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ANTI-ARTHRITIC EFFECT OF BOSWELLIC ACIDS IN COMPLETE FREUND'S ADJUVANT-INDUCED ARTHRITIS

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Abstract

Boswellic acids, the pentacyclic triterpenoids of Boswellia serrata gum resin, have a long record in Indian medicine for joint disease. This review examines the published evidence on their anti-arthritic effect, with attention to complete Freund's adjuvant-induced arthritis in the rat, the model used to test most anti-arthritic candidates. It covers the model, the chemistry of the acids, proposed mechanisms, findings in animal arthritis, pharmacokinetics and the limited human data. It reports no new experimental data. The literature points to inhibition of leukotriene synthesis and inflammatory signalling, but poor bioavailability, variable extracts and thin clinical trials restrict firm conclusions.

1. INTRODUCTION

Rheumatoid arthritis is a chronic, systemic autoimmune disease in which the synovial lining becomes thickened and invaded by inflammatory cells, and cartilage and bone are slowly destroyed [1, 2]. Modern disease-modifying drugs, from methotrexate to biological agents, have changed the outlook for many patients, but they are costly, do not work for everyone, and carry risks of infection and other toxicity [3, 4, 5]. Non-steroidal anti-inflammatory drugs relieve pain without altering the course of the disease, and their gastrointestinal and cardiovascular effects limit long-term use [6]. It is understandable that people with arthritis, and the researchers who study them, keep returning to plant-derived

anti-inflammatories. The gum resin of *Boswellia serrata* Roxb. (Burseraceae), known in India as salai guggal or Indian frankincense, is one of the best-studied examples [7, 8].

This review looks at what has been published on the anti-arthritic effect of boswellic acids, the active triterpenoid acids of the resin, with special attention to arthritis induced in rats by complete Freund's adjuvant (CFA). It reports no new experimental data. CFA arthritis is the workhorse model for screening anti-arthritic compounds, and many of the key claims for boswellic acids rest on it or on closely related adjuvant and protein-induced models [9, 10, 11, 12]. The sections below describe the model and its limits, the chemistry and sources of the acids, the mechanisms proposed, the animal and human findings, pharmacokinetics and safety, and the main gaps. A synthesis of the principal findings is given in the third and fourth sections [13, 14].

The scale of the clinical problem explains the continuing search. Rheumatoid arthritis affects roughly one in a hundred adults in many populations, women more often than men, and untreated disease leads to progressive deformity and disability [2, 3]. Current guidance recommends starting a conventional synthetic disease-modifying drug early and escalating to combinations or biological agents when targets are not met [4, 5]. Many patients nevertheless take supplementary products, partly because they fear the adverse effects of long-term immunosuppression and partly because pain and stiffness persist despite treatment. Any natural product proposed as an adjunct therefore has to be judged against a demanding standard: it must reduce inflammation, preferably protect joint structure, and cause no harm when used beside drugs such as methotrexate [1, 6].

Interest in boswellic acids also reflects a wider pattern in drug discovery. Many anti-inflammatory plants were studied first because of traditional use and later because a molecular target was identified. In the case of Boswellia, the order was roughly the reverse of what researchers would like: the experimental evidence in rodents appeared in the 1980s, the 5-lipoxygenase target was identified in the early 1990s, and good-quality human trials began only later [11, 15, 16]. That sequence helps explain why the preclinical literature is richer than the clinical one.

2. THE ADJUVANT ARTHRITIS MODEL

Pearson described adjuvant arthritis in 1956, when he noticed that rats given an injection of mycobacteria suspended in mineral oil developed a swollen, inflamed polyarthritis within about two weeks [17]. The modern version injects CFA, which contains heat-killed mycobacteria in oil, into the base of the tail or a hind paw footpad. The injected paw swells within hours to days, a local reaction that is largely innate. Around ten to twelve days later the contralateral paw and the forelimbs become inflamed, and the disease peaks at about three weeks, with periosteal new bone formation, bone erosion and weight loss [9, 10, 18]. Susceptible strains such as Lewis rats show the most consistent response, whereas some other strains respond poorly [9, 19].

