Emu Oil: A novel therapeutic for disorders of the gastrointestinal tract?

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Abstract

Gastrointestinal diseases characterized by inflammation, including the inflammatory bowel diseases, chemotherapy-induced mucositis and non-steroidal anti-inflammatory drug-induced enteropathy, currently have variably effective treatment options, highlighting the need for novel therapeutic approaches. Recently, naturally-sourced agents including prebiotics, probiotics, plant-extracts and marine-derived oils known to possess anti-inflammatory and anti-oxidant properties have been investigated in vitro and in vivo. However, animal-derived oils are yet to be extensively tested. Emu Oil is extracted from the subcutaneous and retroperitoneal fat of the Emu, a flightless bird native to Australia, and predominantly comprises fatty acids. Despite the limited rigorous scientific studies conducted to date, with largely anecdotal claims, Emu Oil, when administered topically and orally, has been shown to possess significant anti-inflammatory properties in vivo. These include a CD-1 mouse model of croton oil-induced auricular inflammation, experimentally-induced polyarthritis and dextran sulfate sodium-induced colitis. Recently, Emu Oil has been demonstrated to endow partial protection against chemotherapy-induced mucositis, with early indications of improved intestinal repair. Emu Oil could therefore form the basis of an adjunct to conventional treatment approaches for inflammatory disorders affecting the gastrointestinal system.

Key words

anti-inflammatory, chemotherapy-induced mucositis, Emu Oil, fatty acids, gastrointestinal disorders, ratite.
Introduction

A multitude of factors can influence the function of the human gastrointestinal (GI) tract including genetic predisposition, diet composition, environmental insults and intestinal bacterial communities. Several disorders of the GI tract, including infective enteritides (i.e. fungal, bacterial and viral gastroenteritis),\(^1\) the inflammatory bowel diseases (IBDs; the collective term for a group of chronic, idiopathic GI disorders including ulcerative colitis and Crohn’s disease), chemotherapy-induced mucositis,\(^2\) colorectal cancer,\(^3\) celiac disease\(^4\) and non-steroidal anti-inflammatory drug (NSAID)-induced enteropathy,\(^5\) are associated with inflammation, ulceration, mucosal damage and malabsorption. Current treatment options for mild to moderate ulcerative colitis comprise anti-inflammatory drugs containing 5-aminosalicylic acid, whereas more severe conditions are treated with corticosteroids, immunosuppressants and immunomodulators. However, these therapies are commonly associated with significant adverse effects including infection, implicating difficulty in inducing and maintaining patient remission.\(^6,7\) Although effective treatment options are available for a number of gastrointestinal disorders, such as the infective enteritides, the variable responsiveness of treatments for ulcerative colitis highlights the need to broaden therapeutic approaches, including adjunctive strategies, to attenuate the inflammatory response, prevent mucosal damage and facilitate mucosal healing. Recently, naturally-sourced agents including probiotics,\(^3,8,9\) prebiotics,\(^3,10,11\) plant-extracts,\(^12,13\) growth factors\(^14-16\) and marine-derived oils\(^17,18\) known to possess anti-inflammatory and anti-oxidant properties have been investigated as potential therapeutics. However, there have been surprisingly few investigations of animal-derived oils in this context.

Fatty acids and intestinal inflammation

The favorable effects of diets high in n-3 fatty acids (FAs) on the cardiovascular system, particularly those found in fish oils, were first described in Greenland Eskimos by Dyerberg et al. in 1975.\(^19\) This initial observation prompted focused research on n-3 FAs, the predominant FAs in fish oils. These polyunsaturated FAs have been shown to reduce levels of pro-inflammatory cytokines including tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukin-12 (IL-12) and interleukin-1\(\beta\) (IL-1\(\beta\)) in a severe combined immuno-deficient mouse model of colitis, a bowel condition characterized by inflammation of the colon.\(^20\) For example, Lyprinol, an extract from the New Zealand Green Lipped mussel, has been shown to decrease inflammation and accelerate repair of the intestinal mucosa in a dextran sulfate sodium (DSS) model of colitis.\(^18\) Lyprinol has also improved some features of intestinal mucositis in the experimental setting.\(^21\) However, less attention has been directed towards animal-derived oils with purported anti-inflammatory properties, such as that derived from the Australian ratite bird, the Emu.\(^22,23\)

