

ISSUE	Comments from Arthritis Australia
Questions for consideration	
<p>Should the Therapeutic Goods Administration (TGA) publish on its website information related to products removed from the Australian Register of Therapeutic Goods (ARTG)?</p> <ul style="list-style-type: none"> <li>In order to enhance the transparency of regulatory processes, it is proposed that the TGA will regularly publish on its website those products that have been removed from the ARTG as a result of a regulatory decision.</li> </ul>	<p>Arthritis Australia (AAust) supports publication on the TGA website of products which have been removed from the Australian Register of Therapeutic Goods (ARTG).</p> <ul style="list-style-type: none"> <li>The TGA website should also list products which have had sanctions or incurred penalties, but retained their listing on the ARTG. This will act as a more effective deterrent against transgressions.</li> <li>The TGA should create an email alert service which interested parties can sign up for online. This is a low cost way to keep consumers, health professionals and retailers apprised of products which have been removed or had sanctions taken against them.</li> <li>A consumer who started buying a product because of a false claim has a right to know the truth, so that they have an opportunity to change their behaviour. The approach by the TGA needs to be more proactive and not rely on people to continually check the website for updates. The TGA should implement multiple strategies, in addition to the ones suggested above, to inform health professionals, the retail channel and consumers of any breaches.</li> <li>The TGA should also list on their website those ARTG listed products that are currently under review or re-evaluation.</li> </ul>
<p>Should the Complaints Resolution Panel (CRP) be reconstituted as an independent body?</p> <ul style="list-style-type: none"> <li>Currently the CRP is made up of nominees from industry associations, professional organisations, peak consumer organisations and the TGA, and has an independent chair. Virtually all complaints considered by the CRP are related to members or potential members of the industry associations represented on the Panel.</li> </ul>	<ul style="list-style-type: none"> <li>AAust supports the creation of independent Complaints Resolution Panel (ICRP).</li> <li>Members should be independent because most complaints are related to members of industry associations. There should be an advertisement in national newspapers calling for nominations from the community, professional organisations, industry and academia for membership of the ICRP.</li> <li>The ICRP needs to be provided with resources to respond to complaints in a prompt and efficient matter. A complaint should be forwarded to the</li> </ul>

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<ul style="list-style-type: none"> <li>If an independent complaints resolution body is to be maintained, any perceptions of conflicts of interest could be addressed by requiring members to be independent of the therapeutic goods and advertising industries.</li> </ul>	<p>manufacturer of the product in no more than five working days. This gives an opportunity for a manufacturer to address an issue quickly before a ruling has been made about the complaint.</p> <ul style="list-style-type: none"> <li>If the ICRP takes weeks or months to review a complaint and then makes a ruling, then the damage has already been done. The ICRP should make a ruling, which can still be appealed, in no more than 15 working days. A consumer may spend years and thousands of dollars purchasing an ineffective product based on a false claim. The ICRP must act quickly to prevent this happening and make the financial penalties far outweigh the potential financial gain from breaches.</li> <li>The complaints process needs to focus on minimising the potential exposure to consumers of misleading or false claims. There should be incentives, including reduced sanctions, for manufacturers who swiftly address a breach before the ICRP has made a ruling.</li> <li>There is a need for guidelines, with appropriate compliance monitoring, for word-of-mouth promotion of products to all health professionals.</li> </ul>
<p>Should the CRP consider complaints about all forms of advertising?</p> <ul style="list-style-type: none"> <li>Some media for non-prescription medicines and medical devices are within scope of the CRP's oversight e.g. print, radio and television, but others are currently exempt e.g. in-store promotion.</li> <li>Many complaints handled by the CRP are essentially trivial and straightforward and may be better dealt with in another way.</li> </ul>	<ul style="list-style-type: none"> <li>All forms of advertising should be covered by the ICRP including online, websites and in store promotion.</li> <li>Health claims made on packaging and labelling should be considered advertising. The place a consumer is most likely to see and be influenced by an advertising message is at point of purchase. Any information that appears on a complementary medicine product and packaging is a form of advertising and should be reviewed by the TGA or its representatives. Any complaint regarding claims made on packaging and labelling should be reviewed by the ICRP.</li> <li>Minor, trivial or straightforward complaints can be dealt with by employing full time ICRP officers. Only complaints of a more serious nature or those that cannot be resolved should be forwarded to the newly formed ICRP.</li> <li>If a party makes a complaint to the ICRP, they should be informed of the outcome of the investigation and any action taken.</li> </ul>

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<p>Should civil penalties apply for breaches of the regime?</p> <ul style="list-style-type: none"> <li>• More broadly, there are no provisions for seeking civil penalties or enforceable undertakings for breaches of the advertising provisions of the Legislation.</li> <li>• Any revised sanction and penalty arrangements need to provide a regime that is both a real deterrent against transgression, and ensures the effective remediation of advertisements that are found to be in breach.</li> <li>• The sanctions regime under the legislation could be strengthened to include civil penalty contravention provisions and court-imposed remedial action for advertising breaches.</li> <li>• The TGA could also be given the power to refuse to list a product that was substantially similar to one that had been cancelled unless and until the relevant remedial action had been taken.</li> </ul>	<ul style="list-style-type: none"> <li>• Penalties need to far outweigh any potential benefit. Civil penalties and enforceable undertakings should apply for breaches of the regime. This will act as an effective deterrent and help prevent many potential breaches.</li> <li>• Revised sanction and penalty arrangements need to provide a regime that is a real deterrent against transgression as well as ensures the effective correction of advertisements that are found to be in breach.</li> <li>• The TGA should be given the power to refuse to list a product that was substantially similar to one that had been cancelled unless and until the relevant remedial action had been taken.</li> <li>• For a serious breach, the company which manufactures the product should be required to advertise their correction in the media including publications read by health professionals.</li> <li>• The ICRP should have the resources and power to investigate breaches not just responds to complaints. The increased revenue from the significant increase in penalties and sanctions could be used to fund investigations.</li> </ul>

### Additional recommendations from Arthritis Australia

#### New system for classification

Arthritis Australia proposes that all complementary medicines contain a simple classification system that informs consumers and health professionals of the safety and efficacy of a product. Consumers have the right to make informed decisions about health risks and the scientific evidence surrounding a product. Arthritis Australia has based its classification system on the Arthritis Research UK system of classification. Find attached ***Alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia - A report by the Arthritis Research***. AAust is not advocating that the results from the UK study are adopted, just the classification system.

## Safety classification

A false perception exists among some consumers that complementary medicines pose little or no health risk and have no side effects. Consumers are currently advised that 'if symptoms persist, consult your health professional'. This does not address complementary medicines that pose a health risk or may interfere with the efficacy of prescription medications. Consumers do not always consult with their health professionals. Complementary medicines require a consistent safety classification which consumers can easily understand and identify.

AAust proposes that all compounds be categorised according to their safety profile by using a traffic light system. Where information is available the compound would be categorised on the assumption that it is being taken within the range of recommended doses. Compounds which are safe at the recommended doses may have serious adverse effects when taken at higher doses. It should be emphasised to consumers that most conventional medicines have adverse effects, some serious.

The proposed categorisation is:

### **Traffic light at green**

Compounds with reported adverse effects which are mainly minor symptoms and infrequent. A classification of green does not mean that the compound has no reported adverse effects.

### **Traffic light at amber**

Compounds with reported adverse effects which occur frequently (even if they are mainly minor symptoms) or with more serious adverse effects.

### **Traffic light at red**

Compounds with reported serious adverse effects. Consumers should carefully consider these before deciding whether to take these medicines.















## Scientific evidence effective classification

When consumers see claims like 'clinically tested' or 'clinically proven', how can they be expected to determine if this claim is really evidence-based. The scientific evidence surrounding complementary medicines varies significantly; from the available evidence suggesting the compound is not effective to indicating that there is consistent evidence the compound is effective. The quality of randomised controlled trials (RCTs) can also vary significantly in quality.

Arthritis Australia proposes a new rating for scientific evidence where effectiveness is measured by improvements in pain, movement, or general well-being using the Jadad system for rating RCTs. This scoring system is commonly used to evaluate the quality of published RCTs in the field of complementary medicine. The Jadad scale has levels from 1 (very poor quality) to 5 (very good quality). For simplicity of reporting:-

1. There is, overall, no evidence to suggest the compound works or only a little evidence which is outweighed by much stronger evidence that it does not work.
2. There is only a little evidence to suggest the compound might work. The evidence from studies in this category often come from only a single study which has reported positive results and therefore there are important doubts about whether or not it works.
3. There is some promising evidence to suggest the compound works. The evidence will be from more than one study. However there may also be some studies showing that it does not work. Therefore there remains uncertainty as to whether compounds in this category work or not.
4. There is some consistency of evidence, which will come from more than one study, to suggest that the compound works. Although there are still doubts from the evidence it works, on balance it is more likely to be effective than not.
5. There is consistent evidence across several studies to suggest that this compound is effective.

If the RCTs were for osteoarthritis or rheumatoid arthritis then this would be specified in the effectiveness rating. The following table is to illustrate how this system might work. The results below are for example purposes only.

Therapy	Condition	Effectiveness	Safety classification
Fish oil – Omega-3	Rheumatoid Arthritis	5 	<b>Green</b> 
	Osteoarthritis	1 	<b>Green</b> 
Thunder God Vine	Rheumatoid Arthritis	3 	<b>Red</b> 
Glucosamine sulphate	Osteoarthritis	3 	<b>Green</b> 
Glucosamine hydrochloride	Osteoarthritis	1 	<b>Green</b> 
Willow Bark	Osteoarthritis	2 	<b>Amber</b> 
	Rheumatoid Arthritis	1 	<b>Amber</b> 

Once consumers become familiar with a scoring system, it assists them in making more informed decisions quickly and easily. An explanation of the rating system can be displayed at point of purchase.

An example of an effective evidence based classification is the current energy rating system for appliances. Adopting a similar system with a message like ‘The more stars, the more scientific evidence regarding effectiveness’ is something that consumers would instantly identify with and understand. AAust does not advocate you adopt stars; this is just an example of how effective a rating system can be. Vulnerable consumers, suffering from persistent pain and illness, have the right to know what the true safety and effectiveness of a complementary medicine product is before purchase.



### **Implementing the classification system**

When a company submits a product for listing on Australian Register of Therapeutic Goods (ARTG) they have to supply scientific evidence to support their application. This is when the complementary medicine product being submitted would receive its classification for both safety and efficacy. In most cases the classifications would already exist, for example glucosamine and Omega -3, and the cost of classifying the product should be minimal.

The TGA should list the safety and scientific evidence classification for each complementary medicine on its website and any sanctions or breaches that have taken against the product. Consumers, health professionals and pharmacist can then make an informed decision about a product and the integrity of the company who manufactures it.

### **Consumer complementary medicine information (CCMI)**

Consumer medicine information (CMI) leaflets are designed to inform consumers about prescription and pharmacist-only medicines. Arthritis Australia proposes that consumer complementary medicine information (CCMI) leaflets be produced for all complementary medicines. The CCMI should be produced by the complementary medicine company that makes the particular complementary medicine and be approved by the TGA. The CCMI should be submitted as part of the process of listing the product on the ARTG. The CCMI should be available from different sources, such as within the complementary medicine package, supplied by the pharmacist/health professional as a leaflet. The CCMI should be listed on the TGA website and could be made available to interested consumers groups to maximise its distribution.

### **For further information:**

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*Anthocyanidins*  
*Antler velvet*  
*Articulin-F*  
*Avocado-soybean unsaponifiables (ASU)*  
*Biqi capsule*  
*Blackcurrant seed oil*  
*Borage seed oil*  
*Cannabis oral spray*  
*Capsaicin*

*Cat's claw*  
*Cetylated fatty acids (CFAs)*  
*Chondroitin*  
*Collagen*  
*Devil's claw*  
*Duhuo Jisheng Wan (DJW)*  
*Eazmov*  
*Evening primrose oil (EPO)*  
*Feverfew*  
*Fish oil*  
*Flaxseed oil*  
*Ginger*  
*Gitadyl*  
*Glucosamine*  
*Green-lipped mussel*  
*Homeopathy*  
*Indian frankincense*  
*MSM*  
*Phytodolor*  
*Pine bark extracts*  
*Reumalex*  
*Rosehip*  
*SAMe*  
*Selenium*  
*SKI 306X*

*Stinging nettle*  
*Thunder god vine*  
*Tong luo kai bi*  
*Vitamins A,C,E*  
*Vitamins D and B complex*  
*Willow bark*

# Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia

A report by the Arthritis Research Campaign

The Arthritis Research Campaign (arc) is the fourth largest medical research charity in the UK, and exists to find the cause of and cure for all forms of arthritis and musculoskeletal conditions.

We rely entirely on public donations to fund our research and educational programmes, and spend more than £20 million a year in universities and medical schools to support pioneering biomedical research in order to improve life for people who have arthritis and related conditions.

Our report on *Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia* is the first in a series of ongoing, commissioned reports in areas of public interest.

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None of the products in this report are endorsed by the Arthritis Research Campaign, nor do we recommend particular suppliers.

F. GLOVES.



GELATINE.



CETACEUM.



B. JUNIP.



SYRINGES.



P. ANISI.



R. CALUMB.



SULPHUR.



## EXECUTIVE SUMMARY

Forty-six per cent of people in the UK use complementary medicine at some point in their lives for a wide range of conditions, spending over £450 million a year on acupuncture, chiropractic, homeopathy, hypnotherapy, medical herbalism and osteopathy.<sup>1</sup>

People with arthritis and musculoskeletal conditions, whose symptoms are often chronic, are particularly attracted to try such medicines, with 60 per cent of people trying a variety of products.<sup>2</sup>

The *Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia* report, written and produced by the Arthritis Research Campaign is an evidence-based report on the use of complementary and alternative medicines for arthritis and musculoskeletal conditions. It uses evidence from randomised controlled trials and aims to help people with arthritis or fibromyalgia select which complementary medicines may be beneficial for them.

The report scores medicines according to their effectiveness with 1 indicating that the available evidence suggests that the compound is not effective and 5 indicating that there is consistent evidence that the compound is effective. Effectiveness is measured by improvements in pain, movement, or general well-being. The report also grades the medicines according to safety, providing traffic light classifications for each.

The authors of the report focused on compounds taken by mouth or applied to the skin. They did not look at therapies such as acupuncture and chiropractic massage which have been commonly used for arthritis and musculoskeletal conditions. The role of these will be considered in a subsequent report.

Despite the number of complementary medicines available and used, this report found only 40 with evidence available from randomised controlled trials – the type of studies that give the best evidence on whether a treatment is effective or not. Even for those which had been studied, many had been tested in only a single or just a few studies. This makes it difficult to be sure whether they work or not.

### Rheumatoid arthritis

For people with rheumatoid arthritis (RA) the medicines researched score poorly, with 13 out of 21 complementary medicines (62 per cent) scoring just 1 point i.e. the available evidence suggests that the compound is not effective.

At the other end of the scale, fish body oil scores a maximum 5 for effectiveness among people with RA, offering real benefits. It also receives a green light for safety.

### Osteoarthritis

Alternative medicines appear to be more promising for people with osteoarthritis (OA) with only 6 out of 27 approaches (22 per cent) scoring 1 point.

Found to be safe to use and scoring well are the herbal preparation phytodolor and nutritional supplement SAME, both receiving a 4 for effectiveness. Capsaicin gel, made from chilli peppers, proved the most effective for OA, scoring the full 5 points.

Glucosamine is one of the most widely taken products and there have been many trials conducted. The evidence however is mixed, many trials show benefit while some do not. The evidence is stronger for glucosamine sulphate (which scored 3) compared to glucosamine hydrochloride (which scored 1).

### Fibromyalgia

Only four products were assessed for fibromyalgia but none of them were highly effective with three medicines scoring just 2 out of 5, and the fourth an ineffective 1.

In terms of safety, there is much less information available for complementary medicines in comparison to conventional medicines. However for approximately one quarter of the compounds considered we gave them an “amber” safety classification indicating there were important side effects which had been reported. A “red” safety classification was issued against thunder god vine.

The research studies used in the report are referenced so that you can find out more information on individual medicines should you wish to.

- 1 Thomas KJ, Coleman P. Use of complementary or alternative medicine in a general population in Great Britain. Results from the National Omnibus Survey. *J Public Health* 2004;26:152-7
- 2 Thomas KJ, Nicholl JP, & Coleman P. Use and expenditure on complementary medicine in England: a population based survey. *Complement Ther Med* 2001;9:2-11.
- 2 Bishop FL, Yardley L, Lewith GT. A systematic review of beliefs involved in the use of complementary and alternative medicine. *J Health Psychol* 2007;12:851-67.







# INTRODUCTION

Complementary and alternative medicines (we will call them complementary medicines) are a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. They are defined by the World Health Organisation as: *“A broad set of health care practices that are not part of the country’s own tradition and are not integrated into the dominant healthcare system.”*

The use of complementary medicine is more common than ever amongst patients in the UK: studies have suggested that 46 per cent of us will use complementary medicine at some point in our lives and that ten per cent of us will visit a complementary medicine practitioner each year.<sup>1</sup> It is estimated that over £450 million is spent annually by individuals on the principal types of complementary medicine, namely: acupuncture, chiropractic, homeopathy, hypnotherapy, medical herbalism and osteopathy. One of the most popular complementary medicines for arthritis is glucosamine and the cost of taking these tablets will typically be around £10/month. Complementary medicines are used in a variety of ways: some people use them instead of other medicines, some alongside, some people use them regularly and some intermittently.

People with arthritis and musculoskeletal conditions, whose symptoms are often chronic, may be particularly attracted to try such medicines. There is evidence to suggest that users of complementary medicine want to participate in treatment decisions and are likely to have active coping styles and believe that they can control their health. They value non-toxic, holistic approaches to health. Complementary medicine users also tend to believe that psychological and lifestyle factors are important in the development of illness.<sup>2</sup>


Despite the fact that they are commonly used, there are many areas of ignorance. We have little information available to guide us on how they might work in theory or whether they work in practice. There is little data on how they compare with other available conventional treatments. We also rarely know what is the most effective dose. One key area of ignorance is how they interact with other medications which could change the effectiveness of such medicines. Interactions may

be particularly important since many patients taking complementary medicine do not tell their doctor. Finally, despite the frequent assumption that by being ‘natural’ such compounds are not harmful, we often know little about how safe some of the complementary medicines really are. Underlying these issues is that unlike medically qualified doctors, most practitioners who prescribe complementary medicine are currently not subject to any government regulation.

The Medicines and Healthcare products Regulatory Agency (MHRA) is a government body set up to ensure both the safety and effectiveness of medicines before they are licensed and allowed onto the UK market. This agency has also recently introduced a new scheme for herbal and homeopathic medicines. Most herbal medicines in the UK are unlicensed, since they are not required to have a licence if they are not commercially produced. Since it is often difficult for such herbal medicines to be proven effective, a Traditional Herbal Medicine Registration Scheme was introduced in 2005. Under this scheme herbal medicine products are required to demonstrate only safety and quality.

The purpose of this report is to provide a resource for patients and health care professionals by giving a summary of the current evidence on whether individual commonly-used complementary medicines may be of use in the treatment of some types of arthritis and musculoskeletal conditions. We have focussed on the two most common forms of arthritis, namely rheumatoid arthritis and osteoarthritis as well as the chronic musculoskeletal pain disorder fibromyalgia.

Rheumatoid arthritis (RA) – the most common inflammatory arthritis – is a chronic disease that affects the joints, often those in a person’s wrists, fingers, and feet. Common symptoms of RA include pain, stiffness and fatigue. Osteoarthritis (OA) is an extremely common disorder, increasing with age and is often referred to as “wear and tear” of the joints in the body. The surface of the joint is damaged and the surrounding bone grows thicker. The most common joints affected are those of the knees, hips, hands and spine. Fibromyalgia is one of the most common reasons for being referred to a rheumatologist and the condition involves pain



experienced all over the body accompanied by fatigue, sleep disturbance and tenderness to touch. The condition does not result in any damage to the joints or muscles that can explain the symptoms.

### **How the information in this report was derived**

In this report we have only considered compounds which are taken orally (by mouth) or are applied to the skin. Therefore we have not considered therapies such as acupuncture, chiropractic, massage and several others which have been commonly used for arthritis and musculoskeletal conditions. The role of these complementary therapies will be the topic of a subsequent report. There is a very large number of compounds that have been proposed for use in our three target conditions and this report aims to cover all those where there has been some claim with supporting research evidence.

We have considered trials comparing standard interventions against each other or placebo. In herbalism, the individualised approach, in which patients receive a tailored prescription, has been emphasised. However a recent review concluded that there was a sparsity of evidence regarding individualised herbal medicine and no convincing evidence to support its use.<sup>3</sup>

The search for evidence and its evaluation has been conducted by experts in the fields of evaluating evidence, rheumatology, complementary medicine, nutrition and has also included input from a patient representative. Details of those involved are given in Appendix 1.

### **Classification of complementary medicine effectiveness**

This report focuses on two main questions: are the individual compounds effective in one or more of the conditions considered, and are they safe to take?

#### **1. Are complementary medicines effective?**

In Section 1 of the report, for each complementary medicine considered, we have evaluated whether there is evidence that it works. Effectiveness might

relate to improvement in pain but it also may relate to improvement in movement or, for example, general well-being. In evaluating compounds we have relied heavily on data from randomised controlled trials (RCTs). These are studies where patients are randomly allocated to one of the treatments being compared and then at the end of the study the results are evaluated according to whether patients, for example, on a new treatment had a better outcome than patients on an existing treatment.

These types of study provide the best type of evidence on whether any treatment works or not. Other types of study where patients have chosen the treatments they take themselves are very difficult to interpret because patients with more serious disease might have opted for one treatment and patients with milder disease another. Further, patients who choose, for example, to take a complementary medicine product, do so because they believe it to be effective which might influence the clinical response and their evaluation of it. In RCTs of complementary medicines, one of the treatments is thus often a placebo – a “dummy pill” which does not contain any active ingredient. This allows the effect of treatment to be compared when the patient themselves do not know which treatment they have received.

Some RCTs are of high quality while others have a relatively lower quality. Obviously results from high quality trials are more reliable than those of poor quality. The quality of trials that were included in this report was appraised based on a scoring system called “Jadad scoring scale.” This scoring system is commonly used to evaluate the quality of published RCTs in the field of complementary medicine. The Jadad scale has levels from 1 (very poor quality) to 5 (very good quality). For simplicity of reporting, we have collapsed the scale into two categories: good/high quality (Jadad score 3 or above), and low quality (Jadad score below 3). When discussing individual studies (in Section 1) we have marked trials with low quality by the symbol,<sup>‡</sup> and these studies have been given a lower weighting in coming to our conclusion about the compound.

Based on the evidence available from clinical trials with other supporting information, we have categorised each medicine into one of five categories:

**1**

There is, overall, no evidence to suggest that the compound works or only a little evidence which is outweighed by much stronger evidence that it does not work.

**2**

There is only a little evidence to suggest the compound might work. The evidence from studies in this category often come from only a single study which has reported positive results and there are therefore important doubts about whether or not it works.

**3**

There is some promising evidence to suggest that the compound works. The evidence will be from more than one study. However there may also be some studies showing that it does not work. Therefore we are still uncertain whether compounds in this category work or not.

**4**

There is some consistency to the evidence, which will come from more than one study, to suggest that the compound works. Although there are still doubts from the evidence that it works, on balance we feel that it is more likely to be effective than not.

**5**

There is consistent evidence across several studies to suggest that this compound is effective.

