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REVIEW

The Antiinflammatory Properties of Humic Substances: A Mini Review

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Humic substances are effective in the suppression of delayed type hypersensitivity, rat paw oedema, a graft-versus-host reaction and contact hypersensitivity in rats. They reduce the C-reactive protein levels of patients suffering from osteoarthritis of the knee and the wheel and flare reaction of patients suffering from hay fever. They have also been described as cardioprotective and pro-angiogenic. Toxicity studies have indicated that potassium humate is safe in humans up to a daily dosage of 1 g/kg, whereas fulvic acid is safe in humans up to a daily dosage of 1.8 g per adult. The antiinflammatory action of potassium humate can be contributed to the inhibition of the release of inflammatory-related cytokines, an adhesion molecule, oxidants and components of the complement system. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: inflammation; humic substances; humic acid; potassium humate; fulvic acid.

INTRODUCTION

Long before chemical formulae to cure diseases were developed, humans discovered the healing powers of plants. Humic substances are formed from the decomposition of plants and occur naturally in water, peat, soil and brown coal. These substances have a complex structure and can be fractionated into humin and humic and fulvic acids (MacCarthy *et al.*, 1979). Although they have primarily been used to stimulate plant growth, they have also been applied in the treatment of various diseases in humans. Humic acids are soluble in water only at pH values higher than 2 whereas fulvic acid is soluble in water even at low pH values. Humin, in contrast, is a mixture of materials that are insoluble under all conditions (Pena-Méndez *et al.*, 2005). The richest source of humic acid is found in brown coal, also known as lignite, which is the 'youngest' part of coal. Two different humic substances (i.e. forest and grass humic substances) were characterised with the use of two different spectroscopic techniques, that is, diffuse reflectance infrared Fourier transform and nuclear magnetic resonance (NMR ¹H) (Muscola *et al.*, 2006). Owing to the significant differences found in the chemical compositions of the two samples, an analytical and preparative thin layer chromatography analysis was carried out and indicated the complexity of the molecular structure of potassium humate (Van Rensburg *et al.*, 2010b).

APPLICATION OF PEAT AND MUD PREPARATIONS FOR THE TREATMENT OF INFLAMMATION

The pharmacological properties of products rich in humic acids, derived from peat extracts such as sapropel, Tolpa

peat and mumie, have been extensively reviewed (Schepetkin *et al.*, 2002, 2003). It has been used as a folk medicine for more than 3000 years. Diseases that have been treated include inflammatory-related and ophthalmological diseases, gastric ulcers, acute gastroenteritis, anaemia, hypercholesterolemia, dermatitis, psoriasis, hepatic and viral diseases and diseases of the gall bladder.

Peat preparations have been used as a topical treatment as well as in spas for dermatitis and psoriasis (Wolina, 2009) (Table 1). The topical application of mud and peat reduces the symptoms of patients suffering from rheumatoid arthritis, eczema and psoriasis (Codish *et al.*, 2005; Chadzopulu *et al.*, 2011) (Table 1). These products have been shown to increase T-cell immunity in patients infected with pulmonary tuberculosis and are also effective in the treatment of hepatic diseases and diseases of the gall bladder (Schepetkin *et al.*, 2002). In a study by Krzemiński *et al.* (2005), it was shown that a Tolpa peat preparation (TPP) possesses pro-angiogenic and cardioprotective effects when administered subcutaneously in rats after the induction of myocardial infarction (Table 1).

Mud bath therapy and humate balneotherapy have improved the quality of life of patients suffering from osteoarthritis (Table 1), which is an inflammation-related disease associated with the progressive destruction of cartilage (Bellometti *et al.*, 1997; Iubitskaia and Ivanov, 1999; Codish *et al.*, 2005; Fraioli *et al.*, 2011; Gungen *et al.*, 2012; Chadzopulu *et al.*, 2011), whereas Vysokogorskii *et al.* (2009) described the wound healing properties of a solution of sapropel applied topically to full-thickness planar wounds induced in Wistar rats (Table 1).