What drives the disease is still not fully settled. Arthritis can be transferred by T cells from affected rats to naive recipients, so it is T-cell dependent, and cross-reactivity between mycobacterial heat-shock protein epitopes and host proteins was once a favoured explanation [9, 18]. Later work showed that oil alone, or other non-immunogenic adjuvants, can induce arthritis in susceptible rats, which complicates the story [9]. Billiau and Matthys reviewed how Freund's adjuvants act in several autoimmune models and stressed the strong role of innate immune activation by mycobacterial components [18]. The practical point for a pharmacologist is that the model captures inflammation, immune activation and bone damage in one animal, even if it is not a copy of the human disease [1, 20].

Practical details of the procedure are worth setting out, because they differ between laboratories. Adjuvant is prepared by suspending killed mycobacteria in paraffin or mineral oil, and the amount of mycobacteria, the injection site and the injected volume all influence severity and timing [10, 17]. Injection at the tail base tends to give a more

symmetrical polyarthritis, while a subplantar injection gives a clear primary lesion in the injected paw that is easy to measure [9, 19]. Age, sex and strain of the rat, as well as the diet and the stress of handling, alter the outcome. Without these details a reader cannot judge whether the disease in the control group was severe enough to leave room for improvement, which is the first thing to check in any adjuvant study [10, 20].

Typical readouts include paw volume measured with a plethysmometer, an arthritic score of 0 to 4 for each paw, body weight, and radiographic or histological scoring of joint damage. Serum markers such as C-reactive protein, rheumatoid factor and cytokines including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) are often added, as are haematological indices and tissue markers of oxidative stress [10, 19, 20]. Dosing can start before CFA injection (prophylactic) or after arthritis appears (therapeutic), and the two designs answer different questions. A compound that prevents disease when given early may do little for established joint damage, yet many papers do not state which design they used [10, 20].

Pain and function have to be assessed as well as swelling. Joint pain in arthritic rats is measured by mechanical or thermal withdrawal thresholds, by gait analysis and by the ability to bear weight on the affected limb, and these measures sometimes diverge from paw volume [10, 20]. A compound may reduce swelling and leave pain unchanged, or the reverse. Radiographs and micro-computed tomography show erosions and new bone formation, and histology of the ankle and knee joints gives scores for synovitis, pannus, cartilage damage and bone resorption [1, 19]. Of these, structural measures matter most for a disease in which irreversible damage is the main cause of long-term disability, yet they are the least often reported in natural-product studies [9, 20].

Ethical practice and welfare deserve a mention. Adjuvant arthritis is a painful, progressive condition, and good studies set humane endpoints, provide soft bedding and easy access to food and water, and use the smallest group that gives a meaningful answer. Analgesic cover is limited because it interferes with the very inflammation under study, so refinement relies mainly on careful monitoring and clear stopping rules [10].

The model has well-known limits. It is acute and self-limiting compared with human arthritis, it lacks rheumatoid factor-driven pathology in the human sense, and it is heavily influenced by strain, adjuvant batch and injection technique [9, 10, 19]. Collagen-induced arthritis, with its autoantibody and major histocompatibility complex-linked features, resembles rheumatoid arthritis more closely and has become the preferred second model [19, 21]. Regulatory-minded reviewers also point out that many drugs active in rodent arthritis have not worked in people, so a positive result is a starting point and not an endpoint [20]. Fuller reporting of randomisation, blinding, sample-size rationale and excluded animals would improve the interpretability of these studies [22].

