REVIEW ARTICLE

Treatments for Inflammatory Arthritis: Potential But Unproven Role of Topical Copaiba

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Abstract

Traditional medicines for inflammatory arthritis (IA) include nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors (COXIBs), which have variable clinical benefits and serious side effects. In large-scale randomized, controlled trials (RCTs) in IA, they have demonstrated significant decreases in pain and inflammation but also significant increases in gastrointestinal symptoms, serious bleeding, and cardiovascular events. Copaiba, an essential oil used topically, has potential but unproven benefits, with few to no side effects. Basic research supports its mechanisms of benefit, but human data are sparse and include 1 case series and 1 small RCT examining its benefits for another inflammatory condition, not IA. Providing effective and safe pain relief for patients with IA presents clinical, public health, and research challenges. The clinical challenge is to maximize the benefits of treatment and minimize its risks. Sales of copaiba are increasing and may continue to do so even in the absence of reliable evidence from RCTs, providing a public health challenge. Thus, the research challenge is to test topical copaiba versus a placebo for IA patients against a background of usual care in RCTs of sufficient size, dose, and duration. If such trials show positive results, a logical next step might be head-to-head comparisons against NSAIDs and COXIBs. Evidence from RCTs may support more widespread use or, to paraphrase Huxley, conclude that copaiba is yet another beautiful hypothesis slain by ugly facts.

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Recently, the US Food and Drug Administration (FDA) strengthened its warning about the increased cardiovascular risks of traditional, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclo-oxygenase-2 inhibitors (COXIBs), including myocardial infarction (MI) and stroke.[1] That strengthened warning draws further attention to the need for effective and safe therapies to control symptoms in patients with inflammatory arthritis (IA), in whom the recommended short-term use of NSAIDs is insufficient to address their chronic pain and inflammation.

IA includes rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, and other debilitating conditions. From a clinical perspective, all forms of IA are serious, causing pain and progressive, structural joint damage as well as multiple comorbidities. From a public health perspective, the overall prevalence of IA in the general population is approximately 2% to 3%.[2] RA, a relatively common manifestation of IA, has a prevalence from 0.5% to 1.0%.[3]

With respect to clinical challenges, patients with RA have a 2-fold higher risk of cardiovascular disease (CVD) and higher risks of osteoporosis, interstitial lung disease, infections, malignancies, fatigue, depression, and cognitive dysfunction.[3] Adverse effects are common and can be serious. Adverse effects due to NSAIDs are responsible for more than 100 000 hospitalizations and more than 17 000 deaths each year in the United States.[4]

Other medical therapies of higher potency, including disease-modifying antirheumatic drugs (DMARDs), are being prescribed early to patients with IA for pain and inflammation as well as avoidance of progressive joint damage.[5] DMARDs, however, can have very serious side effects, but they rarely lead to fatalities.

At present, NSAIDs are the major therapies used for acute IA to provide relief of pain and inflammation, but they do not slow the progression of joint damage. NSAIDs include diclofenac, ibuprofen, and naproxen as well as the newer COXIBs. COXIBs were developed to decrease pain and inflammation with a lower risk of gastrointestinal (GI) side effects.[6] That lowered risk is important in IA because such patients are more likely to be taking aspirin to reduce their high risk of CVD, but aspirin also increases GI side effects. Furthermore, most NSAIDs and COXIBs are associated with increased risks of CVD.

A comprehensive meta-analysis of randomized, controlled trials (RCTs) that compared vascular and upper-GI risks[7] showed that COXIBs increased the risk of vascular events by approximately 40%, as did high-dose diclofenac and ibuprofen, but not naproxen. All NSAID regimens approximately doubled the risk of heart failure and increased upper-GI complications, although COXIBs and diclofenac were less gastrotoxic than ibuprofen and naproxen.

To minimize their side effects, NSAIDs and COXIBs are generally reserved for short-term use, which is insufficient to control the chronic pain and inflammation of IA. Furthermore, the US FDA has mandated new warning labels on NSAIDs that indicate that MIs and strokes can occur as early as the first few weeks of treatment.[1] All of those considerations suggest the need to test novel therapies with potential clinical benefits and fewer side effects than traditional medicines.

One such possible, marketed remedy of unproven clinical benefit in humans is the essential oil *Copaifera reticulata* (copaiba). Empirically, many individuals with joint pain and inflammation have used copaiba and reported favorable results. For example, The benefits of naproxen and ibuprofen were reported for a 67-year-old woman with IA who suffered from refractory pain in her finger joints despite courses of treatment with those medications. Both caused major GI side effects.[8] After using topical copaiba, she experienced pain relief without discernible side effects. Such case reports are useful to formulate, but not test, hypotheses.

C reticulata is obtained from copaiba trees. The oil-resin, and more recently the essential oil, are used topically for a variety of painful and inflammatory conditions, including rashes, dermatitis, insect bites, and psoriasis in addition to joint pain.[9] Its anti-inflammatory properties have been attributed largely to the sesquiterpenes β-caryophyllene and α-humulene[9] and to an anti-inflammatory diterpene, kaurenoic acid.[10]

In a recent study of the anti-inflammatory properties of *C reticulata*/*C langsdorffii*,[11] its major components included β-caryophyllene (56.1%), γ-elemene (12.6%), α-humulene (6.4%), and α-copaene (3.7%). The study showed that copaiba liposaccharide induced nitric oxide production ($P < .01$) but not lipopolysaccharide (LPS)-induced prostaglandin E_2 production. In addition, copaiba suppressed the proinflammatory cytokines interleukin (IL) 6, IL-8, and IL-1β in LPS-exposed cells. All of those findings suggest that copaiba provides benefits in the treatment of the inflammatory response. Furthermore, in vitro and in vivo studies have suggested that copaiba oil can ameliorate the outcomes of several inflammation-mediated diseases.[12,13,14]

Thus, basic research supports the oil's mechanisms of benefit, but human data are sparse and include only 1 case series and 1 small RCT that examined its benefits for another inflammatory condition, not IA. In the 1 reported case series, 3 patients with psoriasis—2 receiving an oral and 1 a topical treatment—were followed for 6 weeks. All 3 had attenuation of psoriatic lesions and erythema.[15] Furthermore, in a randomized, controlled, double-blind trial of 10 volunteers with mild acne,[10] possible improvements occurred in the surface area affected with acne, but that finding did not achieve statistical significance. No adverse events were reported in either of the studies, although coapaiba may cause local redness and itching.

Thus, the totality of the currently available evidence is wholly insufficient to judge the benefits and risks of copaiba essential oil for the relief of the pain and inflammation of IA. Providing effective and safe pain relief to patients with IA presents clinical, public health, and research challenges.

The clinical challenge is to maximize the benefits and minimize the risks. Although researchers have accumulated little or no evidence that copaiba provides benefits for humans, they also have found little or no evidence that it offers risks of the magnitude demonstrated for NSAIDs and COXIBs. Nonetheless, sales of copaiba are increasing and may continue to do so even in the absence of reliable evidence from RCTs, which provides challenges for public health.

Thus, the research challenge is to test topical copaiba versus a placebo in IA patients against a background of usual care in RCTs of sufficient size, dose, and duration.[8,16] For example, an initial research strategy might be to test copaiba among IA patients unwilling to take or unable to tolerate NSAIDs and COXIBs.

If such trials are positive, a logical next step would be head-to-head comparisons against NSAIDs and COXIBs. Thus, in the future, evidence from RCTs may either support its more widespread use or, alternatively to paraphrase Huxley, conclude that copaiba is yet another beautiful hypothesis later slain by ugly facts.[17]

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