Ratites

Ratites are flightless birds, with a raft-like breastbone devoid of a keel. In these birds, breast muscles are vestigial to non-existent.\(^24\) The main representatives of this group are the Emu (Dromaius novaehollandiae), native to
barren regions of Australia; the African Ostrich (*Struthio camelus*), native to Africa; the three Kiwi species (*Apterix sp.*), native to humid shady areas of the New Zealand forest; the Cassowary (*Casuarius sp.*), native to New Guinea rainforests; and the Rhea or South American Ostrich (*Rhea americana*) and the Choique (*Pterocnemia pennata*), both native to South America. Currently, certain ratites are farmed in Africa, Australia, Canada, Europe and USA, for commercialization of their meat, skin, feathers, eggs and more recently, their oil. However, the composition of Rhea, Ostrich and Emu Oils, extracted from adipose tissue, is not identical. Indeed, a wealth of anecdotal evidence and more recent (and better controlled) experimental studies suggest that Emu Oil may possess potent anti-inflammatory properties.

**Emu Oil**

Emu Oil is extracted from both the subcutaneous and retroperitoneal fat of the Emu by first rendering the macerated tissue, and then passing the liquefied fat through a series of filters to extract the oil. Some manufacturers also use centrifugation to separate the oil from other extraneous components of the adipose tissue. Native Australian Aboriginals and early white settlers first used Emu Oil to facilitate wound healing, pain alleviation and treatment of inflamed joints. Currently, Emu Oil is readily available for purchase at health food stores and Emu Oil companies worldwide. Manufactured products include 100% pure Emu Oil, Emu Oil capsules, skin and hair care products, massage oil and bath and body products. Applications include the relief of inflammatory arthritic pain in addition to itchiness, redness and irritation associated with skin conditions including dermatitis, eczema and psoriasis. Emu Oil uniquely possesses excellent skin-permeation properties, highlighting its practicality for a wide range of applications, in particular, trans-dermal delivery of other medications. Emu Oil further requires minimal refining, and presents a low health hazard, being readily metabolizable. Its source is also renewable, eco-sustainable and relatively inexpensive.

**Emu Oil composition**

Fatty acids (FAs) represent the predominating component of Emu Oil, with a lipid content of 98.8% for subcutaneous adipose tissue, and 98.0% for retroperitoneal adipose tissue. Emu Oil comprises approximately 42% oleic acid (18:1 n-9), 21% linoleic acid (18:2 n-6), and 21% palmitic acid (16:0), with lower levels of other FAs, including 1% α-linolenic acid (18:3 n-3). Emu Oil also contains variable levels of compounds including carotenoids, flavones, polyphenols, tocopherol and phospholipids in the non-triglyceride fraction, which may confer therapeutic benefits including antioxidant properties. More recently, Beckerbauer *et al.* demonstrated that Emus fed a diet rich in unsaturated fat (soybean oil) produced oil that was more polyunsaturated compared with Emus fed a diet rich in saturated fat (beef tallow). These findings indicate that diet composition can significantly influence the composition of Emu Oil and hence possibly impact on oil efficacy.
**Therapeutic properties of Emu Oil**

In a CD-1 mouse model of croton oil-induced auricular inflammation, topical application of Emu Oil significantly decreased auricular thickness and weight.\(^{31}\) Furthermore, Emu Oil reduced levels of the pro-inflammatory cytokines TNF-\(\alpha\) and IL-1\(\alpha\).\(^{31}\) Cytokines also reported to be directly involved in the development of IBD.\(^{32-34}\)