Positive controls need some thought. Indomethacin and diclofenac are the usual reference drugs in adjuvant arthritis, and methotrexate or dexamethasone are sometimes used. They are not equivalent. A non-steroidal drug will reduce paw swelling and pain-related behaviour quickly, whereas methotrexate affects the immune process and joint damage more slowly [6, 10, 20]. Picking a comparator that matches the proposed mechanism of the test substance makes a result easier to interpret.

3. BOSWELLIC ACIDS AND THEIR CHEMISTRY

The oleo-gum resin of *B. serrata* exudes from cuts in the bark and is made up of volatile oil, polysaccharides and a resin fraction of pentacyclic triterpenic acids [7, 23]. The boswellic acids proper are α- and β-boswellic acid, their 3-O-acetyl derivatives, and the 11-keto compounds, of which 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid (AKBA) are the most studied. Analytical work shows that the content of individual acids varies with the species, the source of the resin and the way it was processed, and AKBA is only a small fraction of most resins [14, 23]. Commercial extracts are commonly standardised to a total

boswellic acid content, and some are enriched in AKBA [24]. These differences are not trivial for interpreting pharmacology.

Structure–activity data show that the details of the molecule matter. Sailer and colleagues compared a series of triterpenic acids and found that a pentacyclic skeleton, a 3α-acetoxy group, a carboxyl group at C-24 and the 11-keto function all contributed to binding to and inhibition of 5-lipoxygenase (5-LOX), whereas the compounds lacking them were weaker [25]. Later work indicated that α- and β-boswellic acids and their acetates, as well as the 11-keto compounds, interact with several targets with different potency [13, 26, 27]. It follows that an extract rich in non-keto acids can behave differently from one rich in AKBA, and a result from one cannot simply be applied to the other [14, 28].

Analytical characterisation underlies every pharmacological claim. High-performance liquid chromatography with ultraviolet detection is the standard method for quantifying individual boswellic acids, and it can separate the keto and non-keto pairs, which differ in polarity and in absorption behaviour [14, 23]. Investigators who report only a total acid content, determined by titration or gravimetry, cannot say how much of the active keto compounds is present. The 11-keto acids absorb at a different wavelength from the others, so detection settings affect the apparent profile [24, 29]. Batch records and reference standards should be quoted in each paper. In their absence, a claim about the dose of AKBA in a study of a crude extract cannot be verified [14, 16].

A short note on nomenclature avoids confusion. Several Boswellia species yield frankincense, and the products traded as olibanum can come from *B. carterii*, *B. sacra* or *B. frereana* as well as *B. serrata*. Their boswellic acid profiles overlap but are not identical, and the traditional Indian use for joint disease refers to *B. serrata* [7, 23]. Papers that use the generic term 'frankincense' without naming the species or the extract should be read with caution.

4. MECHANISMS OF ACTION

The best-known mechanism is inhibition of 5-LOX, the enzyme that converts arachidonic acid to leukotrienes. Safayhi and co-workers showed in 1992 that boswellic acids were specific, non-redox inhibitors of 5-LOX in rat peritoneal neutrophils, which set them apart from redox-type inhibitors that act by reducing the enzyme's iron [15]. AKBA was found to bind in a non-competitive manner to a site separate from the substrate site, and its effect depended on the acid being present as an intact molecule [25, 30]. Subsequent work indicated that the interaction involves the enzyme's interplay with the cell membrane and calcium, which could explain why activity differs between cell-free and cell-based assays [26]. Since leukotriene B_4 attracts and activates neutrophils, this action is a plausible contributor to joint inflammation [7, 8].

Leukotriene inhibition is unlikely to be the whole story. Boswellic acids have been reported to inhibit human leukocyte elastase, to interfere with cyclooxygenase-1, and to modulate complement activation [13, 27, 31]. Acetyl-boswellic acids were shown to inhibit lipopolysaccharide-induced TNF-α formation in monocytes through direct interaction with IκB kinases, and AKBA suppressed the activation of nuclear factor-κB (NF-κB) and the expression of NF-κB-regulated genes, with downstream effects on osteoclastogenesis in vitro [28, 32]. A pure compound from the resin lowered TNF-α, IL-1β, nitric oxide and mitogen-activated protein kinase activity in human peripheral blood mononuclear cells and mouse macrophages [33]. If these results hold in vivo, they could account for effects on cytokine-driven joint damage.