These classifications are based on the results of studies overall. In each study however there are people who seem to respond to treatment and those who do not. Therefore for medicines which we think are effective, this means that a greater proportion of people taking this medicine improved compared with, for example those taking placebo, or roughly the same proportion of people improved compared to another group taking a conventional drug which is known to be effective. It does not mean that everyone taking the medicine will improve. Similarly for medicines which we think are not effective this means, for example, that the proportion of people reporting improvement when taking these medicines was the same as people taking the placebo.

Sometimes in the description of results from studies we describe the differences in improvement on one compound compared to another as “significant”. This means that we are fairly sure that the differences between groups did not arise just by chance but it does not necessarily mean that the differences (e.g. with respect to improvement in pain) are large. In these respects the interpretation of the data is no different from that used for conventional medicines. Thus it should not be assumed that for conventional treatments the level of evidence reaches “level 5” in all the conditions for which they are prescribed.

## **2. Are complementary medicines safe?**

We have also categorised all compounds according to their safety profile. For many compounds it is not easy to do this because there is relatively little information available on safety. Where information is available we have categorised the compound assuming that it is taken within the range of recommended doses. Compounds which are safe at the recommended doses may have serious adverse effects when taken at higher doses. Again, it should be emphasised that most conventional medicines have adverse effects, some serious. However we generally have more information available on conventional drugs in order to determine the frequency and range of such adverse effects. The categorisation we have made is:

**■ Traffic light at Green** Compounds with reported adverse effects which are mainly minor symptoms and infrequent. A classification of Green does not mean that the compound has no reported adverse effects and patients should check in the product information leaflet what these are.

**■ Traffic light at Amber** Compounds with adverse effects reported as common (even if they are mainly minor symptoms) or with more serious adverse effects.

**■ Traffic light at Red** Compounds with serious adverse effects reported. Patients should carefully consider these before deciding whether to take these medicines.

There are some compounds on which there is very little information on adverse effects and we have therefore not been able to classify them. These are therefore indicated by traffic light at Amber together with “No information” written alongside.

### Other key questions

#### *Can I take complementary medicines together with other medicines?*

Complementary medicines can interact with each other and with conventional medicines in the same way that conventional medicines can interact with each other. It is important therefore that if you are taking any type of medicine that you check either with a pharmacist or your doctor whether, in addition, taking a particular complementary medicine could interfere with how it works. In the report we have mentioned some important interactions. However these are not comprehensive lists – they simply mention the most important interactions or relate to common medications.

#### *The complementary medicine I want information about is not covered in Section 1*

Only those compounds, taken orally or applied to the skin, which have been tested in at least one RCT have a specific section about them in this report. If the compound that you are searching for does not appear here that means we could not find any reports of a RCT testing that compound. **This means it is not possible for us to tell whether this compound works or not.** In Section 2 of this publication we list some of these commonly used complementary medicines.

### How to interpret the data

The large letter(s) (RA, OA or F) refer(s) to the condition or conditions (RA = rheumatoid arthritis, OA = osteoarthritis or F = fibromyalgia) for which we have been able to find some research evidence to evaluate whether the compound works or not.

RA

OA

F

The headline name for a compound is the most commonly used name. We also provide information on the family the compound belongs to, its scientific name and any other names by which it is commonly known (including some trade names).

## 9 Capsaicin gel

**Family:** Herbal medicine extracted from chilli peppers (genus Capsicum family).

**Scientific name:** Capsaicin.

**Other names:** Axsain\*, Zacin\*, chilli, pepper gel, cayenne.

**Description of the compound:** Capsaicin, which is the main medicinally active component of chilli peppers, is extracted from the placental tissue and internal membranes of the plant.

A summary of our understanding of how biologically the compound might work in treating rheumatoid arthritis, osteoarthritis or fibromyalgia.

**Mechanism of action:** Several studies have found that capsaicin can deplete Substance P, which plays an important role in the transmission of pain signals from nerve endings to the brain and is involved in activating inflammatory substances in joints.

What is known about the safety of the compound. See section “Are complementary medicines safe?” for how compounds are classified for safety. This section summarises the information available but does not include information on all adverse effects. For many complementary medicines little information is available to determine safety and toxicity.

**Safety and toxicity:** There are no major safety concerns in topical application of capsaicin gel/cream. Most patients will feel a burning sensation when the gel comes into contact with their skin. This is because capsaicin also binds to specific receptors in nerve endings called VR1, producing a burning sensation, which is not caused by any tissue damage. Brief redness of the skin is common, but high doses of capsaicin can cause skin blisters.



It is important to keep capsaicin away from the eyes, mouth and open wounds as it is highly irritant.

Information on where you can obtain the compound. Most are generally available in pharmacies or health food shops but some are only available by purchase over the internet.

**Availability:** Capsaicin is available on prescription as a cream, licensed in the UK for the treatment of pain associated with OA.

Information, if available, on how the complementary medicine may affect how other medicines work. For many complementary medicines little is known about interactions.

**Interactions:** There have been no reported drug interactions.

There is rarely information available on appropriate doses of complementary medicines and where available usually relates only to the effects of doses used in the trials reported.

**Dosage:** Most trials have used either 0.025 per cent or 0.075 per cent of capsaicin gel applied to the skin four times/day.

Provides an overview of the results from RCTs examining the effects of complementary medicine in managing osteoarthritis, rheumatoid arthritis and/or fibromyalgia.

**The role in treatment of arthritis and musculoskeletal conditions:**<sup>†</sup> A review article summarised results of three RCTs that have been published up to 1994 which investigate the effectiveness of topical application of capsaicin gel in treating patients with OA when compared to placebo gel. In these three trials capsaicin (0.025 per cent in two trials and 0.075 per cent in one) was applied four times/day for a treatment period ranging between four and 12 weeks. Capsaicin was found to be more effective than placebo in all three trials, and when data from the trials were analysed together in order to get a single estimate of effectiveness, it was found that capsaicin was four times more effective in improving pain and joint tenderness in patients with OA as compared to placebo gel. In a trial which was published in 1994 and not included in the previously mentioned review, 113 OA patients were

randomly selected to apply either capsaicin cream or placebo to the affected joint four times/day for a period of 12 weeks. At the end of the trial period, significantly more patients using capsaicin cream had reduction in both self-reported and doctor-judged pain. In addition, the severity of pain and joint tenderness was significantly reduced in patients using capsaicin. In a RCT published in 2000, 200 OA patients were randomly selected to apply one of the following four topical creams in affected joints: 0.025 per cent capsaicin cream; placebo cream; glyceryl trinitrate cream; or a cream containing both capsaicin and glyceryl trinitrate creams. After six weeks of treatment, and compared to patients who received the placebo cream, patients given any of the three active treatments had a significant reduction of both joint pain and amount of consumed painkillers. Patients who used the cream that contained both active treatments had the greatest improvement in pain and the most significant reduction of painkillers. Similar beneficial results were found in another RCT (36 people) which evaluated the effectiveness of an ointment containing several herbal compounds, including 0.015 per cent capsaicin (Arthritis Relief Plus) in treating joint pain and stiffness in patients with OA. One RCT investigated the effectiveness of topical application of capsaicin gel in the treatment of fibromyalgia. In this trial, 45 patients with fibromyalgia were randomised to either apply capsaicin gel (0.025 per cent; four times/day) or placebo gel to body areas with pain. After four weeks of treatment, patients who used capsaicin reported less tenderness and experienced significant increase in grip strength when compared to patients on the placebo.

Summarises the most important information from the preceding sections. Results from the high-quality studies were given more weighting in the final conclusion.

**Conclusion:** Capsaicin, which is extracted from chilli peppers, is available on prescription in pharmacies in the form of gel/cream and plasters. Its mechanism of action is mainly related to its ability to deplete Substance P, which is a pain transmitter in human nerves. Results from RCTs evaluating its role in treating patients with OA indicates that it has no major safety problems and can be effective in reducing pain and tenderness in affected joints. Evidence for its effectiveness in patients with fibromyalgia is related to a single trial.

Lists key references if the reader wishes to read reviews or more about individual studies.

### References:

- Zhang WY, Li Wan Po A. The effectiveness of topically applied Capsaicin. A meta-analysis. Eur J Clin Pharmacol 1994;46(6):517-22.
- Altman RD, Aven A, Holmburg CE, Pfeifer LM, Sack M, Young GT. Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. Semin Arthritis Rheum 1994;23(Suppl):25-33.
- McCleane G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. Eur J Pain 2000;4(4):355-60.
- Gemmell HA, Jacobson BH, Hayes BM. Effect of a topical herbal cream on osteoarthritis of the hand and knee: a pilot study. J Manipulative Physiol Ther 2003;26(5):315-23.
- McCarty DJ, Csuka M, McCarthy G, Trotter D. Treatment of pain due to fibromyalgia with topical Capsaicin: a pilot study. Semin Arthritis Rheum 1994;23 (Suppl 3):41-7.

### Classification:

#### Effectiveness score in OA:

5 

#### Effectiveness score in fibromyalgia:

2 

#### Safety classification:

Green 

### Where can I get more information about the individual complementary medicines?

At the end of each compound in Section 1 there are some references to scientific papers listed. These scientific publications report the results of the individual RCTs, or review the results from several RCTs, on which we have based our decision on the effectiveness and safety of the complementary medicines. If you wish to read the individual articles many can be accessed via PubMed which is a publicly available service of the US National Library of Medicine at <http://www.pubmed.com>. Some of the available articles are free while some others can be purchased online.

If you wish to read some other publications about complementary medicines that provide information on the evidence and their safety or provide some more general information on their use, you may find some of the following publications useful:

- The Arthritis Research Campaign (**arc**) also publishes a general information booklet, Complementary and Alternative Medicine for Arthritis: [www.arc.org.uk](http://www.arc.org.uk)
- The Medicines and Healthcare products Regulatory Agency website: <http://www.mhra.gov.uk/index.htm> provides information on the licensing of medicines in the UK. The website has a section devoted to the regulation and safety of herbal medicines and includes information sheets for some complementary medicines: <http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/index.htm>
- Ernst E, Pittler MH, Wider B, editors. The Desktop Guide to Complementary and Alternative Medicine: An evidence based approach. Edinburgh: Mosby Elsevier; 2006. ISBN-3 978-0-7234-3383-5. (This book provides a detailed scientific review of the evidence and safety.)
- Ernst E, Pittler MH, Wider B, editors. Complementary therapies for pain management: An Evidenced Based Approach. Philadelphia: Mosby Elsevier; 2007. ISBN-3 978-0-7234-3400-9
- Barnes J, Anderson LA and Phillipson JD, Herbal Medicines. 3rd ed. London: Pharmaceutical press; 2007. ISBN-3 978-0-8536-9623-0
- Encyclopedia of Alternative Medicine: [www.enotes.com/alternative-medicine-encyclopedia](http://www.enotes.com/alternative-medicine-encyclopedia)

- 1 Thomas KJ, Coleman P. Use of complementary or alternative medicine in a general population in Great Britain. Results from the National Omnibus Survey. J Public Health 2004;26:152-7
  - 2 Thomas KJ, Nicholl JP, & Coleman P. Use and expenditure on complementary medicine in England: a population based survey. Complement Ther Med 2001;9:2-11.
  - 3 Bishop FL, Yardley L, Lewith GT. A systematic review of beliefs involved in the use of complementary and alternative medicine. J Health Psychol 2007;12:851-67.
  - 3 Guo R, Canter PH, Ernst E. A systematic review of randomised clinical trials of individualised herbal medicine in any indication. Postgrad Med J 2007;83:633-7.
- ‡ If there are several trials which have been conducted we will often summarise the information from a published review. We will, however, mention information from individual studies on the proportion of patients withdrawing from treatment and the main adverse effects reported.

This report has been compiled following detailed discussions based on a full review of information available in early 2008. Emerging information from scientific studies was monitored throughout the remainder of 2008 and changes have been made to the classification status of medicines where required. Updates to the report will be published at appropriate intervals.



# 1 Anthocyanidins

**Family:** Food supplements.

**Scientific name:** Anthocyanidins.

**Other names:** Colladeen.\*

**Description of the compound:** A subgroup of flavonoids, which are chemicals derived from non-nutritive components of some plants.

**Mechanism of action:** Several studies in the laboratory have shown that anthocyanidins can act as strong anti-oxidants (i.e. can prevent cell damage in the body by interacting with harmful molecules produced within the cells known as free radicals). Anthocyanidins can also prevent the destruction of collagen in the muscles, a problem that has been observed in some patients with fibromyalgia.

**Safety and toxicity:** Reported adverse effects on short-term usage include stomach upset, skin rash and problems in passing urine. There are no reports on the long-term safety of anthocyanidins.

**Availability:** The compound is available over-the-counter in pharmacies in the form of capsules (Colladeen\*). This dietary supplement can also be ordered via the internet.

**Interactions:** Interactions with other drugs have not been well studied.

**Dosage:** Doses ranging from 40mg/day to 120mg/day have been used in a previous randomised controlled study. No trials have been conducted to establish appropriate dosage in musculoskeletal conditions.

**The role in treatment of arthritis and musculoskeletal conditions:** One small RCT was conducted to evaluate the role of anthocyanidins in treating patients with fibromyalgia. In this trial, 12 patients with fibromyalgia were randomised to receive one of the following three daily doses of anthocyanidins (120mg, 80mg, 40mg/day) or placebo tablets for three months. All patients in this trial were asked to

report daily the severity of their pain and the degree of fatigue and sleep problems in a diary. The degree of improvement in pain, fatigue and sleep were also evaluated by the investigator by interviewing the patients once every month. Anthocyanidin was not effective in reducing pain (as evaluated by the patient and the investigator) at any daily doses during any part of the follow-up. A similar lack of effect on fatigue was also reported by patients, although some beneficial effect was observed by the investigators during the interview. Based on patients' daily reports in diaries, a significant reduction in sleep disturbance was reported by patients who were taking anthocyanidins compared to patients on the placebo. However, such beneficial effects on sleep pattern were not confirmed by the investigators during the interviews. Patients who were on anthocyanidins reported more adverse effects (stomach upset, skin rash and urinary disturbance) than those who were allocated placebo capsules.

**Conclusion:** Anthocyanidins are a subgroup of flavonoids with strong anti-oxidant properties that can theoretically support and prevent the destruction of collagen in muscles. The effectiveness of these food supplements in the treatment of patients with fibromyalgia was only tested in one small RCT, in which no reduction in pain and an unconfirmed improvement in fatigue and sleeping problems were found. The limited data available does not yet allow for reliable evaluation of the role of this treatment for fibromyalgia.

## References:

- Edwards AM, Blackburn L, Christie S, Townsend RGN, David J. Food supplements in the treatment of primary fibromyalgia: a double-blind, crossover trial of anthocyanidins. *J Nutrition Environ Med* 2000;10:189-99.

## Classification:

### Effectiveness score:

1 

### Safety classification:

Amber 



## 2 Antler velvet

**Family:** A dietary supplement (Cervidae family).

**Scientific name:** Elk velvet antler.

**Other names:** Cervus elaphus, deer velvet, velvet deer antler.

**Description of the compound:** This is a nutritional supplement made from deer or elk antlers in early stages of their growth (during the velvet stage). In ancient China, antler velvet has been used as a sexual tonic, but nowadays antler velvet powder is available as a dietary supplement in most western countries and marketed as a general tonic, an anti-stress aid and also as a medication for OA and RA.

**Mechanism of action:** Laboratory studies and experiments on animals have demonstrated that “pilose” which is a protein found in antler velvet has an anti-inflammatory effect. Antler velvet is also rich in chondroitin sulphate, collagen, and glucosamine sulphate. These properties and the composition of the compound could make it a useful treatment in a variety of types of arthritis.

**Safety and toxicity:** No major adverse effects have been reported in previous studies on humans lasting six months. However androgenic (male hormone type) adverse effects have been noted in animal studies.

**Availability:** The compound is available over-the-counter in some health food shops in 250mg and 500mg capsules.

**Interactions:** Not well studied. Theoretically, antler velvet may interact with sexual tonics and hormonal medications (e.g. testosterone).

**Dosage:** Insufficient available evidence on optimal dose in arthritis and related conditions.

### The role in treatment of arthritis and musculoskeletal conditions:

Two RCTs examined the effect in treating RA patients. In the first trial<sup>‡</sup>, 40 patients were randomly assigned to receive one of the following four treatments: placebo capsules, antler velvet capsules 430mg/day, 860mg/day or 1,290mg/day. After one month of treatment, patients who received antler velvet, in any of the tested doses, did not show a significant improvement in their disease condition compared to the placebo group. In the second trial<sup>‡</sup>, 168 patients were randomly selected to receive either antler velvet or placebo capsules. After six months of treatment, neither treatment groups differed significantly with respect to disease activity, pain experience and overall health status. In both trials, antler velvet generally showed excellent tolerability with no apparent adverse effects to necessitate stopping the medication.

**Conclusion:** Antler velvet is a dietary supplement, with no major adverse effects, that is available over-the-counter in some health food shops. The compound has anti-inflammatory properties and is rich in glucosamine and other “building blocks” of joint cartilage. However, based on the results of two RCTs, there is no evidence to suggest that antler velvet is effective in treating RA.

### References:

- Allen M, Oberle K, Grace M, Russell A. Elk velvet antler in rheumatoid arthritis: phase II trial. *Biol Res Nurs* 2002;3(3):111-8.
- Allen M, Oberle K, Grace M, Russell A, Adewale AJ. A randomized clinical trial of elk velvet antler in rheumatoid arthritis. *Biol Res Nurs* 2008;9(3):254-61.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

Green 

<sup>‡</sup> A trial of low quality. Results of this trial were given a lower weighting in coming to our conclusion about the compound.

### 3 Articulín-F

**Family:** Ayurvedic herbal preparation.

**Scientific name:** Herbomineral formulation.

**Description of the compound:** Articulín-F is a mixture of Indian ginseng, *Boswellia serrata*, turmeric and zinc.

**Mechanism of action:** Zinc is believed to be a strong anti-oxidant (i.e. can prevent cell damage in the body by interacting with harmful molecules produced within the cells known as free radicals). Some studies indicate that Indian ginseng has both anti-inflammatory and anti-oxidant properties. Studies on animals found that *Boswellia serrata* exhibits marked sedative and analgesic effects. Other studies have found that turmeric can reduce the activity of a transcription factor in the body called NF-KB. This factor plays a role in the production of inflammatory proteins that are harmful to the joints.

**Safety and toxicity:** Not well studied but the limited data available suggests that the herbal mixture has no major safety problems.

**Availability:** No information on availability in the UK.

**Interactions:** Not well studied.

**Dosage:** Not well studied for patients with musculoskeletal conditions.

**The role in treatment of arthritis and musculoskeletal conditions:** One RCT was conducted to evaluate the role of Articulín-F in treating patients with OA. In this trial, 42 patients with OA were randomised to receive either two capsules/day of Articulín-F or placebo capsules for three months. Treatment with Articulín-F significantly improved the severity of pain, disability scores and the physical function of patients. However, the medication did not have a significant effect on changing the structure of the joints (as evaluated by x-ray examination). No major adverse effects have been reported by patients who received Articulín-F.

**Conclusion:** Articulín-F is a herbomineral medication that is believed to have analgesic, anti-oxidant and anti-inflammatory properties. This Ayurvedic preparation can be purchased via the internet in the form of capsules. The limited data available suggests that it might have some beneficial effects in reducing pain and disability in patients with OA.

#### References:

- Kulkarni RR, Patki PS, Jog VP, Gandage SG, Patwardhan B. Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. *J Ethnopharmacol* 1991;33(1-2):91-5.

#### Classification:

##### Effectiveness score:

2 

##### Safety classification:

Green 

## 4 Avocado-soybean unsaponifiables (ASU)

**Family:** Dietary supplements; avocado is a fruit belonging to Lauraceae family; soybean is a plant belonging to the pea family.

**Scientific name:** Avocado-soybean unsaponifiables.

**Other names:** Piascledine®, Regividerm®, AVOSOY®.

**Description of the compound:** ASU is a therapeutic compound consisting of one-third avocado oil and two-thirds soybean oil.

**Mechanism of action:** Studies in the laboratory have found that this mixed compound can reduce the production/action of various joint inflammatory substances and can prevent the destruction of joint cartilage caused by specific chemicals called interleukins. Other studies have found that ASU can stimulate the production of collagen, which is a natural component of tendons, joints, ligaments and muscles. Studies in animals have confirmed such findings and found that ASU stimulates the production of specific factors in the joints that can prevent cartilage degradation and can also help in the repair of damaged cartilage.

**Safety and toxicity:** ASU is well-tolerated with no major adverse effects reported in most trials. Most commonly reported adverse effects include allergic reactions and stomach upset. Patients who are allergic to banana and chestnut should not take ASU, because they are at a higher risk of developing an allergic reaction.

**Availability:** No information on availability in the UK.

**Interactions:** ASU might increase the risk of bleeding if taken with other medications which affect blood clotting such as aspirin, heparin and warfarin. ASU can also raise the blood pressure significantly when taken concurrently with some anti-depressant drugs called monoamine oxidase inhibitors (MAOIs).

**Dosage:** A dose of 300mg/day of ASU (containing 100mg of avocado and 200mg of soybean) has been used in most previous RCTs.

**The role in treatment of arthritis and musculoskeletal conditions:** The effectiveness of

ASU in treating patients with OA was investigated by four RCTs published in the period between 1997 and 2002. The number of patients included in these studies ranged from 163 to 260 and the period of the trial ranged from three months to two years. Three of these studies suggested that ASU is significantly more effective than placebo in improving symptoms. The fourth trial found no significant difference between ASU and placebo in reducing joint space narrowing and improving disease-related symptoms. In a recent review study, data from 664 OA patients who participated in these four studies were combined to produce a single estimate of effectiveness. Approximately 60 per cent of these patients had knee OA while the rest had hip OA. These patients had been randomised to receive either 300mg ASU (336 people) or placebo (328 people). Based on this combined analysis, the number of patients who reported a favourable effect from ASU was approximately twice as high as that reported by patients given placebo treatment. Compared to placebo, ASU was significantly more effective in reducing pain and problems associated with walking and other activities of daily living with either no or very minor adverse effects.

**Conclusion:** ASU is a dietary supplement consisting of one-third avocado oil and two-thirds soybean oil. Several studies have found that ASU can reduce the production/action of various joint inflammatory substances which can prevent the destruction of joint cartilage and also help in its repair. Evidence suggests that three months intake of 300mg/day ASU is safe and effective in reducing pain and problems associated with walking and other activities of daily living in some patients with OA.

### References:

- Christensen R, Bartels E, Astrup AV, Bliddal H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2008;16(4):399-408.
- Ernst E. Avocado-soybean unsaponifiables (ASU) for osteoarthritis - a systematic review. *Clin Rheumatol* 2003;22(4-5):285-8.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Green 





## 5 Biqi capsule

**Family:** Traditional Chinese medicine.

**Scientific name:** Biqi Jiaonang.

**Description of the compound:** Mixture of Chinese herbs.

**Mechanism of action:** In China, a few studies on animals suggest that herbal components of Biqi can reduce inflammation.

**Safety and toxicity:** Not well studied.

**Availability:** The compound is not available over-the-counter in pharmacies. It can be ordered via the internet.

**Interactions:** Not well studied.

**Dosage:** No trials have been conducted to establish appropriate dosage in musculoskeletal conditions.

**The role in treatment of arthritis and musculoskeletal conditions:** One RCT was conducted to evaluate its role in treating patients with RA. In this trial, 142 RA patients were randomly selected to receive either Biqi capsules or nimesulide tablets (a non-steroidal anti-inflammatory drug; NSAID) for eight weeks. Biqi capsules (66 per cent of patients improved) were as effective as nimesulide (61 per cent of patients improved) in treating RA. The study reported that one patient taking Biqi capsules showed a “mild adverse reaction”.

