

# Immunomodulatory Effects of *Melaleuca alternifolia* Concentrate Abbas

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## ABSTRACT

The inflammatory response is an important part of host defense. Cytokines are small proteins that interact with receptors and act as signaling molecules involved in the inflammatory pathway. Essential oils are volatile oils derived from aromatic plants and include tea tree oil, *Melaleuca alternifolia* Concentrate (MAC) is an extract obtained from essential oil of *Melaleuca alternifolia*. MAC has anti-inflammatory, antimicrobial properties and antioxidant properties. *In vitro* studies have investigated the immunomodulatory effects of MAC. The parameters studied were cytokine production and protein expression in murine and human macrophage-like myeloid leukemia cell lines. The modulation of cytokines by MAC can improve health and prevent infections. The *in vitro* studies have demonstrated the antimicrobial effects of MAC. Taken together, the immunomodulatory and antimicrobial effects of MAC can play an important role as an immunostimulant for prevention of infections. Phase I studies have demonstrated the safety of MAC in humans.

**Key Words:** Inflammation, Cytokines, *Melaleuca Alternifolia* Concentrate (MAC)

## Introduction

### ■ Role of cytokines in inflammation

The inflammatory response is an important part of host defense. But, excessive or persistent inflammation can lead to disease. Inflammation is regulated, partly cytokines, which regulate cellular processes such as proliferation, differentiation, and secretion [1].

Cytokines are small proteins that interact with receptors and act as signaling molecules involved in the inflammatory pathway and can be either pro-inflammatory (IL-1 beta, GM-CSF, IFN-gamma, TNF-alpha) or anti-inflammatory (IL-4, IL-10, and IL-13). Macrophages are important players in the immune response. They increase the production of pro-inflammatory cytokines. Modulating the actions of macrophages can be an important approach for modulating immune reactions [2]. Cytokines are involved in the induction and effector phases of all immune and inflammatory responses. Cytokines represent tools and targets for modulating immune responses [3].

The “good” effects of cytokines include stimulation of the immune system to mount a

defense against foreign pathogens or countering tumors, and reduction of an immune response, in patients with multiple sclerosis to reduce neuronal inflammation. Cytokines may be “bad” if their upregulation is associated with inflammatory diseases, rheumatoid arthritis, asthma and Crohn's disease. Therapeutic modulation of cytokine expression needs to consider which cytokines must be upregulated and which cytokines need to be downregulated [4].

## Literature Review

### ■ Identifying the evidence

The clinical experts (Diabetologists, Cardiologists, Nephrologists, Dietician, and Physicians) conducted a systematic search using Ovid MEDLINE based on the predefined scope of the consensus. The search keywords included type 2 diabetes, management, Iraq, guidelines.

### ■ Essential oils

Essential oils are volatile oils derived from aromatic plants and include tea tree oil, eucalyptus oil, lavender oil, clove essential oil and peppermint oil. Terpenes and terpenoids are components of essential oils. Tea tree oil is processed from the

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plant *Melaleuca alternifolia* by removal of 90%-99% of monoterpenes. The International and Australian standards have defined the range of monoterpene content in tea tree oil to be between 18%-59.5%. Melaleuca Alternifolia Concentrate (MAC) is an extract obtained from essential oil of *Melaleuca alternifolia*. During processing 90%-99% of monoterpene hydrocarbons are removed [2].

Essential Oils (EOs) are associated with diverse pharmacological effects, such as anti-allergic, anticancer, anti-inflammatory, and immunomodulatory effects. Essential oils stimulate the immune system by increasing circulating lymphocytes and enhancing their phagocytic activities also suppress inflammation responses and decrease cytokine production by modulating the key mediators of inflammatory pathways [5].

■ **Melaleuca Alternifolia Concentrate (MAC)**

Melaleuca alternifolia Concentrate (MAC) or tea tree oil is an essential oil extracted from a native Australian plant *Melaleuca alternifolia*. *Melaleuca alternifolia* is widely available over the counter in Australia, Europe, and North America and is marketed as a remedy for various ailments [6]. (Carson CF) *M. alternifolia* has anti-inflammatory, antimicrobial properties and antioxidant properties, The water-soluble components of tea tree oil can inhibit the production of pro-inflammatory mediators by activated human monocytes [7]. The component

terpinen-4-ol and alpha-terpineol have been demonstrated to suppress the production of inflammatory mediators in *in vitro* studies where LPS-stimulated human macrophages were treated tea tree oil. This effect was attributed to  $\gamma$  interference with the NF-kB, p38 or ERK MAPK pathways [8, 9].