Connective tissue is a further target. Reddy and colleagues examined the metabolism of glycosaminoglycans in rats with adjuvant arthritis and found that the boswellic acids reduced the abnormal degradation of these matrix components and lowered the activity of the lysosomal enzymes involved in their breakdown [34]. This fits with a protective effect on cartilage, an outcome that cannot be explained by 5-LOX inhibition alone. Earlier work had already shown that a Boswellia preparation was active in a number of inflammatory and arthritic models in the rat [11, 12]. Together with the cell-based

evidence on cytokines, the data suggest a multi-target profile, which may suit a polygenic disease but makes it hard to say which action matters most in vivo [8, 13].

Inflammatory mediators in the rheumatoid joint give some context for these targets. Synovial fluid and tissue contain leukotriene B_4, prostaglandins, TNF-α, IL-1β and IL-6, together with proteases released from neutrophils and activated synovial fibroblasts [1, 2]. Drugs that block TNF-α or IL-6 signalling are among the most effective in clinical use, whereas inhibition of leukotriene synthesis has not proved a major success in rheumatoid arthritis [3, 5]. This is an uncomfortable fact for any argument built on 5-LOX alone. It is part of the reason that the broader actions of boswellic acids on NF-κB signalling and cytokine formation, if they occur at tissue concentrations, may carry more weight than leukotriene inhibition [7, 28, 32].

Interaction between constituents may matter as well. Boswellic acids differ in potency and sometimes in the direction of their effects on the same target, and in whole resin the other triterpenoids, essential oil components and polysaccharides could modify absorption and activity [13, 23]. Co-administration of boswellic acids with curcumin has been proposed on mechanistic grounds, since both interfere with arachidonic acid metabolism and NF-κB signalling, though the evidence for additive benefit in arthritis is limited [8, 31]. Whether a purified acid or a whole extract is the better candidate cannot be settled from existing data. Purified compounds give clearer pharmacology, but extracts have the support of traditional use and the small human trials that have been done [7, 16, 24].

Caution is needed when moving from cells to animals. Concentrations that inhibit enzymes or transcription factors in vitro are often in the micromolar range, whereas plasma concentrations reached after oral dosing of boswellic acids are low, a matter taken up in the section on pharmacokinetics [14, 29, 35]. Plasma protein binding, tissue distribution and the possibility of active metabolites are not well understood. Some in vitro effects may also be partly attributable to non-specific interactions of lipophilic triterpenoids with membranes and proteins [13, 26]. These points do not cancel the mechanistic findings, but they argue for confirming target engagement in tissue, which few animal studies have attempted.

There is also a question of how a leukotriene inhibitor would be expected to behave in adjuvant arthritis. Leukotriene B_4 drives neutrophil recruitment and is abundant in rheumatoid synovial fluid, so reducing it should lessen early swelling and cell infiltration. Chronic bone and cartilage damage, however, relies on cytokines, osteoclasts and matrix enzymes, which may explain why a mixture of actions is more consistent with the broad improvement reported than a single target [1, 2, 7, 32].

5. EVIDENCE IN ARTHRITIS MODELS

The main published findings on boswellic acids and extracts in arthritis models and related assays are summarised in table 1, and the number of entries in each category is shown in fig. 1. Early studies by Singh and Atal described a salai guggal extract as a new non-steroidal anti-inflammatory agent that was active in several rat models, including adjuvant arthritis, and without the gastric ulceration typical of conventional drugs of that class [11]. Sharma and colleagues reported that purified boswellic acids reduced arthritis induced by bovine serum albumin in rabbits [12]. Later experiments, including topical use, supported activity in various inflammation models [36]. Most work has used rodents, with oral administration of an extract or a mixture of the acids [7, 8, 13].