**Conclusion:** Biqi capsules are a mixture of Chinese herbs that can only be purchased via the internet. A few studies in animals have suggested that herbal components of this capsule have some anti-inflammatory properties. The effectiveness of Biqi capsules in the treatment of RA has not been well studied. One RCT has been conducted which showed that this Chinese medication is as effective as NSAIDs. However, the limited data available does not yet allow for reliable evaluation of the role of this treatment for RA.

### References:


- Liu W, Zhang L, Xu Z. [Clinical observation on treatment of rheumatoid arthritis with biqi capsule]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006;26(2):157-9. [Article in Chinese].

### Classification:

#### Effectiveness score:

2     

#### Safety classification:

**Amber**  (no information)

## 6 Blackcurrant seed oil

**Family:** Herbal medicine of the Saxifragaceae family.

**Scientific name:** Ribes nigrum.

**Other names:** Quinsy Berries, squinancy berries, cassis, red currant, European black currant, mustaherukka, grosellero negro, siyah frenkuzumu.

**Description of the compound:** Ribes nigrum is a plant native to northern parts of Europe and Asia. The fruit of this plant is formed from a very dark purple berry containing seeds. The berries and leaves of this plant are used medicinally for maintaining health and treating several diseases.

**Mechanism of action:** Oil derived from blackcurrant seeds is rich in both omega-3 alpha-linolenic acid (ALA; 13 per cent) and omega-6 gamma-linolenic acid (GLA; 17 per cent). These essential fatty acids are also important for maintaining joints' cell structure and function. Both ALA and GLA are converted in the body to hormone-like substances, called prostaglandins, which regulate the immune system and fight joint inflammation. GLA might also suppress inflammatory responses by directly acting on some inflammatory cells.

**Safety and toxicity:** No studies appear to have been done to determine the safety of blackcurrant seed extract in patients with musculoskeletal conditions. However, studies on other GLA-rich oils suggest that they are relatively safe with no serious adverse reactions.

**Availability:** The compound is available over-the-counter as capsules and as bottled oil. Capsules containing blackcurrant oil are available in doses from 200mg to 1,300mg. Each capsule contains between 14 per cent and 19 per cent GLA.

**Interactions:** Interactions with other drugs have not been well studied.

**Dosage:** No trials have been conducted to establish appropriate dosage in musculoskeletal conditions. Doses of 3g/day and 10.5g/day have been used in previous trials.

### The role in treatment of arthritis and musculoskeletal conditions:

Two RCTs examined the effect of this compound in treating patients with RA. In the first RCT (34 people), 14 patients were randomly selected to receive blackcurrant seed oil 10.5g (15 capsules) daily for 24 weeks, while the other 20 patients received placebo capsules composed of soybean oil for the same period of time. All RA patients, in both groups, were asked to continue their usual diets and medications. Only 50 per cent of patients in the group allocated blackcurrant seed oil capsules completed the 24-week trial. The main two reasons for stopping the medication was the large amount and size of the capsules and perceived lack of effectiveness of the treatment. Compared to the placebo group, patients who were given blackcurrant seed oil during the whole period of the trial had a significant but moderate reduction in joint tenderness, but only mild and non-significant reduction in pain and morning stiffness and overall disease severity. The report states that adverse effects of blackcurrant seed oil were negligible and did not contribute to patients' withdrawal from the trial. However the nature of the adverse effects was not reported. In the second RCT (30 people), 20 patients with RA were randomly selected to receive blackcurrant seed oil 3g (six capsules) daily for six weeks, while the other ten patients received placebo capsules composed of sunflower seed oil for the same period of time. Effects of treatments on morning stiffness, grip strength, pain, and physical function were measured at the end of the trial and again six weeks after treatment. Compared to the placebo group, who showed no improvement at both assessment points, patients on blackcurrant seed oil had significant reduction in morning stiffness at the end of treatment. However this beneficial effect was not observed six weeks after completion of treatment. In addition, blackcurrant seed oil had no significant effect on improving pain, grip strength and physical function, as compared to placebo, at both treatment outcome assessments.

## 7 Borage seed oil

**Conclusion:** Blackcurrant seed oil is rich in both omega-3 and 6-fatty acids that are important for maintaining joints cell structure and function and can fight joint inflammation. This dietary supplement is available over-the-counter as capsules and as bottled oil. It is considered to be a relatively safe medication. However, the little available evidence suggests that blackcurrant seed oil may not be effective in treating RA.

### References:

- Leventhal LJ, Boyce EG, Zuerier RB. Treatment of rheumatoid arthritis with blackcurrant seed oil. *Br J Rheumatol* 1994; 33(9):847-52.
- Watson J, Byars ML, McGill P, Kelman AW. Cytokine and prostaglandin production by monocytes of volunteers and rheumatoid arthritis patients treated with dietary supplements of blackcurrant seed oil. *Br J Rheumatol* 1993;32(12):1055-8.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

Green 

**Family:** Herbal medicine of the Boraginaceae family.

**Scientific name:** *Borago officinalis*.

**Other names:** Star flower oil, bee bread, tailwort, common bugloss, echium amoenum

**Description of the compound:** *Borago officinalis* is an annual herb native to the Mediterranean region, but cultivated in other countries including the UK. The medicinal product is derived from the plant seed oil.

**Mechanism of action:** In addition to its content of tannic, oleic and palmetic acid, the oil derived from borage seed contains very high levels of two types of polyunsaturated omega-6 essential fatty acids: linolenic acid (LA; converted in the body to GLA) and gamma-linolenic acid (GLA; 20 per cent - 26 per cent). GLA is a vital precursor of hormone-like molecules in the body called prostaglandins which regulate the immune system and fight joint inflammation. GLA might also suppress inflammatory responses by directly acting on some inflammatory cells. Sunflower oil and other oils generally used in normal diet contain only LA. Several factors can interfere with the production of GLA from LA in the body. These include aging, dietary deficiencies, viral infections and some diseases. Borage seed oil is the richest source of pure GLA.

**Safety and toxicity:** Reported adverse effects include nausea, indigestion, headache and skin rash. The compound contains small amounts of some liver toxins; however preparations free of these toxins are also available. No studies appear to have been done to determine the safety profile of borage seed extract in patients with arthritis and related conditions. However, studies on other GLA-rich oils suggest that they are relatively safe with no serious adverse reactions.

**Availability:** The compound is available over-the-counter as capsules and as bottled oil. Capsules containing borage seed oil are available in doses from 500mg to 1,300mg. The capsule usually contains 23 per cent GLA.

**Interactions:** Interaction with other drugs has not been adequately studied, but interactions with anti-inflammatory drugs (e.g. cortisone) and anti-coagulants (e.g. aspirin, warfarin) are possible. Some sedatives and medications for hypertension (e.g. beta-blockers) can suppress the anti-inflammatory properties of the compound.

**Dosage:** No trials have been conducted to establish appropriate dosage for arthritis related conditions. Preliminary studies have established that high doses of GLA (more than 1g/day) are needed to partially relieve symptoms.

**The role in treatment of arthritis and musculoskeletal conditions:** Two RCTs evaluated the effect of borage seed oil in treating RA patients. Patients participating in both studies were asked to maintain their usual treatment regimen for RA during the trial period. In the first trial, 37 patients with RA were randomly assigned to receive either borage seed oil, containing 1.4g/day GLA, or a placebo of cotton seed oil. Both study groups were treated for 24 weeks. Compared to the placebo group, who showed no improvement during the trial, patients who received borage seed oil showed an improvement in joint tenderness, number of swollen joints and morning stiffness. In the second RCT, 56 RA patients were randomly assigned to get either borage seed capsules, containing 2.8g/day GLA (double the dose given in the first trial) or placebo capsules containing sunflower seed oil. After six months of treatment, improvement in joint tenderness and morning stiffness was achieved by 64 per cent of patients on borage seed oil compared to only 21 per cent in those who were on placebo treatment. There was a significant difference in the treatment outcome of the two patient groups in favour of borage seed oil. In both RCTs, the number of patients withdrawing from the study, due to treatment ineffectiveness or adverse effects, was small. Reported adverse effects were minor and included belching, diarrhoea and flatulence.

**Conclusion:** Borage seed oil is rich in essential fatty acids that can regulate the immune system of the body and fight joint inflammation. This dietary supplement can be purchased over-the-counter from pharmacies and health food shops in the form of capsules or bottled oil. With respect to its effectiveness in treating patients with RA, the available evidence is suggestive that borage seed oil may result in an improvement in RA disease-related symptoms.

**References:**

- Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with gammalinolenic acid. *Ann Intern Med* 1993;119(9):867-73.
- Zurier RB, Rossetti RG, Jacobson EW, DeMarco DM, Liu NY, Temming JE, et al. Gamma-Linolenic acid treatment of rheumatoid arthritis. A randomized, placebo-controlled trial. *Arthritis Rheum* 1996;39(11):1808-17.

**Classification:**

**Effectiveness score:**

3 

**Safety classification:**

Green 





## 8 Cannabis oral spray

**Family:** Herbal medications.

**Scientific name:** Cannabis oral spray.

**Other names:** Cannabis sativa, Sativex®.

**Description of the compound:** Cannabis oral spray consists of a blend of the whole plant, cannabis, which is indigenous to central Asia and has long been used as a psychoactive drug and for recreational purposes (marijuana). The oral spray, which was made available in Canada in 2005 for reducing pain in chronic diseases, contains approximately equal amounts of two therapeutic constituents tetrahydrocannabinol (THC) and cannabidiol (CBD).

**Mechanism of action:** Laboratory studies have found that THC has analgesic activity by acting on specific receptors in the nervous system. Studies on animals have also found that both THC and CBD have several anti-inflammatory properties and that CBD is capable of suppressing chronic arthritis in rats and mice.

**Safety and toxicity:** The most common adverse effect reported by patients in Sativex® studies has been sleepiness. Other adverse effects include nausea, dizziness and dry mouth. The long-term adverse effects have not been well studied.

**Availability:** Under the current arrangements in the UK, the prescription of Sativex® is only permitted under Home Office licence and it is principally intended for multiple sclerosis patients. Sativex® can not be ordered via the internet and is not available in pharmacies. This oral spray can only be obtained by a written prescription, on a named patient basis, from a medical doctor. Its use is extremely unlikely to be considered for patients with chronic musculoskeletal pain.

**Interactions:** Patients who are on sedatives should take this spray with caution as Sativex® may amplify the effects of such medications. Cannabis oral spray may interact with alcohol particularly in affecting coordination and concentration.

**Dosage:** Not well studied for patients with musculoskeletal conditions. One spray/day (containing 2.7mg of THC and 2.5mg of CBD) to be increased to a maximum of six per day was used in one study.

**The role in treatment of arthritis and musculoskeletal conditions:** One RCT was conducted to evaluate the role of cannabis oral spray in treating patients with RA. In this trial 58 patients with RA, which was not adequately controlled by conventional treatments, were randomised to receive either cannabis oral spray (one spray/day increased to a maximum of six/day) or a placebo spray for five weeks. Patients in both groups were asked to maintain their usual conventional treatment all through the trial. Compared to patients who were on placebo, those who took the cannabis oral spray had moderate improvements in pain, overall disease activity and quality of sleep. However, the degree of improvement in morning stiffness was similar in both groups. Dizziness, light-headedness and dry mouth were reported by 26 per cent, ten per cent and 13 per cent of patients who were on the cannabis spray, respectively. However, none of the patients who experienced these adverse effects had to withdraw from the trial due to these adverse effects.

**Conclusion:** Cannabis oral spray is a herbal remedy with analgesic and anti-inflammatory properties that can only be obtained by a written prescription on a named patient basis from a medical doctor. The use of this spray in patients with musculoskeletal conditions is still in the early stages of research. However, based on the results of only one RCT, this spray might have a moderate beneficial effect in reducing pain and improving the quality of life of patients with RA with no serious short-term adverse effects.

## 9 Capsaicin gel

### References:

- Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45(1):50-2.
- Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001;323(7303):13-6

### Classification:

#### Effectiveness score:

2 

#### Safety classification:

Amber 

**Family:** Herbal medicine extracted from chilli peppers (genus *Capsicum* family).

**Scientific name:** Capsaicin.

**Other names:** Axsain®, Zacin®, chilli, pepper gel, cayenne.

**Description of the compound:** Capsaicin, which is the main medicinally active component of chilli peppers, is extracted from the placental tissue and internal membranes of the plant.

**Mechanism of action:** Several studies have found that capsaicin can deplete Substance P, which plays an important role in the transmission of pain signals from nerve endings to the brain and is involved in activating inflammatory substances in joints.

**Safety and toxicity:** There are no major safety concerns in topical application of capsaicin gel/cream. Most patients will feel a burning sensation when the gel comes into contact with their skin. This is because capsaicin also binds to specific receptors in nerve endings called VR1, producing a burning sensation, which is not caused by any tissue damage. Brief redness of the skin is common, but high doses of capsaicin can cause skin blisters. It is important to keep capsaicin away from the eyes, mouth and open wounds as it is highly irritant.

**Availability:** Capsaicin is available on prescription as a cream, licensed in the UK for the treatment of pain associated with OA.

**Interactions:** There have been no reported drug interactions.

**Dosage:** Most trials have used either 0.025 per cent or 0.075 per cent of capsaicin gel applied to the skin four times/day.

### The role in treatment of arthritis and musculoskeletal conditions:

A review article summarised results of three RCTs that have been published up to 1994 which investigated the effectiveness of topical application of capsaicin gel in treating patients with OA when compared to placebo gel. In these three trials capsaicin (0.025 per cent in two trials and 0.075 per cent in one) was applied four times/day for a treatment period ranging between four and 12 weeks. Capsaicin was found to be more effective than placebo in all three trials, and when data from the trials were analysed together in order to get a single estimate of effectiveness, it was found that capsaicin was four times more effective in improving pain and joint tenderness in patients with OA as compared to placebo gel. In a trial which was published in 1994 and not included in the previously mentioned review, 113 OA patients were randomly selected to apply either capsaicin cream or placebo to the affected joint four times/day for a period of 12 weeks. At the end of the trial period, significantly more patients using capsaicin cream had reduction in both self-reported and doctor-judged pain. In addition, the severity of pain and joint tenderness was significantly reduced in patients using capsaicin. In a RCT published in 2000, 200 OA patients were randomly selected to apply one of the following four topical creams in affected joints: 0.025 per cent capsaicin cream; placebo cream; glyceryl trinitrate cream; or a cream containing both capsaicin and glyceryl trinitrate creams. After six weeks of treatment, and compared to patients who received the placebo cream, patients given any of the three active treatments had a significant reduction of both joint pain and amount of consumed painkillers. Patients who used the cream that contained both active treatments had the greatest improvement in pain and the most significant reduction of painkillers. Similar beneficial results were found in another RCT (36 people) which evaluated the effectiveness of an ointment containing several herbal compounds, including 0.015 per cent capsaicin (Arthritis Relief Plus) in treating joint pain and stiffness in patients with OA. One RCT investigated the effectiveness of topical application of capsaicin gel in the treatment of fibromyalgia. In this trial, 45 patients with fibromyalgia were randomised to either apply capsaicin gel (0.025 per cent; four times/day)

or placebo gel to body areas with pain. After four weeks of treatment, patients who used capsaicin reported less tenderness and experienced significant increase in grip strength when compared to patients on the placebo.

**Conclusion:** Capsaicin, which is extracted from chilli peppers, is available on prescription in pharmacies in the form of gel/cream and plasters. Its mechanism of action is mainly related to its ability to deplete Substance P, which is a pain transmitter in human nerves. Results from RCTs evaluating its role in treating patients with OA indicates that it has no major safety problems and can be effective in reducing pain and tenderness in affected joints. Evidence for its effectiveness in patients with fibromyalgia is related to a single trial.

### References:

- Zhang WY, Li Wan Po A. The effectiveness of topically applied Capsaicin. A meta-analysis. *Eur J Clin Pharmacol* 1994;46(6):517-22.
- Altman RD, Aven A, Holmburg CE, Pfeifer LM, Sack M, Young GT. Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. *Semin Arthritis Rheum* 1994;23(Suppl):25-33.
- McCleane G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. *Eur J Pain* 2000;4(4):355-60.
- Gemmell HA, Jacobson BH, Hayes BM. Effect of a topical herbal cream on osteoarthritis of the hand and knee: a pilot study. *J Manipulative Physiol Ther* 2003;26(5):315-23.
- McCarty DJ, Csuka M, McCarthy G, Trotter D. Treatment of pain due to fibromyalgia with topical Capsaicin: a pilot study. *Semin Arthritis Rheum* 1994;23 (Suppl 3):41-7.

### Classification:

#### Effectiveness score in OA:

5 

#### Effectiveness score in fibromyalgia:

2 

#### Safety classification:

Green 



## 10 Cat's claw

**Family:** Herbal remedy Rubiaceae family.

**Scientific name:** *Uncaria tomentosa*.

**Other names:** Life-giving vine of Peru, una de gato.

**Description of the compound:** Cat's claw is extracted from the stem and root of some woody vines native to South and Central America.

**Mechanism of action:** Studies in the laboratory have found that cat's claw can prevent the activation of several inflammatory substances in the body. Studies have also shown that cat's claw has anti-oxidant properties (i.e. can prevent cell damage in the body by interacting with harmful molecules produced within cells known as free radicals). Studies on animals have also confirmed these anti-inflammatory properties.

**Safety and toxicity:** There is a lack of clinical safety data. No serious adverse effects from cat's claw were reported in one trial whose study subjects were patients with RA. However, there was an isolated report of serious kidney problems in a woman with lupus taking this medication.

**Availability:** The compound is available over-the-counter in pharmacies and health food shops in the form of capsules/tablets. Commercial products contain varying amounts of active material. The herbal remedy can also be ordered via the internet.

**Interactions:** Cat's claw may increase the effect of drugs used to treat hypertension, so should be taken with caution in patients receiving treatment for hypertension. Laboratory studies have also found that cat's claw can stimulate the production of certain immune hormones called cytokines. These cells are important for immunity. For that reason patients who are on medicines that suppress the immune system should be cautious when taking this compound.

**Dosage:** A dose of 60mg/day of the active component (*Uncaria tomentosa*) was used in one randomised controlled study. However, no trials have been conducted to establish appropriate dosage in musculoskeletal conditions.

### The role in treatment of arthritis and musculoskeletal conditions:

One RCT has been conducted to evaluate the role of cat's claw in treating patients with RA. In this trial, 40 patients with RA who were all on conventional treatment with sulfasalazine or hydroxychloroquine, were randomised to receive either cat's claw tablets, with a dose of 60mg/day of *Uncaria tomentosa*, or placebo tablets for 24 weeks (phase A). Patients in both treatment groups were then asked to take cat's claw for an additional 28 weeks (phase B). All patients in both phases were asked to maintain their usual conventional treatment during both phases of the trial. Fifty-three per cent of patients allocated cat's claw in phase A reported a significant reduction in the number of painful joints compared to only 24 per cent of patients who were on placebo tablets during the same phase. However, patients in both groups did not differ with respect to morning stiffness and number of tender or swollen joints. The picture was different when the clinical effectiveness of cat's claw at the end of phase B was compared to the placebo group in phase A, where significant beneficial effects on all clinical aspects were observed in patients who were given cat's claw for a total of 52 weeks. Only minor adverse effects (e.g. stomach upset) were reported in patients who received cat's claw.

**Conclusion:** Cat's claw is a herbal remedy with anti-oxidant and anti-inflammatory properties that is available over-the-counter in pharmacies and health food shops in the form of capsules. Only one RCT was conducted to evaluate its role in treating patients with RA, which showed some clinical benefits (with only minor adverse effects) when taken along with conventional medications.

### References:

- Mur E, Hartig F, Eibl G, Schirmer M. Randomized double blind trial of an extract from the pentacyclic alkaloid-chemotype of *Uncaria tomentosa* for the treatment of rheumatoid arthritis. *J Rheumatol* 2002;29(4):678-81.

### Classification:

#### Effectiveness score:

2 

#### Safety classification:

Amber 

## 11 Cetylated fatty acids (CFAs)

**Family:** Nutritional supplement.

**Scientific name:** Cetylated fatty acids.

**Other names:** Individual CFAs (e.g. cetyl myristoleate), combinations of CFAs (e.g. Celadrin®).

**Description of the compound:** Cetyl myristoleate (a specific CFA) was proposed as a possible treatment for musculoskeletal conditions in the 1970s by an American chemist who found that this fatty acid might be responsible for protecting mice against development of RA.

**Mechanism of action:** The exact mechanisms of action of CFAs in treating musculoskeletal conditions have not been formally studied. However, it has been proposed that they may have a lubricant effect on joints. Similar to the mechanism of action of omega fatty acids, they theoretically have anti-inflammatory effects by enhancing the production of chemicals in the body called prostaglandins. Prostaglandins are hormone-like substances that regulate the immune system and fight joint inflammation.

**Safety and toxicity:** No serious adverse effects have been reported in previous studies.

**Availability:** CFAs are formulated in capsules (350mg) and cream. The medicine is available over-the-counter in pharmacies and health food shops.

**Interactions:** Interactions with other medications have not been examined.

**Dosage:** Optimal dose has not been established, but a treatment regimen consisting of three capsules per day of Celadrin® containing 350mg of CFAs has been used in previous studies.

**The role in treatment of arthritis and musculoskeletal conditions:** Two RCTs evaluated the role of CFAs in treating patients with OA of the knee. In the first trial<sup>‡</sup>, 64 patients with knee OA were randomly assigned to receive either

active capsules (350mg of CFAs, six times a day) or placebo capsules, while continuing their current OA medication. After 68 days of treatment, no improvement in knee extension was reported in either group. However, patients in the active treatment group had significantly increased knee flexion. The second RCT<sup>‡</sup> evaluated the potential beneficial effects of CFA cream. In this trial, 40 patients diagnosed with knee OA were randomly selected to receive a topical treatment of either CFA cream or a placebo cream. Patients in both groups were asked to apply the cream twice daily to the knee. After 30 days of treatment, patients applying the active treatment experienced significant improvement in climbing stairs and standing up from a sitting position. In addition, the overall range of motion of the knee was markedly improved in patients who got CFA cream. In both trials, the medication was well tolerated with no serious adverse effects.

**Conclusion:** CFAs as nutritional supplements are available in capsule and cream form and sold over-the-counter in pharmacies and health food shops. There is a little evidence that the cream may be effective in improving some aspects of range of motion in the knees of patients with OA. However, its mechanism of action, safety profile and effectiveness in relation to conventional medications is still unclear.

### References:

- Hesslink R Jr, Armstrong D 3rd, Nagendran MV, Sreevatsan S, Barathur R. Cetylated fatty acids improve knee function in patients with osteoarthritis. *J Rheumatol* 2002;29(8):1708-12.
- Kraemer WJ, Ratamess NA, Anderson JA, Maresh CM, Tiberio DP, Joyce ME, et al. Effect of a cetylated fatty acid topical cream on functional mobility and quality of life of patients with osteoarthritis. *J Rheumatol* 2004;31(4):767-74.

### Classification:

#### Effectiveness score:

2 

#### Safety classification:

Green 

<sup>‡</sup> A trial of low quality. Results of this trial were given a lower weighting in coming to our conclusion about the compound.

## 12 Chondroitin

**Family:** Nutritional supplement.

**Scientific name:** Chondroitin sulphate.

**Other names:** CSA, CDS, CSC.

**Description of the compound:** A complex sugar derived from cartilage of cows, pigs, and sharks.

**Mechanism of action:** Chondroitin is found naturally in the body and is a vital part of joint cartilage. It gives cartilage elasticity by helping it retain water. Studies in the laboratory have found that chondroitin can reduce the activity of enzymes and substances that break down collagen in joints. Other studies have demonstrated several anti-inflammatory properties of chondroitin. Research on animals has found that chondroitin can prevent degradation of joint cartilage and can also stimulate repair mechanisms.