MECHANISTIC STUDIES

Mechanistic studies done *in vitro* indicated that potassium humate derived from brown coal inhibits degranulation of phagocytes (Joone and van Rensburg, 2004),

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Table 1. A summary of the various successful trials (preclinical and clinical) done on humic substances

Humic substances	Used by/tested in	Route of application	Application
Peat	Humans	Topical and in spas	Treatment of Dermatitis (Wolina, 2009) Psoriasis (Codish <i>et al.</i> , 2005) Rheumatoid arthritis (Güngen <i>et al.</i> , 2012) Wounds (Vysokogorskii <i>et al.</i> , 2009)
Tolpa peat preparation	Rats	Subcutaneous	Cardioprotective and pro-angiogenic (Krzemiński <i>et al.</i> , 2005)
Mud/humate balneotherapy	Humans	Mud bath therapy	Improve quality of life (Chadzopulu <i>et al.</i> , 2011) Wound healing (Vysokogorskii <i>et al.</i> , 2009)
Sapropel	Rats	Topical	Wound healing (Vysokogorskii <i>et al.</i> , 2009)
Sapropel	Humans	Mud bath therapy	Treatment of osteoarthritis (Schepetkin <i>et al.</i> , 2002).
Oxifulvic acid	Rats	Topical	Wound healing (Van Rensburg <i>et al.</i> , 2001).
Oxifulvic acid	Mice	Topical	Inflammation (Van Rensburg <i>et al.</i> , 2001)
Oxifulvic acid	Humans	Topical	Inflammation (Snyman <i>et al.</i> , 2002)
Carbohydrate-derived fulvic acid	Rats	Topical	Wound healing (Sabi <i>et al.</i> , 2011) Eczema (Gandy <i>et al.</i> , 2011).
Carbohydrate-derived fulvic acid	Humans	Topical	Treatment of eczema (Gandy <i>et al.</i> , 2011)
Carbohydrate-derived fulvic acid	Humans	Oral	Safety (Gandy <i>et al.</i> , 2012)
Potassium humate	Rats	Oral	Decrease contact hypersensitivity (Van Rensburg <i>et al.</i> , 2007) Decreases delayed type hypersensitivity (Van Rensburg and Naude, 2009) Decrease graft-versus-host reaction (Van Rensburg and Naude, 2009) Decrease paw oedema and a graft-versus-host reaction (Van Rensburg <i>et al.</i> , 2010b)
Potassium humate	Humans	Oral	Treatment of allergic rhinitis (Gandy <i>et al.</i> , 2010). Treatment of osteoarthritis (Van Rensburg <i>et al.</i> , 2010a)

the activation and/or release of blood products associated with inflammation, such as cytokines and superoxide dismutase, and the migration and adhesion of inflammation-related cells to sites where allergic reactions and tissue damage take place (Van Rensburg and Naude, 2009). Fulvic acid also decreases the release of tumour necrosis factor alpha (TNF-alpha), but at much higher concentrations (>200 µg/ml) (Junec *et al.*, 2009).

On the other hand, Chen *et al.* (2002) indicated that humic acid treatment increased the adhesion as well as the production of oxidants by stimulated neutrophils *in vitro*. Humic substances have also been reported to stimulate the release of pro-inflammatory cytokines such as TNF-alpha *in vitro*, but only in the presence of exogenous lipopolysaccharides (Junec *et al.*, 2009), indicating that these substances should not cause inflammation under normal conditions.

Humic substances also possess antioxidant activities (Aeschbacher *et al.*, 2012; Kučerík *et al.*, 2008; Vašková *et al.*, 2011) and inhibit the expression of complement receptor one and three in lipopolysaccharide-induced human umbilical vein endothelial cells through the inhibition of nuclear factor kappa B activation (Gau *et al.*, 2000). These surface molecules play an important role during inflammation by assisting the cells to adhere to the walls of blood vessels in the vicinity of inflammatory reactions as in the case of patients suffering from autoimmune diseases (Crockard *et al.*, 1992). The previously mentioned results were confirmed with a potassium humate product derived from brown coal (Joone and van Rensburg, 2004). In this way humic substances

protect areas of existing inflammation by stopping inflammatory cells from reaching affected sites, 'sticking' to the nearby blood vessels and releasing toxic substances in these areas. The mechanism of action of humic substances can also contribute to the inhibition of both the classical and alternative pathways of complement activation, as well as the degranulation of phagocytes and the production of inflammation-related cytokines such as IL-1β, IL-6, IL-10 and TNF-α (Van Rensburg and Naude, 2009; Joone and van Rensburg, 2004).

PRECLINICAL TOXICITY AND EFFICACY STUDIES

The pro-angiogenic, angio-immunomodulatory as well as the cardioprotective properties of TPP, administered subcutaneously in rats was described by Tadeusz *et al.* (2005) (Table 1). They came to the conclusion that Tolpa peat can prevent the development of ischemic cardiomyopathy in rats.