What the adjuvant studies tend to report is a pattern: reduced paw swelling in both injected and non-injected limbs, lower arthritic scores, better preserved body weight, lower serum markers of inflammation, and histology showing less synovial infiltration and cartilage damage [11, 34, 36]. Activity was reported to be comparable to, or somewhat weaker than, standard non-steroidal drugs. That the effect appeared in the secondary lesion, which depends on immune activation, is more informative than reduction of the acute primary swelling, since many non-specific anti-inflammatory agents reduce the latter [9, 10]. In practice, the reports are

not uniformly clear about the timing of dosing in relation to adjuvant injection, and some mix prophylactic and therapeutic data [20].

Several design problems limit confidence in these studies. Dose ranges are wide and usually justified only by earlier papers. The boswellic acid content of the extract is not always given, and comparisons between extracts are therefore indirect [14, 23]. Group sizes are often small, blinding is seldom described, and many reports lack a vehicle-treated arthritic group alongside the normal control [22]. The tissue is rarely analysed for boswellic acids, so exposure is inferred [29, 35]. None of these faults is unique to Boswellia, but together they mean that the animal evidence is supportive and consistent in direction while falling short of the quality now expected for a confirmatory preclinical package [10, 20].

Dose and comparator choices need more careful reading than they usually receive. The doses used in rats are given as a mass of extract per kilogram, often a few tens to a couple of hundred milligrams, and allometric scaling to people is rarely discussed [11, 36]. Indomethacin is a common positive control, and activity comparable to indomethacin is sometimes presented as proof of efficacy, even though a non-steroidal drug has no disease-modifying effect [6, 10]. An anti-arthritic claim is stronger if the test substance beats the vehicle for structural outcomes, as shown by radiography or histology, as well as for swelling [9, 34]. Reports that include a methotrexate arm, or that test combinations with existing drugs, would be much more informative for the clinic [3, 4].

It is worth comparing the adjuvant data with the other models used for boswellic acids. In protein-induced arthritis and in carrageenan or other acute oedema tests, the compounds act on early, innate components of inflammation. The adjuvant model adds an immune and bone-damage element, and agreement across models strengthens the case [11, 12, 36]. Collagen-induced arthritis, which would test the immune-dependent mechanism more stringently, has been used far less with this plant [19, 21].

Table 1: Published findings on boswellic acids and Boswellia extracts relevant to arthritis

Compound or model	Reported finding	Ref.
Boswellic acids rat neutrophils	Specific, non-redox inhibition of 5-lipoxygenase.	[15]
AKBA enzyme studies	Non-competitive 5-lipoxygenase inhibition that depended on structural features of the molecule.	[25, 30]
Acetyl-boswellic acids monocytes	Reduced LPS-induced TNF-α formation by acting on IκB kinases.	[28]
AKBA cell lines	Suppressed NF-κB activation and NF-κB-regulated genes.	[32]
Pure compound human and mouse cells	Lowered TNF-α, IL-1β and nitric oxide.	[33]
Salai guggal extract rat	Active in standard rat models including adjuvant arthritis, without gastric ulceration.	[11]
Boswellic acids BSA-induced arthritis	Reduced experimental arthritis in rabbits.	[12]
Boswellic acids adjuvant arthritis	Reduced abnormal glycosaminoglycan degradation and lysosomal enzyme activity.	[34]
Oral dosing volunteers	Limited absorption of boswellic acids, increased by a high-fat meal.	[29]
H 15 extract rheumatoid arthritis	Early studies suggested benefit, but add-on use showed no clear gain.	[37, 38]
Knee osteoarthritis trials	Small placebo-controlled trials reported improved pain and function.	[16, 24]

Topical use raises another possibility. If boswellic acids are poorly absorbed after oral dosing, local application to inflamed tissue may suit them better, and activity of the acids applied to the skin in inflammation models has been described [36]. For an arthritic joint, however, drug has to reach the synovium, and no study has shown that this happens with a boswellic acid gel or cream. The idea is attractive, but evidence for it remains indirect [13, 14].