**Safety and toxicity:** Adverse effects, which are usually mild and infrequent, include stomach upset, headache, increased intestinal gas, diarrhoea and rash.

**Availability:** This nutritional supplement is widely available in pharmacies and supermarkets in the form of capsules. It is usually sold in combination with glucosamine sulphate.

**Interactions:** Theoretically, chondroitin might increase the risk of bleeding if taken with other medications which affect blood clotting like aspirin, heparin and warfarin. For that reason, patients on these medications are advised to take chondroitin under a doctor's supervision. Patients with asthma should take chondroitin with caution as it might exacerbate breathing problems in these patients.

**Dosage:** Most trials have used a dose between 800mg and 1,200mg daily taken in divided amounts.

**The role in treatment of arthritis and musculoskeletal conditions:**

Chondroitin is one of the most commonly investigated complementary medications for OA. A recent review article, published in 2007, summarised results of 19 RCTs that investigated the effectiveness of this dietary supplement in treating patients with knee and hip OA. The number of patients included in these studies ranged from 46 to 631 patients and duration of the trials ranged from 13-132 weeks. Sixteen trials compared the potential benefits of chondroitin with that of a placebo. The other three studies were either available only as conference abstracts (i.e. only a summary of results is available) or had poorly defined comparison groups. Twelve trials out of these 16 found that chondroitin was significantly superior to placebo in relieving pain. Of the 16 trials that compared the role of chondroitin with that of placebo, five trials investigated the potential beneficial effect of chondroitin on structurally increasing the width of joint space. Most of these studies found that chondroitin had a small and insignificant effect, compared to placebo, on the progression of joint space narrowing. Of the 16 trials that compared the clinical effectiveness of chondroitin with that of placebo in terms of reducing dependence on analgesic drugs, 12 trials found that the chondroitin was more effective. The other four trials found that chondroitin and placebo had similar effects. In the vast majority of the trials included in this review, the number and severity of adverse effects reported by patients who received chondroitin was less than, or similar to, those on placebo. Overall, evidence from trials with good study design in allocating patients to treatment groups and trials that used the most appropriate statistical methods had lower estimates of effectiveness of chondroitin, particularly in terms of reduction in joint pain.

## 13 Collagen

**Conclusion:** Chondroitin is found naturally in the body and is a vital part of joint cartilage. It can be purchased in the form of capsules (usually in combination with glucosamine sulphate). Studies in the laboratory and in animals have found that administration of chondroitin can prevent degradation of joint cartilage and can also stimulate its repair mechanisms. The role of chondroitin in the treatment of OA has been the subject of at least 19 RCTs. Evidence from these RCTs is inconsistent, but the majority have demonstrated significant clinical benefits of this dietary supplement in reducing pain and dependence on painkillers. Higher quality trials have, however, been less likely to show benefit. The medication appears to be safe for short-term use. However its long-term safety and effectiveness is still unclear.

### References:

- Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007;146(8):580-90.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Green 

**Family:** Nutritional supplement.

**Scientific name:** Collagen hydrolysate.

**Other names:** Hydrolyzed collagen, purified gelatin, HCP, collagen type 2.

**Description of the compound:** Collagen is a dietary supplement extracted from beef, pork or fish materials (e.g. bones and hides) after being processed to make it more digestible.

**Mechanism of action:** Collagen hydrolysate supplementations are rich in a number of amino acids that play an important role in the synthesis of collagen, which is a major component of joint cartilage. It has been suggested that the consumption of collagen hydrolysate can provide symptomatic improvement in patients with OA by stimulating the synthesis of joint collagen. Some studies have also found that collagen hydrolysate can lead to an improvement in the activity of arthritis in animals. It has been suggested that the potential beneficial effects of collagen hydrolysate in patients with RA is mediated through a process called oral tolerance, where oral administration of collagen will introduce some chemicals which cause joint inflammation to the gastrointestinal system. This, in turn, will suppress the responsiveness of joints to these antigens and will reduce inflammation. The mechanism by which oral tolerance works is still not completely understood.

**Safety and toxicity:** Collagen is considered to be safe with no major adverse effects. Reported adverse effects, which are usually mild, include a feeling of heaviness in the stomach, mild diarrhoea, and skin rash.

**Availability:** Collagen is readily available in most pharmacies in the form of capsules.

**Interactions:** There are no well-known drug interactions with collagen.

**Dosage:** Not well established. Doses between 1g to 10g/day have been used in previous studies.



### The role in treatment of arthritis and musculoskeletal conditions:

Two RCTs were conducted to evaluate the role of collagen hydrolysate in treating patients with OA. In the first trial (81 people, trial duration of two months), patients with OA were randomly selected to receive placebo tablets or one of three gelatine (collagen hydrolyse) preparations. Patients, in the active treatment groups, were treated daily with 10g of each gelatine product (0.5g each tablet). All three gelatine preparations were significantly superior to placebo in reduction of pain, compared to placebo, at the end of the trial period. However, gelatine preparations did not cause any radiological or laboratory changes. The most common adverse effect from gelatine in this trial was heaviness in the stomach. In the second trial (389 people, treatment duration of 24 weeks), patients with OA were randomised in 20 sites in the UK, USA and Germany to receive either 10g of collagen hydrolysate or placebo tablets. Results of this study showed that collagen hydrolysate was relatively safe to use but had no significant effect on reducing pain and improving physical function in the total study group. There was a beneficial effect in patients with severe symptoms at the start of the study. Six RCTs were conducted to evaluate the role of collagen hydrolysate in treating patients with RA, four of which were included in a review article published in 1999. Reports of these six trials were published between 1993 and 1999; the number of patients included ranged from 60 to 274; the period of treatment ranged from 12 weeks to six months; and the dose of collagen hydrolysate used in these trials varied from 1g to 10g/day. Except for the first published trial (60 people, treatment period of three months) which found significant benefits of collagen hydrolyse in terms of pain and a reduction in swelling, all other trials found that collagen hydrolysate did not have a significant effect in reducing pain and joint inflammation in patients with RA.

**Conclusion:** Collagen is a dietary supplement extracted from animal or fish materials and can be purchased from pharmacies and health food shops in the form of capsules. Collagen is rich in amino acids that play an important role in the synthesis of joint cartilage. It has also been suggested that it can have anti-inflammatory effects through a mechanism which is not clearly understood. Trials on its role in treating OA are scarce and yielded mixed results. Trials on its role in treating RA suggest that collagen does not have a significant effect in reducing pain and joint inflammation in these patients.

### References:

- Henderson CJ, Panush RS. Diets, dietary supplements, and nutritional therapies in rheumatic diseases. *Rheum Dis Clin North Am* 1999;25(4):937-68.
- Moskowitz, RW. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum* 2000;30(2):87-99.
- Adam M. Therapie der osteoarthritis welche wirkung haben gelatineparaprate? *Therapiewoche* 1991;41:2456-61 [Article in German].
- Cazzola M, Antivalle M, Sarzi-Puttini P, Dell'Acqua D, Panni B, Caruso I. Oral type II collagen in the treatment of rheumatoid arthritis. A six month double blind placebo controlled study. *Clin Exp Rheumatol* 2000;18(5):571-7.
- McKown KM, Carbone LD, Kaplan SB, Aelion JA, Lohr KM, Cremer MA, et al. Lack of efficacy of oral bovine type II collagen added to existing therapy in rheumatoid arthritis. *Arthritis Rheum* 1999;42(6):1204-8.

### Classification:

#### Effectiveness score in OA:

2 

#### Effectiveness score in RA:

1 

#### Safety classification:

Green 



## 14 Devil's claw

**Family:** Herbal medication of the Bignoniaceae family.

**Scientific name:** Harpagophytum procumbens.

**Other names:** Grapple plant, wood spider, Doloteffin,<sup>®</sup> Rivoltan,<sup>®</sup> iridoid glycoside, WS 1531.

**Description of the compound:** Devil's claw is a plant native to deserts of South and Southeast Africa. Extracts from the plant root are used medicinally to treat several diseases.

**Mechanism of action:** Still not completely understood. Laboratory studies found that extracts from the plant root can block several pathways which cause joint inflammation. These anti-inflammatory properties have been attributed to its active ingredient called harpagoside. However, animal studies found that the analgesic properties of devil's claw cannot only be explained by this ingredient.

**Safety and toxicity:** Although uncommon, serious adverse effects (abnormal heart rhythm and bleeding) can occur in patients taking devil's claw. Other less serious adverse effects include, skin rash, stomach upset, diarrhoea, headache and loss of appetite.

**Availability:** The compound is available over-the-counter in the form of capsules, tinctures and fluid extract. Standardised commercial preparations include Doloteffin,<sup>®</sup> and Rivoltan<sup>®</sup>.

**Interactions:** Drug interactions have been documented with anticoagulants (e.g. aspirin), painkillers (e.g. ibuprofen), heart drugs (e.g. digoxin), stomach acid drugs (e.g. famotidine).

**Dosage:** 500-1,500mg of dried root or capsules three times daily.

**The role in treatment of arthritis and musculoskeletal conditions:** The potential therapeutic effect of devil's claw in treating OA of the hip or the knee has been the subject of investigation by five RCTs dating from 1980 as reported in a systematic review.

Three studies (two of which were considered of high quality) compared the outcome of devil's claw therapy with that of a placebo therapy. Patients who were allocated devil's claw in these three studies had a significant improvement in osteoarthritic pain, compared to those who were on placebo. One study (considered of high quality) compared the level of pain improvement in patients randomly selected to receive devil's claw with that of patients assigned to take phenylbutazone (a conventional treatment). Patients on devil's claw therapy reported fewer adverse effects and had slightly better pain improvement. One study (considered of high quality) compared the overall disease-related symptoms in two groups of patients who were randomly assigned to take either devil's claw or diacerhein (another conventional therapy for OA). The level of symptom improvement was similar in both groups following treatment, but patients allocated devil's claw experienced fewer adverse effects. A more recently published scientific article reviewed the same clinical trials and found that results of trials of high quality suggest that devil's claw is effective in the reduction of pain in patients with OA.

**Conclusion:** Devil's claw is a herbal medication that can be purchased over-the-counter in the form of capsules, tinctures and fluid extract. Its mechanism of action is still poorly understood. Evidence suggests that devil's claw is as effective as other conventional medicines for OA but adverse effects of devil's claw remain a concern.

### References:

- Gagnier JJ, Chrubasik S, Manheimer E. Harpagophytum procumbens for osteoarthritis and low back pain: a systematic review. BMC Complement Altern Med 2004;4:13.
- Brien S, Lewith GT, McGregor G. Devil's claw (Harpagophytum procumbens) as a treatment for osteoarthritis: a review of efficacy and safety. J Altern Complement Med 2006;12(10):981-93.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Amber 

## 15 Duhuo Jisheng Wan (DJW)

**Family:** Traditional Chinese herb.

**Scientific name:** Duhuo Jisheng Wan.

**Other names:** Du Huo Ji Sheng Tang, Du Huo Ji Shang, Du Huo Ji Sheng Wan, Duhuojishengwan.

**Description of the compound:** Duhuo Jisheng Wan is a medicinal formula composed of at least seven Chinese herbs including Radix Angelicae Pubescentis and Herba Taxilli.

**Mechanism of action:** According to traditional Chinese medicine theories, Duhuo Jisheng Wan can relieve pain by “expelling wind, clearing dampness and removing obstruction in Qi (energy)”. The biomedical mechanisms have not been well studied, but some laboratory studies have shown that Duhuo Jisheng Wan can clear inflammation by activating specific anti-inflammatory cells in the body.

**Safety and toxicity:** Reported adverse effects include raised blood pressure, dizziness, drowsiness, nausea, vomiting, diarrhoea and constipation.

**Availability:** Duhuo Jisheng Wan tablets are available to buy via the internet with different brand names (Guang Ci Tang, Plum Flower, Du Huo Ji Sheng Wan herbal pills).

**Interactions:** Data about interactions with other medications is not available.

**Dosage:** 3g of Duhuo Jisheng Wan, three times a day was used in one study.

### The role in treatment of arthritis and musculoskeletal conditions

**musculoskeletal conditions:** One RCT examined the effect of this compound in treating patients with OA of the knee. In this trial, 200 patients were randomly assigned to receive one of the following four treatments: diclofenac tablets (75mg/day), Duhuo Jisheng Wan tablets (9g/day), placebo tablets identical to those of diclofenac and placebo tablets identical to those of Duhuo Jisheng Wan.

The four groups were compared with respect to adverse events and effectiveness over a four week period of treatment. The proportions of patients reporting adverse effects were similar, around 30 per cent, in both groups of patients receiving diclofenac and Duhuo Jisheng Wan treatment, however both these groups reported adverse effects significantly more than the placebo groups. Compared to the corresponding placebo groups, patients who received either Duhuo Jisheng Wan or diclofenac had significantly lower scores for pain and stiffness. However, compared to diclofenac, the beneficial effects of Duhuo Jisheng Wan were slower to develop.

**Conclusion:** Duhuo Jisheng Wan is a Chinese herbal mixture which is available in tablet form and can be purchased via the internet. The compound seems to activate specific anti-inflammatory cells in the body. However, there is little evidence available on treating OA patients with Duhuo Jisheng Wan – the only randomised trial suggests an effect equal to that of NSAIDs, but more evidence is needed before a conclusion can be reached on effectiveness and safety.

### References:

- Teekachunhatean S, Kunanusorn P, Rojanasthien N, Sananpanich K, Pojchamarnwiputh S, Lhieochaiphunt S, et al. Chinese herbal recipe versus diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. BMC Complement Altern Med 2004;4:19-27.

### Classification:

#### Effectiveness score:

2 

#### Safety classification:

Amber 



## 16 Eazmov

**Family:** Ayurvedic herbal preparation.

**Scientific name:** Eazmov herbal preparation.

**Description of the compound:** Eazmov is a mixture of five herbs (ginger, purple nutsedge, guduchi, picrorrhiza and costus).

**Mechanism of action:** Ginger inhibits the production of certain types of prostaglandins involved in joint inflammation. It can also reduce the release of serotonin which is a chemical substance in the body which plays a role in regulating mood, sleep patterns, concentration and pain perception. Both purple nut sedge and guduchi are believed to have potent anti-inflammatory properties. The mechanism of action of costus and picrorrhiza is not well known.

**Safety and toxicity:** Not well studied but the limited data available suggests that the herbal mixture has no major safety problems.

**Availability:** Eazmov is available in the form of capsules and ointment and can be ordered via the internet.

**Interactions:** Not well studied.

**Dosage:** Not well studied for patients with musculoskeletal conditions.

### The role in treatment of arthritis and musculoskeletal conditions:

In this trial, 60 patients with arthritis (in any form, including OA and RA) were randomised to receive either three capsules/day of Eazmov or three capsules/day of 50mg diclofenac. After six months of treatment, patients in both groups were compared regarding pain reduction, duration of morning stiffness and improvement in disabilities and grip strength. Compared to patients who were on diclofenac, patients who received Eazmov had less improvement in almost all aspects of disease severity, including less reduction in pain severity and less improvement in disabilities. However, patients who were allocated Eazmov reported significantly fewer adverse effects.

**Conclusion:** Eazmov is a herbal mixture of five compounds believed to have analgesic and anti-inflammatory properties. This Ayurvedic preparation can be purchased via the internet in the form of capsules or ointment. The limited data available suggests that it is safe to use but its efficacy in treating RA and OA is less than that of non-steroidal anti-inflammatory medications.

### References:

- Biswas NR, Biswas K, Pandey M, Pandey RM. Treatment of OA, rheumatoid arthritis and non-specific arthritis with a herbal drug: A double-blind, active drug controlled parallel study. JK Pract 1998;5:129-32.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

Green 

## 17 Evening primrose oil (EPO)

**Family:** Plant family of Onagraceae.

**Most commonly used commercial name:** Evening primrose oil (EPO).

**Scientific name:** *Oenothera biennis*.

**Other names:** Tree primrose, fever plant, night willow-herb, King's-cure-all, scabish, scurvish, sun drop, suncups.

**Description of the compound:** EPO is a North American native biennial plant, but now found all over the world. The medicinal product is derived from the plant's seeds.

**Mechanism of action:** EPO is a rich source of two types of polyunsaturated omega-6 essential fatty acids: linolenic acid (LA; 70 per cent; converted in the body to GLA) and gamma-linolenic acid (GLA; two–15 per cent). GLA is a vital precursor of hormone-like molecules in the body called prostaglandins which are important for the regulation of pain and inflammation. GLA might also suppress inflammatory responses by directly acting on some inflammatory cells. Sunflower oil and other oils generally used in normal diet contain only LA. Several factors can interfere with the production of GLA from LA in the body. These include aging, dietary deficiencies, viral infections and some diseases. EPO is one of the richest sources of pure GLA.

**Safety and toxicity:** The compound, if taken in the correct dose, has no major safety problems. Common adverse effects include nausea, diarrhoea and skin rash. Patients with epilepsy or seizure disorder should not take this product as it can induce seizures.

**Availability:** EPO is formulated in capsules (500-1,300mg) or oil (150ml) and is sold over-the-counter in chemists.

**Interactions:** Not well studied, but interactions with anti-inflammatory drugs (e.g. cortisone) and anti-coagulants (e.g. aspirin, warfarin) are possible.

**Dosage:** No recommended safe doses have been established for the use in musculoskeletal conditions. A dose of 6g/day (540mg GLA/day) has been used in previous trials.

**The role in treatment of arthritis and musculoskeletal conditions:** Two RCTs examined the effect of this compound in treating RA patients. In the first trial, 49 RA patients, who were on non steroidal anti-inflammatory drugs (NSAIDs) were randomised to take one of the following three treatments for 12 months: EPO (6g/day; 540mg GLA/day), EPO with fish oil, or placebo tablets. Patients were asked to take their normal dose of NSAIDs (e.g. ibuprofen) during the first three months of the trial, but were advised to reduce or stop it according to their symptoms thereafter. Two of the patients on EPO withdrew from the trial because of adverse effects (nausea and diarrhoea). After 12 months of treatment, the difference in treatment outcomes between active treatments and placebo were significant, with 94 per cent of patients who got EPO alone and 93 per cent who received EPO combined with fish oil reporting a significant improvement of disease-related symptoms including pain and morning stiffness compared to only 30 per cent improvement in patients in the placebo group. EPO was also significantly effective in reducing the amount of NSAIDs intake during the trial period. EPO did not seem to modify the long-term disease activity, as symptoms relapsed in most of the patients during the three month period that followed treatment. In the second RCT, researchers evaluated the outcome of 40 RA patients who received six months treatment of either EPO (6g/day; 540mg GLA/d) or olive oil. Four out of 19 patients taking evening primrose had to withdraw because of nausea, flu-like symptoms or deteriorating disease condition. At the end of six months, patients allocated EPO had a significant improvement in morning stiffness, compared to patients assigned olive oil, but there were no significant differences between both treatment groups with respect to pain reduction and overall disease severity. Most patients in this trial did not stop NSAIDs.

## 18 Feverfew

**Conclusion:** EPO is rich in polyunsaturated omega-6 fatty acids that can help in the regulation of pain and inflammation with no major safety problems. Products containing this compound are available in most pharmacies, health food shops and supermarkets. Evidence for the effectiveness of EPO in reducing joint pain in RA patients is not conclusive. However, there is some evidence for effectiveness in improving morning stiffness. EPO does not seem to modify long-term disease activity, so, if used, should be taken along with conventional therapy.

### References:

- Brzeski M, Madhok R, Capell HA. Evening primrose oil in patients with rheumatoid arthritis and adverse effects of non-steroidal anti-inflammatory drugs. *Br J Rheumatol* 1991;30(5):370-2.
- Belch JJF, Ansell D, Madhok R, Dowd AO, Sturrock RD. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. *Ann Rheum Dis* 1988;47(2):96-104.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Green 

**Family:** Perennial plant in the family Compositae (sunflower family).

**Scientific name:** *Chrysanthemum parthenium*, (or *tanacetum parthenium*).

**Other names:** Bachelor's buttons, featherfew, Santa Maria, Mother-herb, altamisa, featherfoil, flintwort, midsummer Daisy, febrifuge plant.

**Description of the compound:** *Chrysanthemum parthenium* or feverfew is a perennial, originally native to Eastern Europe and Asia Minor, but is now cultivated throughout Europe and America. Medicinally-used compounds are prepared from the leaves of the plant.

**Mechanism of action:** Feverfew is believed to have a range of properties, including anti-inflammatory and analgesic. It has been postulated that it reduces the release of an inflammatory substance, serotonin, from blood cells and slows down the production of a chemical transmitter in the body called histamine. Both serotonin and histamine play an important role in migraine headache.

**Safety and toxicity:** No major safety problems have been identified in short-term use. The long-term safety is not known. Reported adverse effects from previous studies (mainly on migraine patients) include mouth ulceration, indigestion, heartburn, colicky abdominal pain, dizziness and skin rash.

**Availability:** Feverfew is available over-the-counter in tea, pill, capsule and tincture forms.

**Interactions:** Clinical interaction with other drugs has not been extensively studied. However, feverfew might increase the risk of bleeding if taken with other medications which affect blood clotting like aspirin, heparin and warfarin.

## 19 Fish oil

**Dosage:** No recommended safe doses have been established for the use in musculoskeletal conditions. Previous RCTs studies of feverfew in migraine patients, which showed encouraging results, used doses between 50 and 140mg of powdered or granulated leaf preparations daily.

**The role in treatment of arthritis and musculoskeletal conditions:** One RCT (41 people), was performed to evaluate its effectiveness in treating patients with RA. Twenty patients were randomly selected to take one daily capsule containing 70-86mg of powdered feverfew leaf for six weeks, while the other 21 patients were randomly selected to take a daily placebo capsule for the same time period. Both treatment groups were asked to continue on their usual medications for RA. No significant differences were found between the two groups in the clinical and laboratory presentation of the disease at the end of the treatment. Only one patient in the treatment group reported minor ulcerations and sore tongue.

**Conclusion:** Feverfew is believed to have anti-inflammatory and analgesic properties. It can be purchased over-the-counter from pharmacies, health food shops and supermarkets. The current limited evidence suggests that this compound has only minor adverse effects in the short-term, but does not suggest a therapeutic benefit to patients with RA.

### References:

- Patrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double-blind, placebo controlled study. *Ann Rheum Dis* 1989;48(7):547-9.
- Ernst E, Pittler MH. The efficacy and safety of feverfew (*Tanacetum parthenium* L.): an update of a systematic review. *Public Health Nutr* 2000;3(4A):509-14.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

Green 

**Family:** Dietary supplements; omega-3 essential fatty acids.

**Scientific name:** Fish oil (fish body oil and/or fish liver oil).

### Description of the compound:

*Fish body oil:* These are dietary supplements derived from tissues of fatty fish like sardines, sprat, salmon, and mackerel.

*Fish liver oil:* These are dietary supplements derived by pressing cooked liver of cod (most commonly), halibut or shark.

**Mechanism of action:** Fish body and/or liver oils are rich in omega-3 essential fatty acids. These fatty acids have strong anti-inflammatory properties. Firstly, they significantly reduce the release of several pro-inflammatory elements from white blood cells. Secondly, they form the building blocks for the production of anti-inflammatory substances in the blood called prostaglandins. Prostaglandins are hormone-like substances that regulate the immune system and fight joint inflammation. Omega-3 fatty acids also play a role in lowering cholesterol and triglyceride levels in blood, hence reducing the risk of heart disease and stroke in patients with inflammatory types of arthritis. Fish liver oil (cod-liver oil – see below) also contains high levels of vitamin A and D. Vitamin A is a strong anti-oxidant (i.e. can prevent cell damage in the body by interacting with harmful molecules produced within the cells known as free radicals). Vitamin D, in addition to its role in maintenance of a healthy musculoskeletal system, plays an important part in the production of proteoglycan in joint cartilage.