The antiinflammatory activity of topically applied oxifulvic acid, a fulvic-acid product derived from bituminous coal, was compared with a 1% preparation of both diclofenac sodium and betamethasone in a murine model of contact hypersensitivity (Van Rensburg *et al.*, 2001) (Table 1). In this experiment, mice were sensitised to dinitrofluorobenzene and then challenged with dinitrofluorobenzene on the dorsal surface of one ear. The mice's inflamed ears were treated with a topical

application of either a placebo cream or a formulation containing oxifulvic acid, diclofenac sodium or betamethasone. The thickness of their ears was measured on a daily basis. Oxifulvic acid, as well as the betamethasone and diclofenac sodium formulations, reduced the cutaneous inflammatory response.

In a preclinical toxicity study in rats treated daily with an oral dosage of potassium humate at 1 g/kg for 1 month, it was found that the dosage had no effect on the safety parameters nor did a dosage of 500 mg/kg body weight have any effect on the pups when it was administered to pregnant female rats (Van Rensburg *et al.*, 2007). In efficacy studies, potassium humate, at an oral dosage of 60 mg/kg, inhibited a delayed type hypersensitivity reaction in rats immunised with sheep red blood cells, a carrageenan-induced oedema and a graft-versus-host reaction in rat models (Van Rensburg *et al.*, 2010b), as well as a contact hypersensitivity reaction in rats sensitised with dinitrofluorobenzene (Van Rensburg *et al.*, 2007) (Table 1). In these studies, potassium humate compared favourably with indomethacin and prednisolone. Interestingly, immune-incompetent rats (induced with cyclophosphamide treatment in the graft-versus-host experiment) treated with potassium humate did not suffer from the normal weight loss as was the case with rats treated with cyclophosphamide alone (Van Rensburg *et al.*, 2010b). Furthermore, a chemical complex was prepared by Anwer *et al.* (2010) with humic acid and aspirin by lyophilization. This complex enhanced the antiinflammatory activity of aspirin alone in the rat paw oedema model (Anwer *et al.*, 2010).

The antioxidant and wound healing properties of sapropels were described by Vysokogorskii *et al.* (2009) suggesting that it might be recommended for inclusion in medicinal formulations, whereas Ozkan *et al.* (2014) described the neuroprotective effects of humic acid, administered intraperitoneally, in a focal cerebral ischemia rat model, which might be due to its antioxidant properties. They speculated that humic acid may be applied as a preventive agent in patients with a high risk of developing ischemia-induced brain injury.

In two separate studies on two different fulvic-acid products, one derived from bituminous coal and the other from a carbohydrate source (CHD-FA), it was found that fulvic acid is safe and effective in the reduction of a contact hypersensitivity reaction in rats when applied topically (Van Rensburg *et al.*, 2001; Sabi *et al.*, 2011) (Table 1).

A study was done to determine the effects of the subcutaneous administration of TPP on spontaneous angiogenesis in rats after the induction of myocardial infarction. The results indicated that this product possesses cardioprotective properties by preventing the development of ischemic cardiomyopathy (Krzemiński *et al.*, 2005) (Table 1).

Trckova *et al.* (2005) reviewed the application of peat as a food supplement for farm animals and came to the conclusion that there are many beneficial properties of peat such as the detoxifying and absorbent effects, stimulation of the immune system and an increase in the growth of the animals. He suggested that, because of the differences in the chemical composition of peat from different areas, it will be necessary to test the effects of each source.

CLINICAL STUDIES

Oxifulvic acid, applied topically to allergic individuals, significantly reduced a wheel and flare reaction after intradermal allergen challenge (Snyman *et al.*, 2002), which was similar to that of hydrocortisone (Table 1).

A pilot study done on atopic people indicated that a 4.5% oxifulvic acid cream applied topically inhibited an elicited inflammatory reaction (Gandy *et al.*, 2011). This study was followed up with a clinical trial in which atopic people were treated for 3 days with daily oral dosages of up to 40 mL of a 3.8% solution of a carbohydrate-derived fulvic acid. A significant decrease in the skin prick test was observed (Table 1). It was concluded that this product was safe at these dosages (Gandy *et al.*, 2012).

In a double blind placebo controlled Phase I study with oxihumate (a bituminous-coal-derived humate product) done on HIV-positive individuals at oral dosages of 2, 4, 6 and 8 g per person per day over a two-week period (Botes *et al.*, 2002), it was demonstrated that, although the product had no positive effect on the viral load and CD4 counts of the patients, it was well tolerated with no side effects. This trial was executed before April 2004, when the national antiretroviral treatment programme was launched in South Africa.