6. PHARMACOKINETICS, SAFETY AND CLINICAL DATA

Bioavailability is the weak point of the pharmacology. In healthy volunteers who took a herbal preparation, boswellic acids were absorbed to a limited degree, with AKBA in particular reaching very low plasma levels, and a high-fat meal increased uptake of several acids [29]. Studies of metabolism in vitro and in animals reported oxidation, hydroxylation and conjugation of the acids, with variation between species [35]. An overall assessment of the in vitro, preclinical and pharmacokinetic data concluded that concentrations reached in plasma after oral dosing are lower than those required for many of the in vitro effects, and that the link between exposure and response is unresolved [14]. It is therefore uncertain whether systemic or local gastrointestinal and synovial exposure explains the benefit observed in arthritic rats [13, 35].

Clinical studies of Boswellia in arthritis are modest in size. In rheumatoid arthritis, an open study and a short placebo-controlled study of an extract known as H 15 suggested benefit, but a controlled trial in patients on established therapy found no clear gain when H 15 was added [37, 38]. In osteoarthritis of the knee, two small randomised double-blind placebo-controlled trials of Boswellia extracts reported improvement in pain and function, one with an extract enriched in AKBA [16, 24]. Because the preparations, doses and populations differ, these studies cannot be pooled easily, and the difference between osteoarthritis and rheumatoid disease means that osteoarthritis results should not be taken to confirm anti-rheumatic activity [3, 8, 14].

Tolerability seems good in the available reports. The adverse events documented in the trials were mainly mild gastrointestinal complaints such as nausea, diarrhoea and epigastric discomfort, with similar rates in placebo groups in some studies [14, 16, 24]. In animal work the extract was reported to lack the gastric ulcerogenicity of non-steroidal drugs, which fits with weak inhibition of cyclooxygenase [11, 27]. Long-term safety, interaction potential with disease-modifying drugs, and use in pregnancy have not been well studied, and the possibility that boswellic acids interact with metabolising enzymes has been raised but not resolved [14, 35]. These gaps matter because patients with rheumatoid arthritis use herbal products alongside methotrexate and other agents [4, 6].

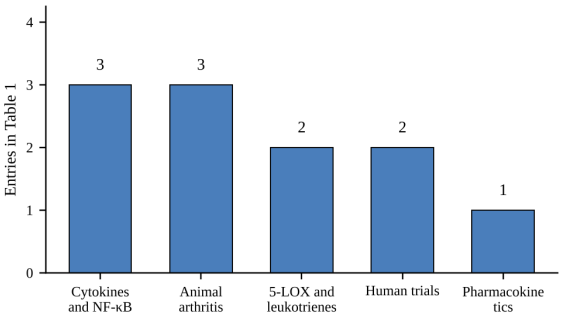


Fig. 1: Number of entries in table 1 by category of evidence

Design weaknesses in the human studies are comparable to those in the animal work. Several trials were small, short, and based on a single extract manufactured by one company, and in some the sponsor also carried out the analysis [16, 24, 37]. Outcome measures were mostly symptom scales rather than structural imaging, and withdrawal rates were not always reported clearly. The rheumatoid studies pre-date the present standards for trials in the disease, which use composite disease activity scores and require radiographic progression to be assessed [4, 37, 38]. One consequence is that even a positive result from these trials cannot be assumed to carry across to a modern patient population on current drug regimens [3, 5].

For practitioners, the sensible message is cautious. A patient who asks about Boswellia should be told that the evidence is encouraging but not strong, that products vary widely in content, and that it should not replace disease-modifying treatment in rheumatoid arthritis [3, 4]. Pharmacists can help by asking what is being taken, checking that the product states its boswellic acid content, and watching for stomach upset. Prescribers should note that a favourable animal result is not a clinical outcome [14, 20].