Interestingly, the anti-inflammatory effects of Emu Oil in croton oil-induced auricular inflammation were more pronounced than application of fish, flaxseed and olive oils, or liquefied chicken fat;\(^{31}\) oils known to contain significantly higher levels of FAs. Snowden and Whitehouse\(^{23}\) assessed the anti-inflammatory activity of five different preparations of Emu Oil, varying in Emu farm location, source of Emu adipose tissue (subcutaneous or retroperitoneal), rendering protocols and storage. Five Emu Oil preparations (Emu Oil [EO] one; commercially available preparation in Western Australia [WA] with added anti-oxidant, EO two; commercially rendered in WA with no additives, EO three; prepared using intra-abdominal fat from WA birds, EO four; prepared using subcutaneous fat from Queensland birds, EO five; commercially rendered from Queensland birds) were topically applied to rat paws, following experimentally-induced polyarthritis. Paw diameter, indicative of arthritic inflammation, was significantly reduced following application of four of the Emu Oil preparations (EO two–five). Furthermore, Emu Oil preparations two and three reduced inflammation to an extent comparable with oral ibuprofen (40 mg/kg), a readily available NSAID.\(^{23}\)

Emu Oil has further been demonstrated to reduce plasma cholesterol concentrations in hypercholesterolemic hamsters compared with hamsters ingesting a saturated fatty acid-enriched diet\(^{35}\) and Emu Oil administration reduced plasma low-density lipoprotein and aortic cholesterol ester concentrations.\(^{35}\) Whitehouse et al.\(^{22}\) indicated that transdermal application of Emu Oil in 15% (v/v) cineol significantly reduced paw swelling in addition to promoting weight gain in a rat model of arthritis.

Bennett et al.\(^{29}\) demonstrated that Emu Oil has both antioxidant properties *in vitro* (radical scavenging activities) and a protective role against oxidative damage (assessed by measuring the ability to inhibit lipid peroxidation of erythrocytes) in a biological membrane model system. Furthermore, Emu Oil afforded greater protection against oxidative damage than the Ostrich and Rhea Oils.\(^{29}\)

Topical application of Emu Oil has been demonstrated to promote wound healing and recovery. In a study by Politis and Dmytrowich,\(^{36}\) Emu Oil lotion (a mixture of Emu fat, oil, vitamin E and botanical oil) was applied to full-thickness skin defects 24 h after surgery in rodents. After the major post-inflammatory stages of wound healing had transpired (6 days postoperatively), wound contraction and infiltration of fronts of epithelialized and granulation tissue were assessed.\(^{36}\) Emu Oil lotion enhanced these parameters twofold, whereas pure Emu Oil did not exert significant effects.\(^{36}\) Improved wound healing with Emu Oil lotion was proposed to have occurred through a mechanism of enhanced keratinization.\(^{36}\) Nevertheless, in a study by Lagniel and Torres, Emu Oil improved recovery of damaged skin in children with second- and third-degree burn injuries caused by fire and hot water.\(^{37}\)
Potential mechanisms of action

The mechanism of action of Emu Oil and the nature of the active factor(s) are yet to be fully elucidated. It has been suggested that the n-3 and n-9 FAs present in Emu Oil may confer anti-inflammatory properties, and efforts to ameliorate several chronic inflammatory diseases, including IBD and rheumatoid arthritis, have been directed towards increasing dietary intake of n-3 and n-9 FAs.18,38 n-3 FAs reduce inflammation both directly (via downregulation of the inflammatory eicosanoid pathways that produce thromboxane B2, prostaglandin E2 and leukotriene B4) and indirectly (by altering the expression of inflammatory genes through effects on transcription factor activation), whereas n-9 FAs inhibit macrophage migration.31 Yoganathan et al.31 demonstrated that the ability of Emu Oil to reduce levels of pro-inflammatory cytokines were more pronounced in an experimental model of inflammation, compared with other oils known to contain higher levels of FAs. This suggests that the anti-inflammatory properties of Emu Oil could not be solely attributed to the FA profile alone.31 It is proposed that the effects of Emu Oil may be attributed to the synergism of FAs and other constituents in Emu Oil and/or the FA ratio. Other minor constituents of Emu Oil in the non-triglyceride fraction, such as antioxidants including carotenoids and flavones, and skin-permeation enhancing factors, are reported to evoke antioxidant or radical scavenging activities, modulate anti-inflammatory, pro-apoptotic and anti-proliferative pathways in intestinal epithelial cells and reduce pro-inflammatory cytokine production and colonic neutrophil infiltration in a mouse model of colitis.41 Furthermore, the high ratio of unsaturated to saturated fatty acids (UFA: SFA, approximately 1.8) may confer protection against oxidative damage.29