■ **Immunomodulatory effects of MAC**

*In vitro* studies have investigated the immunomodulatory effects of MAC. The parameters studied were cytokine production and protein expression in murine and human macrophage-like myeloid leukemia cell lines (Table 1).

The study by Low et al, demonstrated the immunomodulatory effects of MAC. Increasing doses of MAC increased peripheral blood immune cells. MAC increases CD3+ T cells, CD4+ and CD8 + lymphocytes.

■ **In vitro efficacy of MAC**

MAC has antimicrobial properties. Most bacteria are susceptible to TTO at concentrations of 1.0% or less. The spectrum of antimicrobial activity extends to *Mycobacterium avium*, *Escherichia coli*, *Haemophilus influenzae*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*, methicillin resistant *Staphylococcus aureus*, MAC is postulated to act by causing lysis of bacterial cell membrane and the loss of membrane integrity and function manifested resulting in the leakage of ions and the inhibition of respiration. MAC has antifungal activity against *C. albicans*, *Aspergillus*

**Table 1 : In vitro studies of immunomodulatory effects of MAC**

Cell lines	Parameters assessed	Treatment of cell lines	Observations
Murine RAW 264.7 cell line <sup>2</sup>	LPS-mediated proinflammatory cytokine production and LPS-mediated activation of NF =kB signaling in myeloid cells Nuclear factor ( NF)-kB gene expression Cytokine analysis in the supernatant fluid Nitric concentration oxide analysis in the supernatant fluid	Different concentrations of MAC ( 0,01, 0,02, 0,03, 0,04 , 0,05, 0,06, 0,07, 0,1, 0.15 v/v)	MAC demonstrated a dose-dependent inhibition of LPS-induced cytokine production (II-3, IL-10, GM CSF IFN-gamma) by Murine RAW 264.7 cell lines. MAC inhibited NF-kB activation MAC inhibited iNO protein expression No cytotoxicity was observed due to MAC
Human THP1 cell line <sup>2</sup>	LPS-mediated proinflammatory cytokine production and LPS mediated activation of NF =kB signaling in myeloid cells Nuclear factor ( NF)-kB gene expression	Different concentrations of MAC ( 0,01, 0,02, 0,03, 0,04 , 0,05, 0,06, 0,07, 0,1, 0.15 v/v)	MAC demonstrated a dose-dependent inhibition of cytokines (IL-1beta , IL-6,IL-10) MAC inhibited NF-kB activation No cytotoxicity was observed due to MAC
<b>Murine RAW264.7 macrophages and human monocytes<sup>9</sup></b>	LPS mediated stimulation	MAC treatment	MAC significantly increased both the mRNA and protein levels of heme oxygenase-1 (HO-1) via p38 and JNK MAPK activation MAC significantly increased the activation and nuclear translocation of NF-E2-related factor 2 (Nrf2), a key transcription factor regulating HO-1 induction.

*flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Blastoschizomyces*, *Candida glabrata*, *Candida tropicalis*, *Cryptococcus neoformans* and superficial dermatophytes. The antifungal activity of MAC is postulated to be mediated by altering the permeability of the fungal cell wall leading to loss of integrity of the fungal cell membrane, lysis and death. MAC has antiprotozoal activity against *Leishmania major* and *Trypanosoma brucei* and *Trichomonas vaginalis*. MAC is also postulated to have antiviral activity [6]. The anti-parasitic effects of these compounds are mainly due to their anti-histamine and anti-acetylcholinesterase activities as well as their ability to modulate host inflammatory responses. Low rates of resistance of pathogens has been reported to MAC [10].

#### ■ Phase 1 dose defining and safety studies of MAC

Phase 1 dose defining studies were conducted in 29 healthy adults (15 males and 14 females),

aged 19 years -53 years of age. Three doses of MAC were studied namely 600 mg, 750 mg single doses, 900 mg (300 mg three times a day for 5 days). MAC was well tolerated and did not have any adverse effect on blood, liver or kidney. No volunteers complained of adverse reactions. The results of single dose and repeated dose were comparable.

#### Conclusion

The immunomodulatory effects of MAC have been proven through multiple *in vitro* studies. The modulation of cytokines by MAC can improve health and prevent infections. The *in vitro* studies have demonstrated the antimicrobial effects of MAC. Taken together, the immunomodulatory and antimicrobial effects of MAC can play an important role as an immunostimulant for prevention of infections. Phase I studies have demonstrated the safety of MAC in humans.

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