7. LIMITATIONS AND FUTURE DIRECTIONS

Taking the literature as a whole, boswellic acids show a coherent anti-inflammatory profile in cells and in rodent arthritis, but the chain of evidence has weak links. The target

concentrations in vitro exceed those found in plasma, extracts are not standardised across studies, the adjuvant model is a limited representation of rheumatoid arthritis, and human trials in rheumatoid disease are few and inconclusive [9, 14, 38]. The evidence for osteoarthritis is better but belongs to a different disease [16, 24]. A cautious reading is that boswellic acids are credible candidates for adjunctive anti-inflammatory use, not that they have been shown to modify rheumatoid disease [3, 8].

Future work could proceed in a sensible order. Characterised and standardised extracts, or purified acids, are needed so results can be compared [14, 23]. Formulation approaches to raise bioavailability, for example by combining the acids with lipids or phospholipids, deserve study in animals with exposure measured [14, 29]. Models with a stronger autoimmune character, such as collagen-induced arthritis, and therapeutic dosing schedules with blinded scoring of bone damage, would test the claims more rigorously [19, 21]. Finally, properly powered randomised trials in rheumatoid arthritis, with disease activity scores and radiographic outcomes, are needed before the traditional use can be supported by modern standards [4, 5].

A last point concerns choice of model for translation. A single positive adjuvant study carries limited weight, but consistent results across adjuvant, protein-induced and collagen-induced models, ideally in more than one species and laboratory, would be far more persuasive [10, 19, 21]. Reproducibility between sites is rarely tested for natural products. Replication by an independent group using a characterised extract is a more valuable next step than another exploratory screen, and registration of preclinical protocols would reduce selective reporting [20, 22]. The lesson from other anti-arthritic candidates that looked promising in rats and failed in patients is that the first question should be whether the mechanism is relevant to human disease [3, 5].

8. CONCLUSION

The evidence reviewed here supports boswellic acids as pharmacologically active, multi-target anti-inflammatory compounds. They inhibit 5-lipoxygenase and interfere with NF-κB signalling in cells, and they reduce paw swelling, arthritic scores and markers of joint damage in rodent adjuvant and related arthritis models [11, 15, 32, 34]. The effect on the secondary, immune-dependent lesion in particular suggests more than a simple analgesic or anti-oedema action, and the lack of the gastric injury typical of non-steroidal drugs in animals is appealing [9, 27]. A reasonable summary is that the pharmacology is credible, the preclinical case for further work is sound, and the claim of a proven anti-rheumatic effect is premature.

Confidence in these findings is tempered by three things. Absorption of the acids is poor, so the link between the concentrations active in vitro and those reached in tissue is unproven. Extracts and reporting quality vary a great deal. And human data in rheumatoid arthritis are scarce and mixed, while the better trials concern osteoarthritis [14, 24, 29, 38]. Boswellia products may be considered a possible adjunct, in consultation with a clinician, but they are not a substitute for established disease-modifying treatment [3, 4]. The most useful next studies would pair a characterised extract with measured tissue exposure, a therapeutic dosing schedule and structural joint outcomes, so that the animal findings can be judged on the terms a clinician would apply [20, 22].

9. ABBREVIATIONS

AKBA-Acetyl-11-keto-β-boswellic acid, ARRIVE-Animal Research: Reporting of In Vivo Experiments, CFA-Complete Freund's adjuvant, IL-1β-Interleukin-1β, IL-6-Interleukin-6, KBA-11-Keto-β-boswellic acid, 5-LOX-5-Lipoxygenase, NF-κB-Nuclear factor-κB, TNF-α-Tumour necrosis factor-α, LPS-Lipopolysaccharide, BSA-Bovine serum albumin

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Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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