**Safety and toxicity:** Fish body and fish liver oils are considered to be safe at therapeutic doses. The most common adverse effect is stomach upset. However if these oils are consumed in very high doses there is concern about potential environmental contaminants such as methylmercury and polychlorinated biphenyls (PCBs). These compounds can also accumulate in people eating fish frequently. Adverse effects, at therapeutic doses, which are usually minor and uncommon, include stomach upset, flatulence and diarrhoea. It is important not to consume large amounts of fish liver oil (cod-liver oil), so as not to exceed recommended dietary allowance of vitamin A. Excess intake of vitamin A can lead to liver problems and hair loss. Excess vitamin A may also harm unborn babies and therefore cod liver oil and vitamin A supplements should be avoided in pregnancy. Poorly-purified cod-liver oil can contain some contaminants (e.g. mercury, and dioxins), which can lead to health problems. However, most supplement companies test cod liver oil for purity before they become publicly available.

**Availability:** Fish body and liver oils are available over-the-counter in the form of capsules and bottled oil.

**Interactions:** Fish body or liver oils can interfere with blood clotting, so should not be taken together with other medications which prevent clotting (e.g. aspirin and warfarin).

**Dosage:** No recommended safe doses have been established for the use of fish body or liver oils in arthritis and musculoskeletal conditions until now. In the UK, the recommended daily intake of omega-3 fatty acids has been set by the government at a weekly target of 1.5g.

### **The role in treatment of arthritis and musculoskeletal conditions:**

*Fish body oil:* The potential therapeutic effect of fish body oils in patients with RA has been a subject for investigation by several RCTs dating from 1985. However, most of these trials were conducted on a small number of patients. In order to get a better idea of the effectiveness of these supplementations, data from ten of these trials were combined in one report and re-analysed. The quality of the trials included in this review ranged between low and moderate. The report found that, compared to the placebo treatments, fish body oil significantly decreased the number of tender joints and shortened the duration of morning stiffness. However, the oil supplement failed to make a significant change in a number of other disease parameters (e.g. grip strength, blood tests for disease activity and the overall disease severity). A more recent review article gave an overview of all results obtained from a total of 17 RCTs investigating the role of fish body oil in patients with RA. The dose of omega-3 fatty acids used in these trials ranged between 1.6 and 7.1g/day with an average dose of 3.5g/day. Evidence from these RCTs suggest that fish oil supplements are generally safe to use and can significantly reduce joint pain, reduce the duration of morning stiffness, fatigue time and reduce the number of tender or swollen joints. In addition, fish body oil can significantly reduce the usage of painkillers amongst people with RA.

*Fish liver oil (cod-liver oil):* An RCT was conducted to evaluate the role of cod-liver oil in treating patients with OA. In this trial, 86 OA patients were randomly allocated to receive 10ml daily of either cod-liver oil or olive oil for 24 weeks. Patients in both groups were asked to continue with their regular NSAID through the trial period. Approximately 70 per cent of patients in the group taking cod-liver oil completed the 24-week trial, compared to 79 per cent of patients who were given olive oil. However, adverse effects from treatments were not the main reasons for withdrawal. Similar proportions of patients in the cod-liver oil (30 per cent) and olive oil (24 per cent) groups reported adverse effects.



These adverse effects, which were minor and similar in nature in both groups, included stomach upset and dry skin. This study did not find any significant difference between the two treatment groups in the amount by which the patients' pain and disability changed during the study. In addition, both treatments failed to significantly reduce pain and disability symptoms of OA. A recently published RCT evaluated the role of capsules containing a combination of cod liver oil and fish body oil (SSMO1) in treating patients with RA and its potential effect in reducing the daily NSAID requirement in these patients. In this nine month trial, 97 RA patients were randomly selected to receive either ten capsules daily of SSMO1 (containing 1g of cod-liver oil/capsule) or ten capsules of placebo. Approximately 65 per cent of patients in the group allocated cod-liver oil completed the trial, compared to 54 per cent of patients taking the placebo. Withdrawal from the trial was not attributed to adverse effects, but it might have been related to the large number of capsules patients were asked to take every day. In patients who completed the trial, there was no significant difference in the number or type of adverse effects reported by patients in both treatment groups. Most of the adverse effects were mild and gastrointestinal in nature. There was no difference in outcome at 12 weeks of the trial but patients given SSMO1 had a modest improvement in pain after 24 and 36 weeks compared to the placebo group. There was a significant difference between the two treatment groups in the degree of reduction of the daily NSAID requirements with 39 per cent of patients allocated SSMO1 reporting a significant reduction compared to just ten per cent in the placebo group.

**Conclusion:** Fish body oil and fish liver oil (cod-liver oil) are rich in omega-3 essential fatty acids which can regulate the body's immune system and fight joint inflammation. Cod-liver oil is also a rich source of vitamin A (a strong anti-oxidant) and vitamin D (important for maintaining healthy joints).

Products containing fish body and liver oils (capsules and bottled oil) are widely available in supermarkets, pharmacies and health food shops. Evidence suggests that both fish body and liver oils are safe with no major adverse effects if taken at therapeutic doses. There is good evidence that fish body oil can result in improvement in the symptoms associated with RA. There is also some unconfirmed evidence that the combined treatment of fish body and liver oils might be of long-term benefit to patients with RA, particularly in reducing daily requirements of NSAIDs. Evidence for the use of fish liver oil (cod-liver oil) in patients with OA is based on insufficient data.

#### References:

- Cleland LG, Caughey GE, James MJ, Proudman SM. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. *J Rheumatol* 2006;33(10):1973-9.
- Fortin PR, Lew RA, Liang MH. Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. *J Clin Epidemiol* 1995;48(11):1379-90.
- Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106(21):2747-57.
- Calder PC. Polyunsaturated fatty acids, inflammation and immunity. *Lipids* 2001;36(9):1007-24.
- Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr* 2006;83(6 Suppl):1505S-1519S.
- Stammers T, Sibbald B, Freeling P. Efficacy of cod liver oil as an adjunct to non-steroidal anti-inflammatory drug treatment in the management of osteoarthritis in general practice. *Ann Rheum Dis* 1992;51(1):128-9.
- Galarraga B, Ho M, Youssef HM, Hill A, McMahon H, Hall C, et al. Cod liver oil (n-3 fatty acids) as a non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. *Rheumatology (Oxford)* 2008;47(5):665-9.

#### Classification:

##### Effectiveness score of fish body oil in RA:

5 

##### Effectiveness score of fish liver oil in OA:

1 

##### Safety classification:

Green 

## 20 Flaxseed oil

**Family:** Herbal medicine of the Linaceae plant family.

**Scientific name:** *Linum usitatissimum* (or flax plant).

**Other names:** Linseed, brown, golden flaxseed.

**Description of the compound:** The flax plant is native to Egypt, but cultivated in many places, including Europe and the United States. Oil extracted from the plant seeds is used medicinally for treating several diseases.

**Mechanism of action:** Flaxseed oil contains alpha linolenic acid (ALA), which is an omega-3 essential fatty acid. ALA is converted into two important compounds within the body – DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid). Both DHA and EPA play a significant role in the production of anti-inflammatory substances in the blood called prostaglandins. These hormone-like substances regulate the immune system and fight joint inflammation. Flaxseed oil also contains some chemicals called lignans, which have anti-oxidant properties and hence have been used to prevent cardiovascular disease.

**Safety and toxicity:** Adverse effects include stomach discomfort, rash and breathing difficulties. In theory, flaxseed may increase the blood sugar level and increase the risk of bleeding.

**Availability:** Flaxseed oil is available over-the-counter in the form of capsules.

**Interactions:** Flaxseed might increase the risk of bleeding if taken with other medications which affect blood clotting like aspirin, heparin and warfarin.

**Dosage:** No recommended safe doses have been established for its use in musculoskeletal conditions.

### The role in treatment of arthritis and musculoskeletal conditions:

One RCT (22 people) was performed to investigate its potential role in treatment of RA. Patients were randomly selected to be treated with either flaxseed oil or a placebo medication. After three months of treatment, the blood levels of EPA and DHA did not rise, and the two treatment groups showed no difference with respect to symptom reporting, laboratory findings and clinical signs on physical examination.

**Conclusion:** Flaxseed oil, which can be purchased over-the-counter in capsule form, is rich in an omega-3 fatty acid called alpha-linolenic acid (ALA). This fatty acid can help in reducing joint inflammation. The safety profile of flaxseed oil has not yet been fully established. The limited evidence available suggests that flaxseed oil is not effective in the treatment of patients with RA.

### References:

- Nordstrom DC, Honkanen VE, Nasu Y, Antila E, Friman C, Konttinen YT. Alpha-linolenic acid in the treatment of rheumatoid arthritis. A double-blind, placebo-controlled and randomized study: flaxseed vs. safflower seed. *Rheumatol Int* 1995;14(6):231-4.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

Amber 

## 21 Ginger

**Family:** Herbal medicine; Zingiberaceae (ginger family).

**Scientific name:** Zingiber officinale.

**Other names:** Gan Jiang, zingiber, EV.EXT35, African ginger, black ginger, chayenne ginger, Zinaxin\*.

**Description of the compound:** Ginger is a plant native to China, Southeast Asia, West Africa and the Caribbean. The herbal preparation is extracted from the rhizome which is part of the stem of the plant.

**Mechanism of action:** Some studies in the laboratory and on animals have found that extracts from ginger can reduce the production of several chemical substances (including leukotrienes) that promote joint inflammation. Ginger also contains salicylates, which is transformed by the body into a chemical substance called salicylic acid. Salicylic acid inhibits the production of certain prostaglandins in the nerves and this effect relieves pain and discomfort.

**Safety and toxicity:** Ginger is a relatively safe herbal remedy with minor adverse effects. The most commonly reported adverse effects are stomach upset and irritation of the mouth.

**Availability:** Ginger is available over-the-counter in pharmacies and health food shops in the form of capsules and oil.

**Interactions:** Treatment with ginger might increase the risk of bleeding if taken with other medications which affect blood clotting like aspirin, heparin and warfarin.

**Dosage:** No recommended safe and effective doses have been established for use in musculoskeletal conditions. Doses ranging from 510mg/day to 1,000mg/day have been used in previous RCTs.

**The role in treatment of arthritis and musculoskeletal conditions:**

Three RCTs evaluated the role of ginger in the treatment of patients with OA. In the first trial, 67 patients with OA of the hip or knee were randomised to three treatment groups of three weeks each. Either 170mg capsules of ginger extract, 400mg ibuprofen tablets or placebo were administered three times daily. Paracetamol (an analgesic) was administered as a rescue drug for pain relief during the study. Patients who were randomised to either ibuprofen or ginger had a significant reduction in pain scores and reported less consumption of paracetamol compared to those who got placebo tablets, but ibuprofen was more effective than ginger in both treatment outcomes. In the second trial, 29 patients with knee OA were randomised to receive a three month treatment of either 250mg of ginger capsules four times a day or an identical number of placebo capsules (phase A). Patients taking ginger were then given the placebo, and patients who were on placebo were given ginger capsules for an additional three months (phase B). At the end of phase A, patients who were treated with ginger had a significant reduction in pain and disease-related disability when compared to patients who were allocated placebo during the same phase. However, no significant difference between treatment groups was observed at the end of phase B of the trial. In the third trial, 247 patients with knee OA were randomised to receive either 255mg of ginger capsules twice a day or an identical number of placebo capsules. Paracetamol was administered as a rescue drug for pain relief during the study. After six months of treatment, 63 per cent of patients who were treated with ginger had significant reduction in knee pain compared to 50 per cent of the placebo group. The severity of pain and overall improvement of OA-related symptoms were also significantly reduced in the group taking ginger compared to the placebo group. However, both groups were similar with respect to their perceived improvement in quality of life and the ginger group reported more gastrointestinal adverse effects (e.g. heartburn), but these adverse effects were relatively mild and tolerable in patients.

## 22 Gitadyl

**Conclusion:** Ginger extracts are available over-the-counter in pharmacies in the form of capsules and oil. Theoretically, ginger can reduce the activity of several chemical substances that promote joint inflammation. Results from RCTs evaluating its role in treating patients with OA found that it has a high safety profile and can have moderate beneficial effects in reducing pain and disability in these patients.

### References:

- Bliddal H, Rosetzky A, Schlichting P, Weidner MS, Andersen LA, Ibfelt HH, et al. A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. *Osteoarthritis Cartilage* 2000;8(1):9-12
- Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis Rheum* 2001;44(11):2531-8.
- Wigler I, Grotto I, Caspi D, Yaron M. The effects of Zintona EC (a ginger extract) on symptomatic gonarthrosis. *Osteoarthritis Cartilage* 2003;11(11):783-9.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Green 

**Family:** A remedy composed of a mixture of herbal medications.

**Scientific name:** Gitadyl herbal mixture.

**Description of the compound:** Gitadyl is a herbal medication containing feverfew 110mg, American aspen 90mg, and milfoil 60mg.

**Mechanism of action:** Feverfew inhibits the release of an inflammatory substance from blood cells called serotonin. It also inhibits the production of a chemical transmitter in the body called histamine. Both histamine and serotonin play important roles in the function of the immune system and pain transmission and perception. Several previous studies (laboratory-based and on animals) have found that American aspen (poplar bark) and milfoil have anti-inflammatory effects.

**Safety and toxicity:** Adverse effects include mild skin rash and stomach upset, but no major adverse effects have been reported.

**Availability:** No information available.

**Interactions:** Interactions with other medications have not been well studied.

**Dosage:** Not well studied. Three tablets of Gitadyl per day have been used in one study.

**The role in treatment of arthritis and musculoskeletal conditions:** One RCT examined the use of this compound in treating patients with OA. In this trial, 35 patients were randomly selected to receive either three tablets of gitadyl per day or 1,200mg of ibuprofen daily. After three weeks of treatment, patients in both groups had almost the same level of pain reduction and improved walking ability. Stomach upset was more commonly reported by patients who received ibuprofen.

## 23 Glucosamine

**Conclusion:** Gitadyl is a herbal mixture which can be ordered via the internet in tablet form. Ingredients of this remedy fight joint inflammation and suppress pain transmission. The effectiveness of Gitadyl for OA is uncertain as only one small RCT has been conducted to test the potential therapeutic benefits of this compound. Evidence from this trial suggests that Gitadyl is a safe drug with an analgesic effect similar to that of ibuprofen (e.g. Voltaren).

### References:

- Rytting K, Schlamowitz PV, Warnoe O, Wilstrup F. [Gitadyl versus ibuprofen in patients with osteoarthritis. The result of a double-blind, randomized cross-over study]. Ugeskr Laeger 1991;153(33):2298-9. [Article in Danish].

### Classification:

#### Effectiveness score:

2 

#### Safety classification:

Green 

**Family:** Nutritional supplement.

**Scientific name:** Glucosamine sulphate, glucosamine hydrochloride.

**Other names:** Glucose-6-phosphate, GS, amino monosaccharide, sulfated monosaccharide, chitosamine, D-glucosamine.

**Description of the compound:** Amino sugar derived from shellfish or prepared in the laboratory.

**Mechanism of action:** Glucosamine is found naturally in the body. It plays an important role in the synthesis of glycosaminoglycans and glycoproteins which are essential biochemical components (i.e. the building blocks) of many structures of the joints, including the ligaments, tendons, cartilage and the synovial fluid. It has been suggested that the mechanism by which these joint structures are built and maintained contributes to the development and the progression of OA. Studies on animals have found that administration of glucosamine can delay the degradation of cartilage as well as rebuild it.

**Safety and toxicity:** Adverse effects, which are usually mild and infrequent, include stomach upset, constipation, diarrhoea, headache and rash. The drug should not be taken by patients who are allergic to shellfish. Adverse effects, which are usually mild and infrequent, include stomach upset, constipation, diarrhoea, headache and rash.

**Availability:** This nutritional supplement is widely available in pharmacies and supermarkets in the form of capsules and cream. The compound is available in two main formats: glucosamine hydrochloride and glucosamine sulphate.

**Interactions:** There are several reports of interaction between glucosamine and anti-diabetic treatments. Glucosamine might increase the blood sugar level in diabetics requiring therapeutic adjustments to their diabetic control. There are also some reports of possible interaction with chemotherapy drugs and drugs that lower blood cholesterol.



**Dosage:** Most trials used a standard dose of 500mg of glucosamine sulphate or glucosamine hydrochloride taken three times each day.

**The role in treatment of arthritis and musculoskeletal conditions:** Glucosamine is one of the most commonly investigated complementary medications for OA. As mentioned earlier, there are two forms of glucosamine that can be purchased for the treatment of OA: glucosamine sulphate and glucosamine hydrochloride. We will present the evidence with respect to the effectiveness of these two preparations separately.

*Glucosamine sulphate:* A recent updated review article, published in 2005, summarised results of 18 RCTs that investigated the effectiveness of this dietary supplement in treating patients with OA. The number of patients included in these studies ranged from 30 to 319 and duration of the trials ranged from three weeks to three years. In all the 13 RCTs which compared glucosamine sulphate to placebo, the number and severity of adverse effects reported by patients who were given glucosamine sulphate were not significantly different from those reported by patients who got placebo. Seven trials out of these 13 found that the glucosamine sulphate was significantly better than placebo in relieving pain, and three trials out of five found that glucosamine sulphate was significantly better than placebo in improving problems associated with walking and other activities of daily living. However, no trials found that glucosamine sulphate was significantly effective, as compared to placebo, in improving all the main symptoms of the disease (pain, disability and joint stiffness). Based on this review article, trials that used the preparation of one company (Rotta Pharm) showed a positive effect for pain and function while those that used other preparations found that neither significantly improved. In addition, evidence from trials that used the best methods to ensure that the patients did not know which treatment they were getting (glucosamine or placebo) did not show significant benefits in relieving pain and improving physical function in patients who received glucosamine sulphate. More recently, two RCTs published in 2007 (222 people; two years of treatment) and 2008 (318 people; six months of treatment) evaluated the efficacy of glucosamine sulphate in the treatment of

hip and knee OA, respectively. Results of these two trials were inconsistent, with the first trial demonstrating no beneficial effects of glucosamine sulphate, compared to placebo, in relieving pain and improving function, and the second trial demonstrating a clear significant benefit of glucosamine over placebo, and an even stronger effect than paracetamol (a commonly used painkiller) in improving both pain and function. A review article summarised results of trials that compared the clinical effectiveness and safety of glucosamine sulphate with those of NSAIDs. Two trials out of three found that glucosamine sulphate was significantly more effective than NSAIDs in reducing pain, while the third found that both medications had similar effects. One trial out of two found that glucosamine sulphate was significantly better than NSAIDs in improving physical function, while the second trial found that both medications had similar effects. Three trials out of four found that the number and severity of adverse effects reported by patients taking glucosamine sulphate were significantly less than those reported by patients who were given NSAIDs.

*Glucosamine hydrochloride:* Two RCTs were conducted to evaluate the role of glucosamine hydrochloride in the treatment of patients with knee OA. In the first trial (118 people, eight week period), 49 per cent of patients who were randomly selected to receive 1,500mg/day of glucosamine hydrochloride reported that they were “better than at the start of the trial”. The same positive response was reported by 40 per cent of the patients who got placebo capsules, suggesting that glucosamine hydrochloride is not significantly superior to placebo in improving OA-related symptoms. In addition, this trial found that glucosamine hydrochloride was not significantly better than placebo in reducing pain, stiffness and physical function in these patients. In the second trial (1,583 people; 24-week period), patients with knee OA were randomly assigned to receive one of the following five treatments: glucosamine hydrochloride (1,500mg/day), chondroitin sulphate (1,200mg/day), both treatments, celecoxib (NSAID) or placebo capsules. Patients who received glucosamine hydrochloride or chondroitin sulphate did not achieve a significant improvement in pain, stiffness and physical function when compared to patients who were assigned the placebo. The only two groups of patients

who achieved significant improvement in OA-related symptoms when compared to placebo were those who were assigned celecoxib and those who had moderate-to-severe knee pain at the outset of the trial and were given both glucosamine hydrochloride and chondroitin sulphate during the trial. In both RCTs, adverse effects of glucosamine hydrochloride were only mild and infrequent.

**Conclusion:** Glucosamine is a nutritional supplement which is derived from shellfish or prepared in the laboratory. It is widely available in pharmacies, health food shops and supermarkets in two preparations: glucosamine sulphate and glucosamine hydrochloride. Studies in animals have found that glucosamine can both delay degradation and repair damaged cartilage. The role of glucosamine in the treatment of OA has been a subject of at least 21 RCTs. Despite some mixed results, the majority of trials that have evaluated the effectiveness of glucosamine sulphate demonstrated significant clinical benefits when compared to placebo or NSAIDs. Evidence from trials on glucosamine hydrochloride is scarce and much less convincing. The medication, in both its sulphate and hydrochloride preparations, appears to be safe with only mild and infrequent adverse effects.

## References:

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## Classification:

### Effectiveness score for

#### Glucosamine sulphate:

3 

### Effectiveness score for

#### Glucosamine hydrochloride:

1 

### Safety classification:

Green 

## 24 Green-lipped mussel

**Family:** Nutritional supplement.

**Scientific name:** *Perna canaliculus*.

**Other names:** New Zealand mussel, greenshell mussel, Seaton®, GLM, Lyprinol®.

**Description of the compound:** A dietary supplement extracted from *perna canaliculus*, a bivalve mollusc native to New Zealand.

**Mechanism of action:** The mechanism of action of green-lipped mussel is not well established. Extracts from *perna canaliculus* contain omega-3 fatty acids, amino acids, minerals and carbohydrates. Studies in the laboratory and in animals have shown that omega-3 fatty acids have anti-inflammatory properties and are important for maintaining joint cell structure and function, and this might be one of the mechanisms by which green-lipped mussel works in some people.

**Safety and toxicity:** Occasional reports of gastrointestinal discomfort (e.g. nausea and flatulence) have been documented. However the compound does not seem to have any major safety concerns.

**Availability:** The compound is available over-the-counter in the form of capsules and gel.

**Interactions:** Not well studied, but interactions with anti-coagulants (e.g. aspirin, warfarin) are possible.

**Dosage:** No recommended safe doses have been established for use in musculoskeletal conditions.

**The role in treatment of arthritis and musculoskeletal conditions:** A recent review article summarised results of four RCTs that have been published investigating the effectiveness of green-lipped mussel in treating OA. The number of patients with OA included in these trials ranged from 30 to 80 patients, and the duration of the trials ranged from three and six months. Three of these trials (two of them low quality) compared the potential beneficial effects of green-lipped mussel supplements with placebo capsules. Results of these trials showed that green-lipped mussel is more effective than placebo in improving some clinical manifestations of the disease. It

was effective in reducing pain, improving function and overall quality of life of patients when taken along with usual painkillers (e.g. paracetamol, NSAIDs). The fourth trial<sup>‡</sup> compared the effectiveness of two forms of the compound (the lipid extract vs. the powder) and found that both forms were effective with 73 per cent and 87 per cent showing significant improvement in the group who got the lipid extract and the group who got the powder, respectively. With respect to RA, a recent review of medical literature identified and summarised results of four RCTs. The number of patients with RA included in these trials ranged from six to 47 patients, and the duration of the trials ranged from three and six months. All, except one trial found that green-lipped mussel was no better than placebo in improving the health of patients with RA.