The most conclusive findings were the results obtained from two clinical trials. In the first trial, potassium humate was administered orally in patients suffering from allergic rhinitis (Gandy *et al.*, 2010), and in the second trial, it was administered in patients suffering from osteoarthritis of the knee (van Rensburg *et al.*, 2010a). In the first trial, potassium humate decreased the wheel and flare reaction of the patients, and in the second trial, it improved the physical functioning of the patients and decreased the levels of C-reactive protein (CRP) in the blood of patients on the product (Fig. 1) (Table 1). This was confirmed by Gungen *et al.* (2012) who found that mud pack therapy slows down

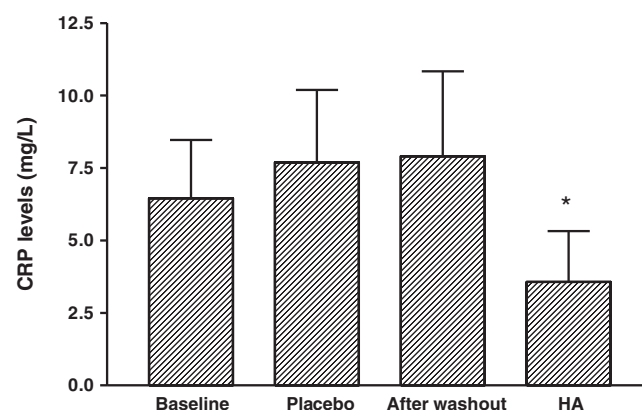


Figure 1. Effect of potassium humate (HA) versus placebo (before and after a 2 week washout period) on high sensitivity C-reactive protein (hs-CRP) levels of patients suffering from osteoarthritis of the knee**. *Significant ($p < 0.5$) reduction in hs-CRP compared with placebo values. **Van Rensburg C. E. J., Badenhorst B. E., Gandy J. J. and Snyman J. R., 2010b. The Open Conference Proceedings Journal 1:69–74. This is an open access article licenced under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.

the progression of knee osteoarthritis. Although CRP is not directly involved in the inflammatory process, it is widely used as a marker of inflammation (Boylan *et al.*, 2001; Koenig *et al.*, 1999; Nakayama *et al.*, 1993). For example, Nakayama *et al.* (1993) reported that a strong association exists between an increase in CRP levels and the progression of atherosclerosis, whereas McIntire *et al.* (1997) found the measurement of CRP useful for monitoring patients suffering from inflammatory bowel disease.

CONCLUSIONS AND FUTURE DIRECTIONS

Inflammation plays a role during viral and bacterial infections (Nakayama *et al.*, 1993), autoimmune diseases (Nathan, 2002), cancer (Balkwill and Mantovani, 2001; Coussens and Werb, 2002; Baumgarten and Frasor, 2012), allergies (Venge, 1994), Alzheimer disease (Holmes *et al.*, 2009) and cardiovascular conditions (Ridker *et al.*, 2000). An association between inflammation and malignancies has also been described (Lu *et al.*, 2006). The effective control of inflammation could be used to protect candidates predisposed to these conditions (Abou-Raya and Abou-Raya, 2006). This could also be the case with other inflammatory-related diseases (Coussens and Werb, 2002; Halliday *et al.*, 2000; Nakayama *et al.*, 1993).

Unfortunately, the use of non-steroidal anti-inflammatory drugs can lead to an increased risk of gastrointestinal complications such as ulcerative colitis, intestinal ulcers, intestinal perforations, damage to the small bowel (Somasundaram *et al.*, 1995; Davis, 1995; Thieffin and Beaugerie, 2005; Sostres *et al.*, 2010) and large intestines (Davis, 1995), as well as an increased risk of cardiovascular complications (Bjarnason *et al.*, 1993; McIntire *et al.*, 1997; Fosslien, 2005). These drugs have therefore become unsafe for use by patients already predisposed to these conditions. Interestingly, a humic acid preparation (TPP) significantly accelerated the healing of gastric ulcers induced in rats (Brzozowski *et al.*, 1994) (Abshenas *et al.*, 2014). A chemical complex was prepared with humic acid and aspirin by lyophilisation. This complex enhanced the anti-inflammatory activity of aspirin alone in the rat paw oedema model (Anwer *et al.*, 2010).

In conclusion, products derived from humic substances have been used and tested over centuries for inflammatory-related diseases (Table 1) suggesting that it can be a possible safe alternative for the treatment and/or prevention of diseases associated with inflammation.

Conflict of Interest

The author is involved in the distribution of a potassium humate preparation on the market for the treatment of various inflammatory-related diseases.

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