Emu Oil and gastrointestinal disorders

Emu Oil requires extensive testing, both topically and orally, with respect to its reported therapeutic benefits. Only in recent years have more rigorous studies of Emu Oil been conducted in pre-clinical models of gut disease. Lindsay et al.26 proposed a potential mechanism of action of Emu Oil following oral administration to rats with chemotherapy (5-Fluorouracil; 5-FU)-induced mucositis. In this study, Emu Oil decreased acute small intestinal inflammation assessed by myeloperoxidase activity (found in the intracellular granules of neutrophils) 96 h after 5-FU-administration. Emu Oil also improved mucosal architecture in the small intestine by lengthening crypts to a greater extent than the 5-FU control, during early recovery from chemotherapy-induced mucositis in rats.26 These results highlighted the possibility of a more rapid rate of recovery following Emu Oil administration during the long-term recovery phase of mucositis, which has not yet been tested.26 In a preliminary study in rats, Abimosleh et al.42 indicated that orally-administered Emu Oil improved selected parameters associated with the manifestation of DSS-induced colitis, characterized by inflammation and ulceration of the large bowel. Following Emu Oil treatment in colitic rats, this study revealed that proximal and distal colonic crypts were significantly lengthened to a greater extent than in colitic controls.42 Furthermore, histological damage severity observed in the proximal and distal colon of Emu Oil-treated rats was significantly decreased, indicating a lesser degree of tissue damage.42
Importantly, this could represent a new mechanism of action for Emu Oil, suggesting therapeutic promise in the stimulation of the intestinal repair process. Moreover, no significant effects were evident with the $^{13}$C-sucrose breath test in healthy rats receiving orally-administered Emu Oil, confirming the maintenance of small intestinal functional health by Emu Oil and supporting its safety for oral administration.$^{42}$ Further scientific validation of Emu Oil for its potential to treat gastrointestinal diseases characterized by inflammatory processes should be explored. There are well established animal models of intestinal disease$^{43-46}$ and several novel methods for detection of gastric functions. These include absorptive function,$^{46,47}$ gastric emptying,$^{48}$ intestinal transit$^{49}$ and a breath test for the non-invasive assessment of small intestinal mucosal injury,$^{47}$ which could greatly facilitate experimental and clinical studies associated with Emu Oil ingestion. Once the mechanism of Emu Oil action has been confirmed in pre-clinical settings of bowel, joint or systemic inflammation, early-phase clinical trials for these disorders would be indicated.

**Conclusions**

Gastrointestinal diseases and disorders that include ulcerative colitis, Crohn’s disease and NSAID-enteropathy are characterized by intestinal inflammation, mucosal injury, ulceration and malabsorption. As current therapies for these conditions are variably effective, the development of novel treatment strategies is desirable. Emu Oil could therefore represent a safe, renewable and economical alternative to pharmaceutical options in this context. Although strictly controlled extraction methods seek to minimize the impact of processing on the heterogeneity of Emu Oil preparations, the diet, location and genetic profile of individual birds, would likely influence Emu Oil composition and hence, clinical efficacy. To this end, further development of Emu Oil for gut disorders will require its application to *in vitro* assays of physiological processes such as inflammation and intestinal barrier function, followed by the correlation of these results with *in vivo* indications of efficacy. These assays could then be used as a component of quality assurance to predict the clinical efficacy of individual Emu Oil preparations. Moreover, future studies of Emu Oil in the context of IBD could include targeted microencapsulation, or enema delivery methods, in an attempt to increase the bioavailability of active Emu Oil constituents at the specific site of inflammation.

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