**Conclusion:** Green-lipped mussel is a dietary supplement extracted from a type of mussel native to New Zealand. It can be purchased over-the-counter in the form of capsules. Its mechanism of action in the management of patients with arthritis and musculoskeletal conditions is poorly understood, but the compound contains omega-3 fatty acids, which exert anti-inflammatory and joint-protecting properties. Current evidence suggests that this compound might be of some benefit to patients with OA when taken along with paracetamol or NSAIDs. However, the current evidence suggests it is not effective in treating patients with RA.

### References:

- Cobb CS, Ernst E. Systematic review of a marine nutraceutical supplement in clinical trials for arthritis: the effectiveness of the New Zealand green-lipped mussel *Perna canaliculus*. Clin Rheumatol 2006;25(3):275-84.
- Brien S, P. Prescott, Coghlan B, Bashir N, Lewith G. Systematic review of the nutritional supplement *Perna canaliculus* (Green Lipped Mussel) in the treatment of osteoarthritis. QJM 2008;101(3):167-79.

### Classification:

#### Effectiveness score in OA:

3 

#### Effectiveness score in RA:

1 

#### Safety classification:

Green 

<sup>‡</sup> A trial of low quality. Results of this trial were given a lower weighting in coming to our conclusion about the compound.

## 25 Homeopathy

**Description of the compound:** Homeopathy is a form of treatment founded by Samuel Hahnemann in the 18th century. According to The Society of Homeopaths in England, homeopathy is based on the theory of “treating like with like” and based on an observation that symptoms of an illness are identical to those experienced by a healthy person treated for that illness. Homeopathic remedies are produced by a sequence of dilutions of an active substance causing similar symptoms in the belief that this will reduce the likelihood of harm.

**The philosophy behind the practice of homeopathy:** Similar to traditional Chinese medicine, homeopathy is a holistic method of treatment and hence, the mechanism of action of its remedies is not clear. Remedies are often diluted to the point where there may be no molecules of original substance left.

**Safety and toxicity:** Homeopathic remedies are considered to be safe, although allergic reactions (e.g. rash) have been reported by some patients. Worsening of symptoms might also occur in some patients at the beginning of treatment.

**Availability:** Homeopathy is a system of treatment practised by professional homeopaths who are qualified to prescribe remedies according to their diagnosis of the disease. However, homeopathic remedies are readily available over-the-counter in pharmacies and health food shops throughout the UK. These remedies, which are in the form of granules, tablets, powders or drops, are mainly for symptomatic treatment of disease-related symptoms (e.g. for pain).

**Interactions:** Interactions with other drugs have not been well studied, although this is unlikely to occur given the high dilution of these remedies.

**Dosage:** Not well studied. There are many homeopathic remedies that can be used in the treatment of various forms of arthritis. Patients should follow the dosage recommended by the homeopath or the homeopathic pharmaceutical company.

**The role in treatment of arthritis and musculoskeletal conditions:** A systematic review identified three RCTs of oral or topical homeopathic treatment of OA; two trials were conducted on patients with knee OA and one trial was on patients with hip and/or knee OA; the number of patients included in these trials ranged from 36 to 184 and the duration of treatment from two to five weeks. The first trial (65 people) compared oral administration of a homeopathic remedy *Rhus toxicodendron*, and *Lacc Vaccinum* for one month with placebo drops and paracetamol tablets for the same treatment period. A significant, but similar, reduction of pain was observed in the two treatment groups. The second trial (36 people) compared oral administration of a homeopathic remedy, *Rhus toxicodendron* (group 1); oral administration of 600mg/day of an NSAID, *Fenoprofen* (group 2); and oral administration of placebo tablets and drops (group 3). After two weeks of treatment, significant reduction in pain was only achieved by patients in group 2 (i.e. those on NSAIDs). The third trial (184 people) compared topical application of a homeopathic remedy “SRL” for four weeks with that of an NSAID gel (*Piroxicam*). Patients who were given homeopathic gel had a more favourable reduction in pain on walking. Two trials investigated homeopathic treatment for patients with fibromyalgia. The first trial (62 people), oral administration of a homeopathic remedy, prescribed by a homeopath, was compared to placebo oral drops. After four weeks of treatment, patients who got homeopathic drops showed significantly greater improvement in the number of tender points, pain levels and in quality of life compared to the placebo group. In the second trial (30 people), oral administration of a homeopathic remedy (*Rhus toxicodendron*) was compared to placebo tablets. After four weeks of treatment, and similar to the results of the first trial, patients who were assigned homeopathic tablets showed significantly greater improvement in number of tender points and in quality of life compared to the placebo group. A systematic review identified three RCTs of homeopathic treatment for RA. Results were inconsistent, with one trial (of reasonable quality, but with high drop-outs) showing a significant benefit from homeopathy and two trials (one of reasonable

## 26 Indian frankincense

quality) showing no significant effect. More recently, a larger RCT (112 people) compared the potential beneficial effects of a mixture of 42 homeopathic medicines taken orally with that of placebo tablets. After three months of treatment, the study found no evidence that homeopathy improved the symptoms of RA (pain, morning stiffness and mobility).

**Conclusion:** Homeopathic remedies are widely available over-the-counter in pharmacies and health food shops throughout the UK. The mechanism of action of these remedies is not clear. There is no evident safety risk and interactions with other drugs are unlikely. Even though isolated reports have suggested positive effects of homeopathy in the treatment of fibromyalgia, evidence is still not conclusive. Trials which investigated the role of these remedies in OA and RA yielded inconsistent results.

### References:

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- Fisher P, Greenwood A, Huskisson EC, Turner P, Belon P. Effect of homeopathic treatment on fibrositis (primary fibromyalgia). *BMJ* 1989;299(6695):365-6.

### Classification:

#### Effectiveness score in OA:

1 

#### Effectiveness score in RA:

1 

#### Effectiveness score in fibromyalgia:

2 

#### Safety classification:

Green 

**Family:** Ayurvedic medicine; Burseraveae family.

**Scientific name:** *Boswellia serrata*.

**Other names:** Resin, olibanum, salai guggal, 11-keto  $\beta$ -boswellic acid, acetyl-11-keto  $\beta$ -boswellic acid (AKBA), African elemi, Arabian incense (Bakhour), *Boswellia serrata* gum resins, boswellic acids, boswellic, Sallaki®, S-compound®, 5-LOXIN®.

**Description of the compound:** Indian frankincense is a plant extract which is used as an Ayurvedic remedy for the treatment of a number of diseases.

**Mechanism of action:** Indian frankincense prevents the production of some hormone-like substances in the body that act as triggers for joint inflammation.

**Safety and toxicity:** The compound is safe to use in a daily dose of 1g. High doses of Indian frankincense can have serious adverse effects on the liver.

**Availability:** The compound is available over-the-counter in health food shops in capsules containing active plant extract.

**Interactions:** Interactions with other medications have not been well studied.

**Dosage:** Not well studied. A daily dose of 1g has been used in RCTs in patients with OA.



### The role in treatment of arthritis and musculoskeletal conditions:

Some RCTs used Indian frankincense combined with other herbal compounds in patients with RA, so information about its potential therapeutic effects could not be extracted from these studies. Three RCTs examined the use of Indian frankincense in treating patients with OA of the knee. In the first trial, 30 patients were randomly assigned to receive either Indian frankincense capsules (333mg of the compound per capsule, three times daily) or placebo tablets. After eight weeks of treatment, patients who were allocated active treatment had moderate improvement in pain, knee flexion and walking distance compared to patients in the placebo group. The compound was well-tolerated by patients with only minor stomach upsets reported. The second RCT (66 people; six months of treatment) compared the potential beneficial effects of Indian frankincense (same dose as previous trial) with that of valdecoxib (an NSAID) in treating patients with knee OA. Patients in both groups showed considerable improvement in pain, stiffness, and ability to perform physical activity during the trial, but the onset of action was slower in patients who were given Indian frankincense. After one month of cessation of treatment, patients who were assigned Indian frankincense experienced a significant improvement in symptoms compared to patients who received valdecoxib, which might indicate that this compound has a relatively long-lasting effect. Only minor gastrointestinal adverse effects were reported by patients in both treatment groups. The third trial (75 people; three months of treatment) evaluated the effectiveness and safety of a medication called 5-LOXIN®. This drug is composed of Indian frankincense extract enriched with an anti-inflammatory acid called AKBA. Patients who participated in this trial were randomly allocated to receive one of the following three treatments: 100mg of 5-LOXIN®/day, 250mg of 5-LOXIN®/day or placebo tablets. All through the trial period, patients in the three treatment groups were compared with respect to the degree of pain reduction and level of improvement in physical functioning.

Compared to the placebo group, patients who were on either low or high doses of 5-LOXIN® had a significantly greater improvement in pain and physical function. Patients who were on 250mg of the drug had the quickest improvement (as early as seven days after the start of treatment). In addition, the level of an inflammatory and cartilage-destroying chemical in the knee fluid was significantly reduced in patients taking 5-LOXIN®. Only minor adverse effects (gastrointestinal and mild fever) were reported by patients across all treatment groups.

**Conclusion:** Indian frankincense is an Ayurvedic remedy that can be purchased over-the-counter in capsule form. The compound can prevent the production of inflammatory substances in the joints. Current evidence, based on three RCTs, suggest that this compound might have some beneficial effects in treating patients with knee OA, and that this effect might last for a period of time after cessation of treatment.

### References:

- Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee – a randomized, double blind, placebo controlled trial. *Phytomedicine* 2003;10(1):3-7
- Sontakke S, Thawani V, Pimpalkhute S, Kabra P, Babhulkar S, Hingorani L. Open, randomized, controlled clinical trial of Boswellia serrata extract as compared to valdecoxib in osteoarthritis of knee. *Indian J Pharmacol* 2007;39:27-9.
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### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Green 



## 27 MSM

**Family:** Organic sulphur (nutritional mineral).

**Scientific name:** Methylsulfonylmethane.

**Other names:** OptiMSM®.

**Description of the compound:** Methylsulfonylmethane or MSM is a dietary sulphur found in fresh raw foods including fruits, vegetables and meat. The therapeutic compound, MSM, is a white crystalline substance that contains 34 per cent sulphur.

**Mechanism of action:** Laboratory studies have elicited the anti-inflammatory and the anti-oxidant effects of MSM. Sulphur, which is a major component of MSM, plays an important role in the formation of collagen and glucosamine (both of which are vital for healthy bones and joints) and in the production of immunoglobulins, which offer numerous immune system benefits.

**Safety and toxicity:** Current evidence suggests that MSM is well tolerated as a short-term treatment even with high doses. Only mild adverse effects have been reported, the most common of which was gastrointestinal discomfort. To date, the long-term adverse effects of MSM have not been studied.

**Availability:** MSM is sold as such or as an ingredient in many over-the-counter medications for treatment of OA. MSM is formulated in capsules (1,000mg) or ointment (250-500mg).

**Interactions:** There are no well-known interactions of MSM at this time. However, the compound has been reported to improve the effect of glucosamine in reducing pain and swelling in patients with OA.

**Dosage:** A daily dose of 1,500mg for up to three months has been used in one RCT of MSM in patients with OA. However, doses up to 2,600mg per day have been previously used in non-RCT studies.

**The role in treatment of arthritis and musculoskeletal conditions:**

Three RCTs examined MSM's effect in treating patients with OA. In the first trial, 118 patients with knee OA were randomly allocated to receive one of four treatments: glucosamine (1,500mg/day); MSM capsules (1,500mg/day); both capsules; placebo capsules. Patients were asked to continue on treatment for 12 weeks. Compared to patients who were given a placebo, a significant improvement in pain and joint swelling was achieved by patients allocated MSM capsules and in patients receiving glucosamine. The degree of pain reduction achieved by the MSM group was similar to that achieved by the glucosamine group. However, glucosamine seemed to have a better effect, as compared to MSM, in reducing joint swelling. The group of patients who were assigned both glucosamine and MSM had the most significant reduction in both pain and swelling compared to the other three treatment groups. In addition, this group (i.e. the group receiving combined treatment) had the best functional ability of joints at the end of the trial period. MSM was well tolerated by patients with no significant adverse effects reported. In the second RCT, 50 patients with knee OA pain were assigned either MSM capsules (6g/day; four times the dose of the previous study) or placebo capsules. After 12 weeks of treatment, patients on MSM showed some improvement of pain and physical function compared to those who took placebo, but there was no difference in stiffness. However, such improvement was achieved by only 25 per cent of patients taking MSM. In the third trial which has only been published as a conference summary (quality unknown) 60 patients with knee OA pain were randomised to take either MSM capsules (3,375mg/day) or placebo capsules. After 12 weeks of treatment, patients who were on MSM showed improvement in pain and general functional well-being compared to those who took placebo, but MSM did not have an effect on improving knee function (e.g. walking, climbing stairs).

## 28 Phytodolor

**Conclusion:** MSM is rich in organic sulphur which is an important “building block” for healthy bones and joints and offers numerous immune system benefits. The compound is sold over-the-counter in the form of capsules or ointment. The small amount of evidence available from short-term RCTs shows that MSM may have a moderate effect in improving joint pain, joint swelling and general functional well-being in patients with OA. In a single trial this effect was greater in combination with glucosamine.

### References:

- Usha PR, Naidu MU. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clin Drug Investig* 2004;24(6):353-63.
- Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF. Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial. *Osteoarthritis Cartilage* 2006;14(3):286-94.
- Debi R, Fichman G, Bar Ziv Y, Kardosh R, Debbi E, Halperin N, et al. The role of MSM in knee osteoarthritis: a double blind, randomized, prospective study. *Osteoarthritis Cartilage* 2007;15(Suppl 3):C231.

### Classification:

#### Effectiveness score:

2 

#### Safety classification:

Green 

**Family:** Herbal extracts mixture.

**Scientific name:** *Populus tremula*, *Fraxinus excelsior*, *Solidago vigaurea*.

**Other names:** STW1.

**Description of the compound:** Phytodolor is a German herbal preparation consisting of three medicinal extracts: aspen (*Populus tremula*), common ash bark (*Fraxinus excelsior*) and golden rob herb (*Solidago vigaurea*).

**Mechanism of action:** Previous studies have found that aspen contains salicin, which is transformed by the body into another chemical substance called salicylic acid. Similar to acetylsalicylic, salicylic acid inhibits the production of certain prostaglandins in the nerves and this effect relieves pain and discomfort. Some studies have also shown that both common ash bark and golden rob herb have analgesic properties. In addition, common ash bark can act as an anti-oxidant (i.e. can reduce oxidative damage of joint structures). An anti-inflammatory mechanism of action of this herbal mixture has also been suggested by some studies in the laboratory and on animals.

**Safety and toxicity:** No major adverse effects have been reported in previous trials. Reported adverse effects include stomach upset, diarrhoea and skin allergy.

**Availability:** Available for purchase in some pharmacies in the UK.

**Interactions:** No interaction with other medicines has been reported.

**Dosage:** Most RCTs used 30 to 40 drops of the compound, three times a day.

### The role in treatment of arthritis and musculoskeletal conditions:

A recently published review article analysed 13 double-blind randomised trials which investigated the effectiveness of phytodolor in treating patients with OA, RA and other types of arthritis. At least six of these trials were specifically conducted on patients with OA, two of which evaluated the effectiveness of phytodolor as compared to placebo; two compared the potential therapeutic effect of the herbal mixture with that of NSAIDs and one compared its effectiveness with that of placebo or an NSAID. Results of all trials which had a placebo comparative group demonstrated that phytodolor is significantly more effective in improving joint mobility and reducing pain and consumption of painkillers. All trials which had an NSAIDs comparative group found that phytodolor is as effective as diclofenac and piroxicam in reducing pain, swelling and stiffness in joints. The remaining trials included in this review were conducted on patients with different types of degenerative and inflammatory types of arthritis. Results of these trials indicated that phytodolor is superior to placebo in improving pain and mobility and in reducing dependence on painkillers. None of the trials included in this review specifically studied patients diagnosed with RA. For that reason, it is not possible to reach a definite conclusion with respect to the separate potential effectiveness of this compound in treating patients with this disease.

**Conclusion:** Phytodolor is a German herbal preparation, which is now available for purchase in some pharmacies in the UK in the form of a tincture. Evidence for its effectiveness in treating patients with OA is encouraging. However more studies are still needed to evaluate its role in treating patients with RA.

### References:

- Ernst E, Chrubasik S. Phyto-anti-inflammatories. A systematic review of randomized, placebo-controlled, double-blind trials. *Rheum Dis Clin North Am* 2000;26(1):13-27.
- Gundermann KJ, Müller J. Phytodolor--effects and efficacy of a herbal medicine. *Wien Med Wochenschr* 2007;157 (13-14):343-7.

### Classification:

#### Effectiveness score:

4 

#### Safety classification:

Green 



## 29 Pine bark extracts

**Family:** Herbal extract; dietary supplement.

**Scientific name:** *Pinus pinaster* ssp. *Atlantica*.

**Other names:** French *pinus maritime* bark, Pycnogenol®, *pinus maritima*, *pycgenol*, *PYC*.

**Description of the compound:** *Pinus pinaster* is a pine native of France. The water extract of the bark of this plant is used medicinally to treat several diseases, including some types of arthritis.

**Mechanism of action:** This compound, which is available in the UK market with the trade name Pycnogenol®, is rich in plant pigments called bioflavonoids. Several studies in the laboratory have found that some of these bioflavonoids have anti-inflammatory and anti-oxidant actions (i.e. are capable of reducing joint inflammation and inhibiting cell-damaging molecules). Other studies have found that this compound can reduce the production of specific enzymes that break down joint cartilage.

**Safety and toxicity:** No major adverse effects have been reported in previous trials. Reported adverse effects include stomach upset and headache.

**Availability:** Pine bark is available in pharmacies and health food shops in the form of capsules.

**Interactions:** Pine bark can theoretically lower blood pressure and blood sugar level. These effects have also been reported in some RCTs. For that reason, patients with hypertension and/or diabetes should be cautious while taking this compound.

**Dosage:** Optimal dose has not been established, but a treatment regimen consisting of two capsules of Pycnogenol® 50mg per day has been used in previous studies.

**The role in treatment of arthritis and musculoskeletal conditions:** Two RCTs have been conducted to evaluate the role of pine bark in treating patients with OA. In the first trial, 156 patients with OA, who had pain not adequately controlled by NSAIDs,

were randomly selected to receive either 100mg daily of pine bark or placebo capsules. Patients in both groups were informed that they were free to use NSAID treatment throughout the trial. After three months of treatment, there was a 56 per cent reduction in pain in the group that were allocated pine bark compared to only ten per cent reduction in the placebo group. Significant reduction in joint stiffness and foot and ankle swelling and improvement in physical function were also achieved by the group on the active treatment. Pine bark was significantly more effective than placebo in all these aspects of the disease. In addition, the use of NSAIDs dropped by 58 per cent in patients taking the active treatment compared to only one per cent in the placebo group. This trial also found that the group allocated the active treatment had a significant reduction in gastrointestinal symptoms compared to almost no reduction in the placebo group. This might be related to the lower consumption of NSAIDs in the active treatment group. In the second trial, 100 patients with mild knee OA were randomly allocated to receive either 150mg Pycnogenol® or placebo. Patients were treated for three months and after the treatment, patients receiving Pycnogenol® reported an improvement in function and lower levels of pain in comparison to the group taking placebo who showed no improvement.

**Conclusion:** Pine bark is a herbal extract which is available in the UK market with the trade name Pycnogenol®. This compound is rich in several bioflavonoids that have both anti-inflammatory and anti-oxidant actions. The little available evidence is suggestive that this compound may result in an improvement in OA disease-related symptoms.

### References:

- Belcaro G, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G, et al. Treatment of osteoarthritis with Pycnogenol. The SVOS (San Valentino Osteo-arthritis Study). Evaluation of signs, symptoms, physical performance and vascular aspects. *Phytother Res* 2008;22(4):518-23.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Green 







## 30 Reumalex

**Family:** A remedy composed of a mixture of herbal medications.

**Scientific name:** Reumalex herbal mixture.

**Description of the compound:** Reumalex is composed of 100mg of white willow bark, 40mg guaiacum resin, 35mg black cohosh, 25mg of sarsaparilla and 17mg of poplar bark.

**Mechanism of action:** Willow bark contains an ingredient called salicin, which is transformed in the body into another chemical substance called salicylic acid. Salicylic acid inhibits the production of certain prostaglandins in the nerves and this effect relieves pain and discomfort. Several previous studies (laboratory-based and on animals) have found that guaiacum, sarsaparilla and poplar bark have anti-inflammatory effects. The mechanism of action of black cohosh is not clear.

**Safety and toxicity:** The following adverse effects have been reported in a previous study: headache, diarrhoea and stomach upset.

**Availability:** Available via the internet.

**Interactions:** Interactions with other medications have not been examined.

**Dosage:** Two tablets of the herbal mixture have been used in one study.

### The role in treatment of arthritis and musculoskeletal conditions:

One RCT has evaluated the potential beneficial effect of Reumalex in patients with arthritis related conditions. In this trial, 52 patients with OA and 20 patients with RA were randomly assigned to receive either two tablets/day of Reumalex or placebo tablets. After two months of treatment, patients on the active treatment showed a slightly better improvement in pain experience, compared to those on placebo. However, the overall disease activity and the use of other painkillers remained similar in both groups. The numbers of patients withdrawing from the trial due to adverse effects of Reumalex was small (four out of 35 patients; 11 per cent). Reported adverse effects which led to withdrawal were headache, diarrhoea and stomach upset.

**Conclusion:** Reumalex is a mixture of herbal preparations in tablet form that can be purchased via the internet. Ingredients of Reumalex can fight joint inflammation and can reduce the production of pain-inducing chemicals in the nerves. Apart from its mild analgesic effect, which is possibly attributed to its ingredient willow bark, there is no convincing evidence that Reumalex is effective in treating RA or OA.

### References:

- Mills SY, Jacoby RK, Chacksfield M, Willoughby M. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double-blind study. Br J Rheumatol 1996;35(9):874-8.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

Green 

## 31 Rosehip

**Family:** Herbal medicine; Rosaceae family.

**Scientific name:** Rosa canina.

**Other names:** Rose hips, rosehip drink, LitoZin, Hyben Vital, Burr rose, camellia rose, Cherokee rose, chestnut rose, cabbage rose, Cili, coumaric acid, dog rose, French rose, gooseberry rose, hansa, hedge-pedgies, hips, hip berry, Japanese rose, Virginia rose.

**Description of the compound:** Rosa canina is a wild rose species native to some regions in Europe, Africa and Asia. The medicinally used compound is extracted from the fruits that develop usually after the bloom has died.

**Mechanism of action:** Rosehip extract contains polyphenols and anthocyanins. These ingredients are believed to help relieve joint inflammation and prevent joint damage. The compound is also rich in vitamin C which has anti-oxidant properties.

