REVIEW ARTICLE

The anti-inflammatory 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-vs-host reaction and contact hypersensitivity in rats. They reduce the CRP (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 cardio protective and pro-angiogenic. Toxicity studies have indicated that potassium humate is safe in humans up to a daily dosage of 1g/kg, whereas fulvic acid is safe in humans up to a daily dosage of 1.8 g per adult. The anti-inflammatory 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.

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

INTRODUCTION

Long before chemical formulae to cure diseases were developed, man 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 mixure 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; i.e DRIFT (diffuse reflectance infrared Fourier transform) and NMR 1H (nuclear magnetic resonance) (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 and 2003). It has been used as a folk medicine for more than 3 000 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) (Tabel 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 (Krzeminski et al 2005) it was shown that a Tolpa peat preparation (TPP) possesses pro-angiogenic and cardio protective effects when administered subcutaneously in rats after the induction of myocardial infarction (Table 1).

Mud bath therapy and humate balneotherapy has 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; Iubutskaia and Ivanov 1999; Codish *et al*., 2005; Fraioli *et al*., 2011; Güngen *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 (Jooné and van Rensburg, 2004), 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 TNF-alpha, but at much higher concentrations (>200 μg/ml) (Junec et al 2009).

On the other hand Chen el al (2002) indicated that humic acid treatment increased the adhesion as well as the production of oxidants by stimulated neutrophils *in vitro*. Humic substances has also been reported to stimulate the release of pro-inflammatory cytokines such as tumour necrosis factor alpha (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 (CR1) and three (CR3) in lipopolysaccharide (LPS)-induced human umbilical vein endothelial cells (HUVECs) through the inhibition of nuclear factor kappa B (NF-κB) 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 above-mentioned results were confirmed with a potassium humate product derived from brown coal (Jooné 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 Naudé, 2009; Joone and van Rensburg, 2004).

PRECLICAL 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) (Tabel 1). They came to the conclusion that Tolpa peat can prevent the development of ischemic cardiomyopathy in rats.

The anti-inflammatory 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, diclofene 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 respons.

In a preclinical toxicity study in rats treated daily with an oral dosage of potassium humate at 1g/kg for 1 month, it was found that the dosage had no effect on the safety parameters nor did a dosage of 500mg/kg 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 60mg/kg, inhibited a delayed type hypersensitivity reaction in rats immunised with sheep red blood cells, a carrageenan-induced oedema and a graft-vs-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-vs-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). Futhermore a chemical complex was prepared by Anwer et al (2010) with humic acid and aspirin by lyphilization. This complex enhanced the anti-inflammatory 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 wheras 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 cardio-protective properties by preventing the development of ischemic cardiomyopathy (Krzeminski 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).

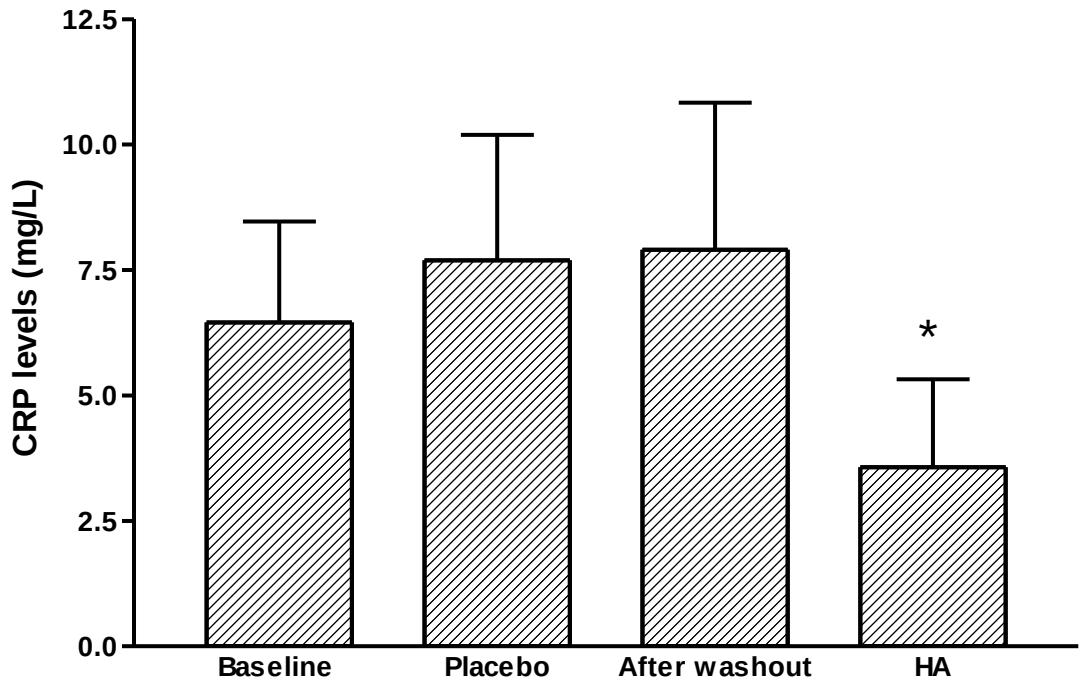
A pilot study done on atopic people indicated that a 4.5% oxifulvic acid cream applied topically inhibited an elicited inflammatory reaction (Gandy *et al*., 2011). This study was followed up with a clinical trial in which atopic people were treated for three days with daily oral dosages of up to 40ml 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 2g, 4g, 6g and 8g 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 (ART) 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 (Figure 1) (Table 1). This was confirmed by Gűnen et al (2012) who found that mud pack therapy slows down the progression of knee osteoarthiris. 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 McIntre al (1997) found the measurement of CRP useful for monitoring patients suffering from inflammatory bowel disease.

