, 75, 100]
	For patients [94, 95]

CAMs complementary and alternative medicines

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