**Safety and toxicity:** Adverse effects are usually mild but include allergy, constipation, diarrhoea, and heartburn.

**Availability:** The compound is available over-the-counter in health food shops in capsules containing rosehip powder.

**Interactions:** Interactions with other medications have not been well studied.

**Dosage:** Not well studied. 5g/day of rosehip have been used in previous trials.

### The role in treatment of arthritis and musculoskeletal conditions:

Two recently published systematic reviews identified two RCTs that examined the clinical effectiveness of the compound in patients with OA. In the first trial, 100 patients with hip and/or knee OA were randomly assigned to receive either LitoZin tablets (5g/day of rosehip) or placebo over four months. Rosehip, in comparison with placebo, significantly improved hip flexion but did not significantly improve the range of rotation of the hip and the degree of flexion of the knee after four months of treatment. In addition, significantly more patients in the active treatment group reported reduction of pain compared with the placebo group at the end of the trial. In the second RCT, 112 patients with OA in multiple sites were randomly assigned to receive either Hyben Vital tablets (5g/day of rosehip) or placebo over three months. Compared to patients who received placebo, patients given rosehip showed significant reduction of pain: 66 per cent vs. 36 per cent, some disease-related symptoms (e.g. morning stiffness) and reported a significant decline in their consumption of painkillers. In both trials, the active treatment was well tolerated with only minor gastrointestinal adverse effects reported (e.g. diarrhoea). A third trial (94 people; 15 weeks duration), which was not included in the previously mentioned reviews, was conducted to compare the treatment outcome of rosehip powder (LitoZin; 5g) versus placebo in patients with OA. After three weeks of treatment, rosehip resulted in a significant reduction in pain scores and consumption of painkillers compared to placebo. However, rosehip did not significantly reduce stiffness and disability and did not improve the overall severity of the disease. After 15 weeks of treatment, patients who were given rosehip had a significant reduction in pain, stiffness, disability and consumption of painkillers and significant improvement in overall disease severity compared to patients on placebo.

## 32 SAME

**Conclusion:** Rosehip is a herbal medication, with anti-inflammatory properties, that is available over-the-counter in capsule form. The evidence available suggests that rosehip may be relatively safe to use and may be effective in relieving some symptoms associated with OA.

### References:

- Rosnagel K, Roll S, Willich SN. [The clinical effectiveness of rosehip powder in patients with osteoarthritis. A systematic review.] MMW Fortschr Med 2007;149(11):51-6. [Article in German].
- Chrubasik C, Duke RK, Chrubasik S. The evidence for clinical efficacy of rose hip and seed: a systematic review. Phytother Res 2006;20(1):1-3.
- Rein E, Kharazmi A, Winther K. A herbal remedy, Hyben Vital (stand. powder of a subspecies of Rosa canina fruits), reduces pain and improves general wellbeing in patients with osteoarthritis--a double-blind, placebo-controlled, randomised trial. Phytomedicine 2004;11(5):383-91.
- Warholm O, Skaar S, Hedman E, Molmen HM, Eik L. The effects of a standardized herbal remedy made from a subtype of Rosa canina in patients with osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. Curr Ther Res 2003;64:21-31.
- Winther K, Apel K, Thamsborg G. A powder made from seeds and shells of a rose-hip subspecies (Rosa canina) reduces symptoms of knee and hip osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial. Scand J Rheumatol 2005;34(4):302-8.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Green 

**Family:** Nutritional supplement.

**Scientific name:** S-adenosylmethionine.

**Description of the compound:** A chemical compound derived from two acids: methionine, an amino acid also found in protein-rich foods; and adenosine triphosphate (ATP), a nucleic acid and the end-point of all energy-gaining reactions in the human body. SAME was discovered in 1952 and was first studied as a possible treatment for depression.

**Mechanism of action:** SAME is found naturally in the body. It contributes to several biochemical pathways and in the synthesis of hormones and neurotransmitters. Studies in the laboratory suggested that SAME has some analgesic activity and stimulates the synthesis of collagen and proteoglycans, the major constituents of joint cartilage. The mechanism of action of SAME as a potential anti-depressant is still unknown.

**Safety and toxicity:** Adverse effects, which are usually mild and infrequent, include nausea, restlessness, headache, dry mouth and stomach upset. Severe adverse effects, in the form of anxiety and mania, have also been reported in patients with depression.

**Availability:** This nutritional supplement is available over-the-counter in some UK pharmacies in the form of capsules.

**Interactions:** Theoretically, SAME might increase the risk of bleeding if taken with other medications which affect blood clotting like aspirin, heparin and warfarin. For that reason, patients on these medications are advised to take SAME under a doctor's supervision. The drug can also magnify the activity of anti-depressants.

**Dosage:** Optimal dose has not been well established. Most previous studies have used doses of 400-1,600mg daily.



### The role in treatment of arthritis and musculoskeletal conditions:

The potential beneficial role of SAME has been a subject of investigation in RCTs on patients with OA and fibromyalgia. A review article, published in 2002, analysed RCTs that investigated the effectiveness of this medication in treating patients with OA. Eleven RCTs were included; one trial compared the effect of SAME with that of a placebo; nine trials compared SAME with aspirin or an NSAID and one compared SAME with a placebo and an NSAID. The number of patients included in these studies ranged from 36 to 493 patients and duration of the trials ranged from ten days to 84 days. The SAME dosage used in these trials was 1,200mg/day (six trials), 600mg/day (three trials), 400mg/day (one trial), and in one study the dose varied between patients. Data from all these trials were combined and re-analysed. SAME was significantly better than placebo and had an effect similar to that of NSAIDs in reducing functional limitations attributed to the disease. In terms of pain reduction, SAME had an effect equivalent to that of NSAIDs. Two trials compared the effect of SAME versus that of a placebo in reducing pain in patients with OA: both of them reported a significant superiority in favour of SAME. The combined re-analysis of the ten trials which had NSAID comparative groups, found that patients treated with SAME were 58 per cent less likely to experience adverse effects than those treated with NSAIDs, regardless of the dose of SAME and the duration of treatment. A more recent RCT (published in 2004) compared the effectiveness of SAME to celecoxib (an NSAID; COX-2 inhibitor) for pain control, functional improvement and reported adverse effects in patients with OA. The study found that SAME had a slower onset of action but was as effective as celecoxib in relieving pain and improving the physical function after 16 weeks of treatment. With respect to its role in treating patients with fibromyalgia, three out of four published RCTs found that SAME was effective, when compared to placebo, in reducing the number of tender points and/or the intensity of tenderness in these points. The three studies also found that SAME was effective, compared to placebo, in reducing depressive symptoms in patients with fibromyalgia. The fourth RCT found that SAME was not significantly better than placebo in reducing almost all disease-related symptoms.

However, the number of patients who took part in these four trials was small (17 to 44 patients) and duration of the treatment was short (ten days to six weeks).

**Conclusion:** S-adenosylmethionine (or SAME) is a chemical compound found naturally in the body. In addition to its potential anti-depressant properties, studies in the laboratory suggest that SAME has some analgesic activities. It also stimulates the synthesis of major constituents of joint cartilage. The chemical compound can be purchased from pharmacies in the form of capsules. Evidence from RCTs suggests that it is effective in reducing functional limitations, and to a lesser extent pain in patients with OA. Evidence for its effectiveness in patients with fibromyalgia, from a small number of trials only, suggests that SAME might be of benefit in reducing body tenderness and depressive symptoms.

### References:

- Najm WJ, Reinsch S, Hoehler F, Tobis JS, Harvey PW. S-adenosyl methionine (SAME) versus celecoxib for the treatment of osteoarthritis symptoms: a double-blind cross-over trial. *BMC Musculoskelet Disord* 2004;26:5-6.
- Soeken KL, Lee WL, Bausell RB, Agelli M, Berman BM. Safety and efficacy of S-adenosylmethionine (SAME) for osteoarthritis. *J Fam Pract* 2002;51(5):425-30.
- Sarac AJ, Gur AJ. Complementary and alternative medical therapies in fibromyalgia. *Curr Pharm Des* 2006;12(1):47-57.

### Classification:

#### Effectiveness score in OA:

4 

#### Effectiveness score in fibromyalgia:

2 

#### Safety classification:

Green 

## 33 Selenium

**Family:** Dietary supplement; trace element.

**Scientific name:** Selenium.

**Other names:** Selenomethionine.

**Description of the compound:** Selenium is a trace mineral which is important for many vital functions in the body. For medicinal purposes, the mineral is usually derived from yeast.

**Mechanism of action:** Some previous studies have found that patients with RA have low levels of selenium in their blood compared to people without the disease. The mechanism of action of selenium in treating arthritis and musculoskeletal conditions is not well understood, but it might be related to its anti-oxidant properties. Selenium is a crucial component of a number of enzymes, some of which are involved in specific pathways in the body that can prevent cell damage (usually by interacting with harmful molecules produced within the cells known as free radicals).

**Safety and toxicity:** Selenium supplementation is safe if taken in a dose not exceeding its recommended dietary allowance (which is 80-200mcg per day). However, this mineral can be toxic if taken in high doses. Such toxicity may cause gastrointestinal symptoms, liver and kidney problems, skin changes and hair loss.

**Availability:** Selenium is always included in vitamin preparations and mineral supplements which can be bought from pharmacies and health food shops. Selenium is also available as a single dietary supplement in the form of capsules.

**Interactions:** Interactions with other medications are unlikely if taken in low or moderate doses.

**Dosage:** No recommended effective and safe doses have been established for use in musculoskeletal conditions. Most trials used a dose of 200mcg.

### The role in treatment of arthritis and musculoskeletal conditions:

A recent review article identified three complete reports of RCTs of selenium treatment of RA. The number of patients included in these trials ranged from 40 to 70 patients and the period of treatment ranged from two to six months. The active treatment in all trials was selenium taken in the form of capsules (200mcg/day in two trials and 256 mcg/day in one trial). The control group in all trials was composed of patients on placebo capsules. In the first trial (40 people; six month period), there was no significant difference between patients who were assigned selenium or placebo in all aspects of disease severity, including pain, morning stiffness and number of swollen joints. In the second trial<sup>‡</sup> (55 people; three month period), there was no significant difference between patients taking selenium or placebo in pain reduction, morning stiffness and number of swollen joints. However, patients on selenium had better arm movement and perception of better general health. The third trial (70 people; three month period) found that there was no significant difference between patients who were on selenium or placebo in terms of pain reduction, morning stiffness, number of swollen joints and the use of NSAIDs.

**Conclusion:** Selenium is a dietary supplement that is available to buy over-the-counter from pharmacies and health food shops, mainly as an ingredient in multi-vitamin capsules. The mechanism of action of selenium in treating arthritis is not well understood, but it might be related to its anti-oxidant properties. Current evidence, based on published RCTs, suggests that selenium supplements are not effective in treating patients with RA.

### References:

- Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. *Rheumatology (Oxford)* 2007;46(8):1223-33.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

Green 

<sup>‡</sup> A trial of low quality. Results of this trial were given a lower weighting in coming to our conclusion about the compound.

## 34 SKI 306X

**Family:** Herbal mixture.

**Scientific name:** SKI 306X.

**Other names:** CarathronQ®, JOINS®.

**Most commonly used commercial name:** SKI 306X.

**Description of the compound:** SKI 306X is a mixture of three herbal medications prepared from Clematis mandshurica, Trichosanthes kirilowii and Prunella vulgaris. This compound is widely used in Korea and other South Eastern Asian countries for treating OA.

**Mechanism of action:** Laboratory studies and experiments on animals have found that SKI 306X has a protective effect on the cartilage of joints. The compound prevents the destruction of proteoglycan and collagen which are major components of cartilage. Other studies have demonstrated that SKI 306X can prevent the release and activity of several inflammatory substances in joints.

**Safety and toxicity:** Not well studied (particularly in the long-term), but heartburn and stomach upset have been reported by some patients during the first four weeks of treatment.

**Availability:** SKI 306X 200mg tablets are manufactured by two pharmaceutical companies in Korea and Australia (JOINS® and CarathronQ®, respectively). Each tablet contains 100mg of Clematis mandshurica extract. It can be purchased via the internet.

**Interactions:** Interactions with other drugs have not been well-studied.

**Dosage:** 600mg/day in three divided doses.

### **The role in treatment of arthritis and musculoskeletal conditions:**

Two RCTs examined the effect of this compound in treating OA patients. In the first trial, 96 patients with OA were randomly selected to take one of the following four treatments: placebo, SKI 306X at 600mg/day, 1,200mg/day or 1,800mg/day. After four weeks of treatment, SKI 306X taken in any of the previously mentioned doses, was significantly more effective than placebo in reducing pain associated with OA. However, there were no significant differences between the three doses in terms of pain reduction and overall satisfaction with treatment. Apart from stomach upset, there were no significant adverse events reported by patients taking SKI 306X. In the second RCT, 249 patients with OA were randomly selected to receive either SKI 306X tablets (600mg/day) or diclofenac tablets (100mg/day). After four weeks of treatment, the two medications were almost equally effective in reducing pain and achieving overall patient satisfaction. Identical proportions in both treatment groups (5.6 per cent) had to stop their medications during the study due to adverse effects (which were mainly gastrointestinal in nature, heartburn). One RCT examined the effect of SKI 306X in treating patients with RA. In this trial, 183 patients were randomly selected to take SKI 306X (600mg/day) or celecoxib (NSAID; 400mg/day). After six weeks of treatment, SKI 306X and celecoxib were equally effective in reducing pain scores and relieving other disease-related symptoms (e.g. morning stiffness). The two groups showed little difference with respect to the frequency of use of other medications for RA and with respect to the number of drug-related adverse effects. Adverse effects, which were mainly gastrointestinal (stomach-ache), were reported by 30 per cent and 24 per cent of patients who received SKI 306X and celecoxib, respectively.

**Conclusion:** SKI 306X is a herbal mixture which is available in tablet form and can be purchased via the internet. It has a protective and anti-inflammatory effect on the cartilage of joints. There is some evidence that SKI 306X may be effective in relieving pain related to OA and RA – with an effect similar to NSAIDs. More studies are needed to further determine its effects and safety profile in the long-term.

## 35 Stinging nettle

### References:

- Jung YB, Roh KJ, Jung JA, Jung K, Yoo H, Cho YB, et al. Effect of SKI 306X, a new herbal anti-arthritis agent, in patients with osteoarthritis of the knee: a double-blind placebo controlled study. Am J Chin Med 2001;29(3-4):485-91.
- Lung YB, Seong SC, Lee MC, Shin YU, Kim DH, Kim JM, et al. A four-week, randomized, double-blind trial of the efficacy and safety of SKI 306X: a herbal anti-arthritis agent versus diclofenac in osteoarthritis of the knee. Am J Chinese Medicine 2004;32(2):291-301.
- Song YW, Lee EY, Koh EM, Cha HS, Yoo B, Lee CK, et al. Assessment of comparative pain relief and tolerability of SKI306X compared with celecoxib in patients with rheumatoid arthritis: a 6-week, multicenter, randomized, double-blind, double-dummy, phase III, non-inferiority clinical trial. Clin Ther 2007;29(5):862-73.

### Classification:

#### Effectiveness score in OA:

3 

#### Effectiveness score in RA:

2 

#### Safety classification:

Green 

**Family:** Herbal medicine; Urticaceae.

**Scientific name:** Urtica dioica.

**Other names:** Common perennial nettle.

**Description of the compound:** Stinging nettle is a plant native to Europe, Asia, and North America.

**Mechanism of action:** The leaf is covered in tiny hairs which, having a high silicon content, are extremely brittle. When the leaf touches the skin the round tips of the hairs break off. The sharp point of the hair then penetrates the skin and several chemicals, including histamine and serotonin are produced. These two elements can be effective in reducing pain by stimulating pain neurons, giving a counter-irritant effect which can override musculoskeletal pain symptoms.

**Safety and toxicity:** The compound is applied topically to the painful area. Common adverse effects include skin itching and tingling sensation.

**Availability:** Available over-the-counter and in herbal stores in the form of an ointment, tincture or dried leaf.

**Interactions:** Unlikely, as the compound is applied topically to the skin.

**Dosage:** There is little information on dosage, but in one study leaves from the nettle plant were applied twice to the painful area for 30 seconds once a day for one week.

### The role in treatment of arthritis and

**musculoskeletal conditions:** Two RCTs evaluated the role of stinging nettle in the treatment of patients with OA. The first trial (27 people; 12 weeks of treatment) examined the effect of nettle as a possible local analgesic for patients with osteoarthritic pain at the base of the thumb. Patients were told that the study was testing two types of nettle leaf: they were allocated, randomly, to apply either a stinging nettle leaf or a placebo leaf daily for one week to the area with pain; while current treatment was continued. They then stopped treatment for five weeks and then applied the other leaf for one week. Patients using the nettle leaves reported less pain and disability compared to those who used the placebo leaves. The difference in pain reduction remained significant during the first week following treatment, and then disappeared gradually thereafter. The second RCT (42 people) examined the potential beneficial effects of stinging nettle in a group of patients with knee OA. Patients were allocated, randomly, to apply either stinging nettle or another type of nettle, believed to be of no benefit in treating OA, to their knees. After one week of treatment, patients in both treatment groups had a similar mild and insignificant reduction in pain scores. Patients using stinging nettle had only minor and short-term skin irritation following the application of the sting to the skin.

**Conclusion:** Stinging nettle is a topical medication that is used by some patients with OA to relieve pain. When applied to the skin, the compound gives a counter-irritant effect which can override musculoskeletal pain. There is little evidence available on the use of nettle leaves for OA – with one study suggesting a positive effect in the short-term treatment of OA of the thumb and another study suggesting no beneficial effect in the short-term treatment of knee OA.

### References:

- Randall C, Randall H, Dobbs F, Hutton C, Sanders H. Randomized controlled trial of nettle sting for treatment of base-of-thumb pain. *J R Soc Med* 2000;93(6):305-9.
- Randall C, Dickens A, White A, Sanders H, Fox M, Campbell J. Nettle sting for chronic knee pain: a randomized controlled pilot study. *Complement Ther Med* 2008;16(2):66-72.

### Classification:

#### Effectiveness score score:

1 

#### Safety classification:

Green 





## 36 Thunder god vine

**Family:** Traditional Chinese herbal medicine; of the botanical family “Celastraceae”.

**Scientific name:** Tripterygium wilfordii Hook.

**Other names:** T Wilfordii Hook F (TWHF), Lei gong teng, Lei-kung teng, Huang-teng ken, Tsao-ho-hua, yellow vine root, early rice flower, three-wing nut.

**Description of the compound:** Tripterygium is a perennial vine which grows in the mountains of China, Taiwan and Myanmar. With the exception of its root pulp (which is used medicinally), all other components of the vine are poisonous. In China, extracts from the vine’s roots made with ethyl acetate and chloroform-methol are packaged into capsules and have been used to treat a broad spectrum of autoimmune and inflammatory diseases including RA. Extracts made with chloroform-methol are also named T2.

**Mechanism of action:** Studies in the laboratory and on animals show that thunder god vine reduces the production of the proteins responsible for inflammation of joints. These studies have also found that thunder god vine has an immunosuppressive activity (i.e. it is capable of reducing the activity of the body’s immune system).

**Safety and toxicity:** Well documented adverse effects include stomach pain, diarrhoea, nausea, headache, skin rash, hair loss, infertility in men and amenorrhea (failure to menstruate) in women. The herb can also be extremely poisonous if it is not extracted properly.

**Availability:** In the UK, thunder god vine, as a single herb, was removed from the English edition of the Chinese Pharmacopoeia in the year 2000, probably due to its serious adverse effects. Information regarding availability in the UK is not available. Small doses of the herb are also included in some commercially available herbal preparations.

**Interactions:** Interactions with other drugs are not well studied. However, patients taking other immunosuppressive drugs (e.g. cyclophosphamide and methotrexate) should not take thunder god vine.

**Dosage:** No recommended safe doses have been established. Life-threatening adverse effects were reported when, mistakenly, 180mg of the T2 extract was taken for two weeks.

**The role in treatment of arthritis and musculoskeletal conditions:** Three reports of RCTs on patients with RA were found. None of these trials were particularly large (the largest involved only 70 RA patients). Trials used different types or doses of the compound. In the first RCT (70 people), patients were divided into two groups: group 1 consisted of 35 patients who were treated with chloroform-menthol (T2) extract of thunder god vine (60mg/day) for 12 weeks and then with placebo for the subsequent four weeks. Group 2 was also composed of 35 patients, but were treated with the placebo drug during the first 12 weeks and with T2 for the subsequent four weeks. At the end of the first 12 weeks, group 1 patients (allocated T2), showed

significant improvements in all aspects of disease activity except for the level of rheumatoid factor in their blood. Considerable deterioration of disease activity was observed in group 1 patients when they stopped taking T2. In the second RCT (35 people), patients with RA were divided into three groups. The first and second groups were treated with an ethanol/ethyl alcohol extract of thunder god vine for 20 weeks in a dose of 180mg/day and a dose of 360mg/day, respectively. Patients in the third group were given a placebo drug during the same time period. Overall, a favourable outcome of treatment was achieved by 80 per cent of patients who had 360mg/day of the compound, by 40 per cent of those who took 180mg/day, and by none in the placebo group. In the third RCT (61 people), patients were treated with thunder god vine cream or a placebo cream for six weeks. A favourable outcome was achieved by 58 per cent of patients who used thunder god vine cream compared to only 20 per cent of patients who used the placebo. Many patients participating in these three RCTs had adverse effects from the drug with up to 63 per cent of them experiencing skin rashes.

**Conclusion:** Thunder god vine has anti-inflammatory and immunosuppressive actions. These properties render the compound a potentially useful substance for treating RA. This herbal medication is available in the form of capsules that can be purchased via the internet. Studies on its effectiveness and safety are scarce. However, based on three RCTs published so far, it appears that thunder god vine may be effective in treating symptoms of RA, but there are serious safety concerns.

### References:

- Cibere J, Deng Z, Lin Y, Ou R, He Y, Wang Z, et al. A randomized double blind, placebo controlled trial of topical *Tripterygium wilfordii* in rheumatoid arthritis: reanalysis using logistic regression analysis. *J Rheumatol* 2003;30(3):465-7.
- Canter PH, Lee HS, Ernst EA. Systematic review of randomised clinical trials of *Tripterygium wilfordii* for rheumatoid arthritis. *Phytomedicine* 2006;13(3):371-7.
- Tao X, Sun Y, Dong Y, Xiao Y L, Hu DW, Shi YP. A double blind, controlled trial of *Tripterygium wilfordii* glycosides in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1987;30(Suppl. 5):S59.
- Tao X, Younger J, Fan FZ, Wang BP, Lipsky PE. Benefit of an extract of *Tripterygium Wilfordii* Hook F in patients with rheumatoid arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum* 2002;46(7):1735-43.

### Classification:

#### Effectiveness score:

3 

#### Safety classification:

Red 

## 37 Tong lu kai bi

**Family:** Chinese herb, traditional Chinese medicine (TCM).

**Scientific name:** Tong lu kai bi.

**Other names:** Tong Ren Da Huo Luo Wan.

**Description of the compound:** A mixture of traditional Chinese medicines for RA.

**Mechanism of action:** According to traditional Chinese medicine, this pill can “dispel wind and remove dampness, relax muscles and tendons”.

**Safety and toxicity:** There is little information available.

**Availability:** No information available for the UK.

**Interactions:** No available information.

**Dosage:** 1-2 pills (3.6g each), twice a day, as instructed by the drug manufacturing company.

**The role in treatment of arthritis and musculoskeletal conditions:** One RCT conducted in China evaluated the potential beneficial effects of this Chinese herbal compound in patients with RA. A total of 120 patients were randomly assigned to either tong lu kai bi tablets or placebo tablets. Moderate improvement and marked improvement was achieved by 43 per cent and 45 per cent, respectively, of patients taking the active treatment. Moderate improvement and marked improvement was achieved by 55 per cent and 27 per cent of patients on the placebo treatment.

**Conclusion:** Tong lu kai bi is a Chinese herb being used by some patients with RA. The mechanism of action and safety of these pills is still largely unknown, and there is little evidence available at present on which to judge whether or not this Chinese herb is effective in the treatment of RA.

### References:


- Shi Y, Zhang H, Du X, Zhang M, Yin Y, Zhou C, et al. A double blind observation for therapeutic effects of the tong lu kai bi tablets on rheumatoid arthritis. A potential new treatment for rheumatoid arthritis. J Tradit Chin Med 1999;19(3):166-72.