Figure 1



Effect of potassium humate vs placebo (before and after a 2 week washout period) on hs-CRP levels of patients suffering from osteoarthritis of the knee **.

*Significant ($p<0.5$) reduction in hs-CRP compared to placebo values.

**Van Rensburg CEJ, Badenhorst BE, Gandy JJ and Snyman JR. 2010(b). The Open Conference Proceedings Journal 1:69-74.

CONCLUSIONS AND FUTURE DIRECTIONS

Inflammation plays a role during viral and bacterial infections (Nakayama *et al*., 1993), autoimmune diseases (Nathan, 2002), cancer (Balkville 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 2000; Nakayama *et al.*, 1993).

Unfortunately, the use of non-steroidal anti-inflammatory drugs (NSAID) can lead to an increased risk of gastrointestinal complications such as ulcerative colitis, intestinal ulcers, intestinal perforations, damage to the small bowel (Somasundarum *et al*., 1995; Davis, 1995; Thiefin 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 (Answer *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.

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 et al 2009) Psoriasis (Codish et al 2005) Rheumatoid arthritis (Gűngen et al., 2012) Wounds (Vysokogorskii et al 2009)
Tolpa peat preparation	Rats	Subcutaneous	Cardioprotective and pro-angiogenic (Krzeminski et al 2005).
Mud/humate balneotherapy	Humans	Mud bath therapy	Improve quality of life (Chadzopaulu et al 2011) Wound healing (Vysokogorslii at al., 2009).
Sapropel	Rats	Topical	Wound healing (Vysokogorskii et al 2009)
Sapropel	Humans	Mud bath therapy	Treatment of osteoarthritis (Schepetkin 2002).
Oxifulvic acid	Rats	Topical	Wound healing (Van Rensburg et al 2001).
Oxifulvic acid	Mice	Topical	Inflammation (Van Rensburg et al 2001)
Oxifulvic acid	Humans	Topical	Inflammation (Snyman et al 2002)
Carbohydrate derived	Rats	Topical	Wound healing (Sabi et al 2011)

fulvic acid			Eczema (Gandy et al 2011).
Carbohydrate derived fulvic acid	Humans	Topical	Treatment of eczema (Gandy et al 2011).
Carbohydrate derived fulvic acid	Humans	Oral	Safety (Gandy et al 2012).
Potassium humate	Rats	Oral	Decrease contact hypersensitivity (Van Rensburg et al 2007). Decreases delayed type hypersensitivity (Van Rensburg and Naude 2009). Decrease graft vs host reaction (Van Rensburg and Naude 2009). Decrease paw oedema and a graft-vs-host reaction (Van Rensburg et al 2010b).
Potassium humate	Humans	Oral	Treatment of allergic rhinitis (Gandy et al 2010). Treatment of osteoarthritis (Van Rensburg et al 2010a).

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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