### Classification:

#### Effectiveness score:

1 

#### Safety classification:

**Amber**  (no information)

## 38 Vitamins A,C,E (anti-oxidant vitamins)

**Family:** Nutritional supplement.

**Scientific name:** Vitamin A (retinoids), vitamin C (L-ascorbate), vitamin E (tocopherols and tocotrienols).

**Description of the compound:** Vitamins are nutritional substances that are required in small amounts in the diet. Vitamins A and E are fat-soluble vitamins, while vitamin C is a water soluble vitamin. Fat-soluble vitamins are stored in the body in fat cells, but need to be replenished at regular intervals. Except for vitamin B12, all water soluble vitamins are stored in the body for only a brief period of time and then excreted through urine. For that reason, water-soluble vitamins need to be taken daily. For medicinal purposes, vitamins can be derived naturally from dietary sources (natural vitamins) or can be produced in laboratories (synthetic vitamins).

**Mechanism of action:** Vitamins A, C and E have anti-oxidant activity i.e. they can prevent bone and joint cell damage by interacting with harmful molecules produced within these cells known as free radicals. Some studies in the laboratory and on animals have found that vitamin E might have the potential to treat OA by stimulating the growth of cartilage cells. Other studies have found that vitamin E has some anti-inflammatory properties. With respect to vitamin C, studies have found that this vitamin can stimulate the synthesis of collagen and proteoglycan (both of which are important components of joint cartilage) and can protect against degeneration of cartilage in animal studies.

**Safety and toxicity:** Being water soluble, an excess in vitamin C intake is not stored in the body, but excreted through urine. Thus, it is considered a very safe dietary supplement. Vitamins A and E are fat soluble vitamins (and stored in the body), so excess of intake of these vitamins can cause health problems. Chronic toxicity from vitamin A can appear with long-term intake of more than 50,000 units of this vitamin. Signs of vitamin A toxicity include dry skin, skin rash, bone pain, hair loss, sleep problems and gastrointestinal symptoms.

Most adults can tolerate up to 100-800mg daily of vitamin E, but long-term intake of large doses (more than 1,000mg daily) can cause headache, nausea, blurred vision, disturbed functions of the thyroid gland. Recently, it has been recommended that high-dose intake of vitamin E (more than 400mg/day) should be avoided.

**Availability:** Anti-oxidant vitamins are readily available in most pharmacies in the form of capsules (ACE vitamins), combined with selenium (Selenium ACE) or as ingredients of multivitamin supplements.

**Interactions:** No serious drug interactions have been reported with low or medium intake anti-oxidant vitamins.

**Dosage:** No recommended effective and safe doses have been established for use in arthritis and related conditions. Most trials used a dose of 1,200mg/day of vitamin E, 50,000 iu of vitamin A, and 1g/day of vitamin C.

**The role in treatment of arthritis and musculoskeletal conditions:** A recent review article identified four reports of RCTs of anti-oxidant vitamin treatment of RA. Three of these trials investigated the potential beneficial role of vitamin E, while the fourth studied the effectiveness of Selenium ACE treatment. The number of patients included in these trials ranged from 20 to 85 patients and the period of treatment ranged from two weeks to six months. In the first trial<sup>‡</sup> (42 people; 12 week period), there was no significant difference between patients on vitamin E supplements (1,200mg/day) or placebo in morning stiffness, number of swollen joints and degree of joint tenderness, but there was a significant difference in pain reduction in favour of patients taking vitamin E. In both the second trial (41 people; three week period) and third trial (85 people; three week period), there was no significant difference between patients allocated vitamin E supplements (1,200mg/day) or patients given 150mg/day diclofenac (an NSAID) in all aspects of disease severity at the end of treatment for both trials.



In the fourth trial<sup>‡</sup> (20 people; six month period), there was no significant difference between patients who received Selenium ACE supplements or patients on placebo in all aspects of disease severity at the end of the trial. A recent review article identified eight reports of RCTs of anti-oxidant vitamin treatment of OA. Six of these trials investigated the potential beneficial role of vitamin E; one trial studied the effectiveness of vitamin A, and one trial studied the effectiveness of Selenium ACE. The number of patients included in these trials ranged from 30 to 136 patients and the period of treatment ranged from ten days to two years. Two trials out of four demonstrated the effectiveness of vitamin E supplements in reducing pain and overall disease-related symptoms in OA patients when compared to placebo treatment. The other two trials found no significant benefits of vitamin E supplements. Two trials, out of two, found no significant difference between OA patients who received vitamin E supplements or diclofenac with respect to pain reduction and overall improvement of most disease-related symptoms. One trial (133 people; two week period) compared the treatment outcome of patients with OA who were randomly selected to receive either vitamin C supplements (1g/day) or placebo tablets. Compared to the placebo group, patients on vitamin C supplements reported a significant reduction of joint pain and a significant improvement in physical function at the end of the trial. One trial<sup>‡</sup> (30 people; six month period) compared the treatment outcome of patients with OA who were randomised to receive either Selenium ACE supplements or placebo tablets. There was no significant difference in the level of pain reduction and the degree of general health improvement at the end of the trial period.

**Conclusion:** Vitamins are organic essential nutrients, which are available in most pharmacies in the form of capsules. Vitamins A, C and E have anti-oxidant activity, so theoretically can play a role in the treatment of arthritis-related conditions preventing bone and joint cell damage. Studies in the laboratory and on animals have found some scientific basis for their use in the treatment of arthritis related conditions. However, current evidence, from studies on humans, suggests that anti-oxidant vitamins are not effective in treating patients with RA. Evidence from trials of effectiveness of vitamin E in treating patients with OA is inconclusive (i.e. provides mixed results). Evidence for the use of vitamin C in treating OA is encouraging, but still preliminary and needs confirmation by larger trials.

#### References:

- Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. *Rheumatology (Oxford)* 2007;46(8):1223-33.

#### Classification:

##### Effectiveness score in OA:

2 

##### Effectiveness score in RA:

1 

##### Safety classification:

Green 

<sup>‡</sup> A trial of low quality. Results of this trial were given a lower weighting in coming to our conclusion about the compound.

## 39 Vitamins D & B complex (non-anti-oxidant vitamins)

**Family:** Nutritional supplement.

**Scientific names:** Vitamin D (cholecalciferol), vitamin B3 (niacinamide), vitamin B12 (Cobalamin), vitamin B9 (folic acid).

**Description of the compound:** Vitamins are nutritional substances that are required in small amounts in the diet. Vitamins D and K are fat-soluble vitamins, while B complex vitamins are water soluble. Fat-soluble vitamins are stored in the body in fat cells, but need to be replenished at regular intervals. Water soluble vitamins are stored in the body for only a brief period of time (several weeks to several months) and then excreted through urine. The only exception for this is vitamin B12 which is stored in the liver for a longer period (up to four years). For medicinal purposes, vitamins can be derived naturally from dietary sources (natural vitamins) or can be produced in laboratories (synthetic vitamins).

**Mechanism of action:** Vitamin D is essential for the processing of calcium and the maintenance of healthy bones and joints. In addition, vitamin D can stimulate the synthesis of proteoglycan, which is an important component of joint cartilage. The beneficial effects of vitamin D and vitamin B3 supplementations in patients with OA have been well documented in several observational studies. Several studies have found that vitamin B12 plays a role in regulating bone metabolism. Another study found that patients with OA have low intake of vitamin B9 (folic acid).

**Safety and toxicity:** Vitamin B9 (folic acid) supplementation is safe, even with high doses. Apart from occasional gastrointestinal symptoms and itching, vitamin B12 has a high safety profile. Vitamin D can be toxic if taken in high doses. A daily dose of 250mcg (10,000 units) for a period of six months can result in an increase in the level of calcium in the blood which in turn can lead to severe gastrointestinal symptoms, headache, lack of energy and weakness.

**Availability:** Non-anti-oxidant vitamins are readily available in most pharmacies and health food shops, in the form of capsules, as ingredients of multivitamin supplements. Vitamins D, B9 and B12 are also available as single or combined (e.g. B9 and B12) dietary supplements.

**Interactions:** No serious drug interactions have been reported with low or medium intake of non-anti-oxidant vitamins.

**Dosage:** No recommended effective and safe doses have been established for use in the treatment of arthritis-related conditions. Previous RCTs have used daily doses of 3g of vitamin B3, 6,400mcg of vitamin B9 and 20mcg of vitamin B12.

**The role in treatment of arthritis and musculoskeletal conditions:** Two RCTs were conducted to evaluate the role of non-anti-oxidant vitamins in treating patients with OA. In the first trial (72 people, 12 week period), patients with OA were randomly selected to receive either vitamin B3 (niacinamide; 3g/day) supplementations or placebo tablets. At the end of the trial period neither treatment group reported reduction of pain, but the overall disease-related symptoms improved by 29 per cent in patients assigned the vitamin and worsened by ten per cent in patients on the placebo. In particular, niacinamide seemed to be effective in improving joint mobility compared to placebo. No major adverse effects were reported in patients taking the vitamin, but the number of adverse effects was higher in the niacinamide group. In the second RCT (29 people, two month period), patients with hand OA were randomised to receive one of the following three treatments: vitamin B9 (folic acid; 6,400mcg/day); a combination of vitamin B9 (6,400mcg/day) and vitamin B12 (20mcg/day); or placebo tablets. At the end of the trial period, patients who received vitamin B9 and B12 had significantly better hand grip values compared to the other two treatment groups.

## 40 Willow bark

**Conclusion:** Non-anti-oxidant vitamins include vitamins D and B complex. Vitamin D can stimulate the production of proteoglycan, which is an important component of the joint cartilage. The mechanism of action of vitamins belonging to vitamin B complex in treating patients with arthritis-related conditions is not well studied. Vitamins belonging to group B complex are relatively safe, but vitamin D can be toxic in large doses. No RCTs have investigated the role of vitamin D supplementation in treating patients with OA or RA. Evidence from trials of vitamin B supplementations in OA suggests that vitamins B3, B9 and B12 might be of some benefit, particularly in improving joint mobility and hand grip.

### References:

- Wang Y, Prentice LF, Vitetta L, Wluka AE, Cicuttini FM. The effect of nutritional supplements on osteoarthritis. *Altern Med Rev* 2004;9(3):275-96.
- Jonas WB, Rapoza CP, Blair WF. The effect niacinamide on osteoarthritis: a pilot study. *Inflamm Res* 1996;45(7):330-4.
- Flynn MA, Irvin W, Krause G. The effect of folate and cobalamin on osteoarthritic hands. *J Am Coll Nutr* 1994;13(4):351-6.

### Classification:

#### Effectiveness score:

2 

#### Safety classification:

Green 

**Family:** Herbal medicine of Salicaceae (Salix) family.

**Scientific name:** Willow.

**Other names:** Salix spp., basket willow, bay willow, beta-salicin, black willow, brittle willow, crack willow, daphne willow, populin, purple willow, salicin, salicortin, salicoylsalicin, salicyl alcohol, salicylate, salicylic acid, salicyluric acid, salidroside, saligenin, salipurposide, Salix alba, Salix daphnoides, Salix fragilis L., Salix pentandra, Salix purpurea, white willow, white willow bark, willow tree, willowprin.

**Description of the compound:** The bark of some, but not all, species of Salix trees has been used for treating inflammatory and arthritis related conditions since ancient times. Extracts from the following species of Salix trees have been used as sources of willow: Salix purpurea (purple willow), Salix fragilis (crack willow), Salix alba (white willow), Salix daphnoides (violet willow) and Salix pentandra (bay willow). These Salix species are also considered the natural source of acetylsalicylic acid (also known as aspirin).

**Mechanism of action:** Willow bark contains an ingredient called salicin, which is transformed in the body into another chemical substance called salicylic acid. Similar to acetylsalicylic, salicylic acid inhibits the production of certain prostaglandins in the nerves and this effect relieves pain and discomfort. Willow bark showed anti-inflammatory activity in several laboratory-based studies.

**Safety and toxicity:** Willow bark should be used with caution in patients with gastrointestinal problems, liver problems and diabetes. Common adverse effects include stomach upset, increased blood pressure and allergic reactions. Overdose can lead to serious consequences including stomach ulcers and bleeding.

**Availability:** The compound is available over-the-counter in health food shops in tablets containing 120-240mg of the active ingredient salicin.

**Interactions:** Similar to aspirin, willow bark interacts with the following drugs: anticoagulants (e.g. heparin, aspirin); acetazolamide; drugs for hypertension; anti-inflammatory drugs (e.g. cortisone and NSAIDs) and beta blockers (e.g. propranolol).

**Dosage:** Daily dosage corresponding to 240mg of salicin has been used in previous studies on patients with OA and RA. Assalix®, a commercial willow bark preparation, contains 240mg of salicin per tablet.

### The role in treatment of arthritis and musculoskeletal conditions:

Two RCTs were found examining its effectiveness in treating patients with hip/knee OA. In the first trial, 127 patients were randomised to receive one of the following three treatments: willow bark corresponding to 240mg of salicin/day, diclofenac 100mg/day, or placebo. After six weeks of treatment, patients who were on diclofenac had the best level of pain relief, while patients assigned willow bark did not significantly differ from the placebo group with respect to pain reduction. In the second trial, 78 patients were randomly assigned to either willow bark corresponding to 240mg of salicin/day or placebo tablets. After two weeks of treatment, patients taking willow bark achieved a 14 per cent reduction in pain experience, compared to only two per cent reduction in the placebo group (i.e. willow bark had a moderate analgesic effect). The compound was well-tolerated by patients who received it in both RCTs. Lack of effectiveness was the most common reason for withdrawal. One RCT evaluated the potential therapeutic effects of willow bark in patients with RA. In this trial 26 patients were randomly selected to receive either willow bark extract, corresponding to 240mg salicin/day or placebo tablets. After six weeks of treatment, patients taking willow bark achieved a 15 per cent reduction in pain experience compared to a four per cent reduction in the placebo group, but the study's authors concluded that this difference may be due to chance.

**Conclusion:** Willow bark is a herbal preparation that is available over-the-counter in the form of tablets. Its mechanism of action in relieving pain is attributed to its active ingredient salicin which inhibits the production of pain-inducing chemicals in the nerves. Current, limited, evidence suggests that willow bark may have a moderate effect in treating patients with pain due to OA and RA. In the single study evaluating it against an NSAID for OA, it was not as effective for pain relief. It appears relatively safe when taken in recommended doses.

### References:

- Schmid B, Ludtke R, Selbmann HK, Kotter I, Tschirdewahn B, Schaffner W, et al. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. *Phytother Res* 2001;15(4):344-50.
- Biegert C, Wagner I, Ludtke R, Kotter I, Lohmuller C, Gunaydin I, et al. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *J Rheumatol* 2004;31(11):2121-30.

### Classification:

#### Effectiveness score in OA:

2 

#### Effectiveness score in RA:

1 

#### Safety classification:

Amber 

## SECTION 2

Only those compounds which have been tested in at least one RCT have a specific entry about them in Section 1. If the compound that you are searching for does not appear there that means we could not find any reports of an RCT in which it was tested. This means it is not possible for us to tell whether this compound works or not. In this section we list some commonly used complementary medicines for which we could not find any RCTs and therefore cannot evaluate whether or not they are effective.

Two of the compounds included in this list have been studied in RCTs, but only as an ingredient of a multi-component medication: milfoil as an ingredient of Gitadyl and poplar bark as an ingredient of Reumalex, but the individual effectiveness was not investigated using RCTs.

Although we could not find any RCTs investigating the safety and effectiveness of any of the compounds included in this list, most of them have been studied in the laboratory, on animals and/or in humans in non-randomised studies. Results from studies in the laboratory can only provide data on mechanisms of action and toxicity of the compound. Results from studies on animals can develop a preliminary understanding of safety and effectiveness of the compound but cannot necessarily be directly applied to humans. A non-randomised trial is a type of experimental study in humans where patients are not randomly allocated to get either the active treatment or placebo. This type of study is affected, not only by differences in the treatment applied, but also by differences in the characteristics of the patient groups. For that reason RCTs are needed before a conclusion can be reached with respect to the safety and effectiveness of these compounds.

### Compounds for which no RCTs were identified (with other names and components in brackets)

1. 5-HTP
2. Aloe vera (lily of the desert, plant of immortality, medicine plant)
3. Artrosilium (organic silica, currant and Queen of the Meadow [meadowsweet])
4. Basil (holy basil, tulsi, *ocimum sanctum*)
5. Bee stings (bee venoms, Nectar Ease)
6. Black cohosh (*actaea racemosa*)
7. Chlorella pyrenoidosa (green algae)
8. Cider vinegar (apple cider vinegar)
9. Co-enzyme Q10 (CellSparc 360 combined with fish oil and Tocotrienolsvit E)
10. Curcuma longa (curcumin, turmeric)
11. Echinacea
12. Emu oil (emuline)
13. Garlic (*allium sativum*)
14. Ginkgo biloba
15. Ginseng (Siberian ginseng)
16. Green tea
17. Guaicum resin
18. Kava kava (*piper methysticum*)
19. Melatonin
20. Milfoil (yarrow, *achillea millefolium*) *see Gitadyl*
21. Nicotinamide adenine dehydrogenase (NADH)
22. Noni juice (*morinda citrifolia*)
23. Organic silica (*Bambusa vulgaris*)
24. Phosphatidyleserine
25. Poplar bark (American aspen, white poplar) *see Reumalex*
26. Qianggu
27. Sarsaparilla (*Smilax*)
28. Serum dehydroepiandrosterone sulphate (DHEAS)
29. Solidago virgaurea (*solidago canadensis*; goldenrod)
30. St John's wort (*hypericum perforatum*)
31. Tipi (contains Indian ginseng, Indian frankincense and turmeric)
32. Valeriana officinalis (valerian)
33. White royal jelly
34. Wintergreen oil (contains methyl salicylate)
35. Withania somnifera (ashwagandha, Indian ginseng, winter cherry)
36. Zinc and copper



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## Abbreviations

**RCT:** Randomised controlled trial

**RA:** Rheumatoid arthritis

**OA:** Osteoarthritis

**F:** Fibromyalgia

**NSAIDs:** Non-steroidal anti-inflammatory drugs

**CAM:** Complementary and alternative medicines

## Glossary

**Effectiveness and efficacy:** The *efficacy* of a compound can be established when tested under strictly controlled conditions: for example when all aspects of treatment are exactly the same apart from one aspect such as real capsule versus “placebo” capsule. If however a study compares two completely different treatments (care from a general practitioner versus care from a herbal medicine practitioner) and finds that one is better than another, we can’t be sure precisely what aspect of the care resulted in a better outcome because there were lots of differences. In such circumstances we say that such care was *effective*. In this booklet however we have used the word effectiveness for any comparisons between treatments.

**Essential fatty acids:** Fats that the body cannot make itself and must be supplied through foods or dietary supplements.

**Fibromyalgia (F):** A chronic, widespread pain in muscles and soft tissues surrounding the joints throughout the body.

## Non-steroidal anti-inflammatory drugs (NSAIDs):

Medicines that can relieve pain, swelling, stiffness, and inflammation. These drugs are often used in conventional treatment of arthritis and musculoskeletal conditions.

**Osteoarthritis (OA):** A progressive condition caused by gradual loss of joint cartilage resulting in inflammation and changes in adjoining joint structures, causing pain, swelling, and stiffness.

**Placebo:** A drug that contains no active ingredients. Placebos should be indistinguishable from the active intervention to ensure that the participant does not know which treatment group he/she was allocated to (the active treatment group or placebo group).

**Randomised controlled trial (RCT):** An experiment in which two or more medications, possibly including a control treatment (placebo) or no treatment, are compared by being randomly administered to participants. RCTs provide the best evidence on the effectiveness of treatments.

**Rheumatoid arthritis (RA):** An inflammatory disease that affects various body tissues but particularly involves the lining of the joint. The inflammation often affects the joints of the hands and the feet and tends to occur equally on both sides of the body.

**Significant:** This term is used in a statistical sense to denote that the authors of a study are fairly sure that differences between two different compounds assessed were not due to chance. It does not however mean that any differences were clinically important. For example the proportion of patients having pain relief on drug A may be only slightly higher than drug B and the difference is statistically significant. In contrast we may see very large differences in the proportion of patients improving between drug A and B: however if the study was based on a very small number of patients, the differences might have arisen by chance.

## SUMMARY TABLE

		Effectiveness score	Safety classification
1 Anthocyanidins	F	1	Amber
2 Antler velvet	RA	1	Green
3 Articulín-F	OA	2	Green
4 Avocado-soybean unsaponifiables (ASU)	OA	3	Green
5 Biqi capsule	RA	2	Amber (no information)
6 Blackcurrant seed oil	RA	1	Green
7 Borage seed oil	RA	3	Green
8 Cannabis oral spray	RA	2	Amber
9 Capsaicin gel	OA F	5 2	Green
10 Cat's claw	RA	2	Amber
11 Cetylated fatty acids (CFAs)	OA	2	Green
12 Chondroitin	OA	3	Green
13 Collagen	OA RA	2 1	Green
14 Devil's claw	OA	3	Amber
15 Duhuo Jisheng Wan (DJW)	OA	2	Amber
16 Eazmov	OA RA	1	Green
17 Evening primrose oil (EPO)	RA	3	Green
18 Feverfew	RA	1	Green
19 Fish oil: Fish body oil Fish liver oil	RA OA	5 1	Green
20 Flaxseed oil	RA	1	Amber
21 Ginger	OA	3	Green
22 Gitadyl	OA	2	Green



		Effectiveness score	Safety classification
<b>23</b> Glucosamine: Glucosamine sulphate Glucosamine hydrochloride	<b>OA</b>	<b>3</b> <b>1</b>	<b>Green</b>
<b>24</b> Green-lipped mussel	<b>OA</b> <b>RA</b>	<b>3</b> <b>1</b>	<b>Green</b>
<b>25</b> Homeopathy	<b>OA</b> <b>RA</b> <b>F</b>	<b>1</b> <b>1</b> <b>2</b>	<b>Green</b>
<b>26</b> Indian frankincense	<b>OA</b>	<b>3</b>	<b>Green</b>
<b>27</b> MSM	<b>OA</b>	<b>2</b>	<b>Green</b>
<b>28</b> Phytodolor	<b>OA</b>	<b>4</b>	<b>Green</b>
<b>29</b> Pine bark extracts	<b>OA</b>	<b>3</b>	<b>Green</b>
<b>30</b> Reumalex	<b>OA</b> <b>RA</b>	<b>1</b>	<b>Green</b>
<b>31</b> Rosehip	<b>OA</b>	<b>3</b>	<b>Green</b>
<b>32</b> SAmE	<b>OA</b> <b>F</b>	<b>4</b> <b>2</b>	<b>Green</b>
<b>33</b> Selenium	<b>RA</b>	<b>1</b>	<b>Green</b>
<b>34</b> SKI 306X	<b>OA</b> <b>RA</b>	<b>3</b> <b>2</b>	<b>Green</b>
<b>35</b> Stinging nettle	<b>OA</b>	<b>1</b>	<b>Green</b>
<b>36</b> Thunder god vine	<b>RA</b>	<b>3</b>	<b>Red</b>
<b>37</b> Tong luo kai bi	<b>RA</b>	<b>1</b>	<b>Amber</b> (no information)
<b>38</b> Vitamins A,C,E (anti-oxidant vitamins)	<b>OA</b> <b>RA</b>	<b>2</b> <b>1</b>	<b>Green</b>
<b>39</b> Vitamins D & B complex (non-anti-oxidant vitamins)	<b>OA</b>	<b>2</b>	<b>Green</b>
<b>40</b> Willow bark	<b>OA</b> <b>RA</b>	<b>2</b> <b>1</b>	<b>Amber</b>

# APPENDIX 1

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**Jane Tadman (Representative from  
the Arthritis Research Campaign)**









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