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Setarud (IMOD™) as a Multiherbal Drug with Promising Benefits in Animal and Human Studies: A Comprehensive Review of Biochemical and Cellular Evidences

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ABSTRACT

This review focuses on the efficacy of Setarud (IMOD) that is an effective new drug in the management of different conditions in animal and human. IMOD is a new natural mixture that demonstrated immune modulating activity in preliminary investigations. To conduct this review, all relevant databases were searched up to 20th August 2011 for the term IMOD or Setarud and all human, animal and *in vitro* studies considered the effects of IMOD. A total of 13 studies were included. Some human studies showed anti-inflammatory and anti-oxidative stress effects of IMOD by lowering tumor necrosis factor alpha (TNF-α) and CD4 (a glycoprotein expressed on the surface of T helper cells, monocytes, macrophages and dendritic cells) that are involved in process of inflammation and oxidative stress consequences. The positive effects of IMOD in the control of experimental models of colitis, diabetes, hyperchlosteromia, polycyctic ovary syndrome and liver injury were found that were mediated mainly through antioxidant and anti-inflammatory properties. IMOD has also enhanced secretion of insulin from the rat isolated pancreatic islets and human B lymphocyte. It is concluded that IMOD has optimistic effects on oxidative stress and pro-inflammatory conditions in various diseases which most probably is resulted from combinational effects of herbs and the elements present in the mixture of IMOD.

Key words: IMOD, setarud, disease models, new drug, review, oxidative stress, molecular biology

INTRODUCTION

Setarud (IMOD) is a new naturally-derived immunomodulater prepared as the outcome of an invention referring to a method for preparing a mixture of *Rosa canica*, *Tanacetum vulgare* and *Urtica dioica* comprising selenium and urea treated by pulsed electromagnetic field of high frequency. IMOD has been patented in USA and Europe (Novitsky *et al*., 2007) for its effects on Human Immunodeficiency Virus (HIV) infection by increasing CD4 and reduction of tumor necrosis factor alpha (TNF-α). The herbs used in this complex have strong anti oxidative stress potential that is useful in many oxidant-related diseases (Hasani-Ranjbar *et al*., 2009a; Bitiren *et al*., 2010). The safety of IMOD has been already approved in preclinical (Khorram-Khorshid *et al*., 2008a) and clinical studies (Khairandish *et al*., 2009). IMOD was found effective in oxidative-stress-related disorders and immunoinflammatory-based diseases like

type 1 diabetes (Mohseni-Salehi-Monfared *et al*., 2010), colitis (Baghaei *et al*., 2010), pancreatic Langerhans islet transplant (Larijani *et al*., 2011) and polycystic ovary syndrome (Rezvanfar *et al*., 2011). The present study aimed to update the current knowledge on the efficacy and safety of IMOD by reviewing all human and animal and *in vitro* studies performed since its introduction to the world.

MATERIALS AND METHODS

Data source: Embase, Scopus, PubMed, Google Scholar and Iranmedex databases were searched up to 20 August 2011 for the initial terms of IMOD or Setarud.

All of the human and animal studies, *in vitro* studies that considered the effects of IMOD were included.

RESULTS AND DISCUSSION

Human studies: Of publications in the initial database search, 4 trial studies on the beneficial effects of IMOD were reviewed. Information of these clinical trials are summarized in the Table 1. A significant potential of IMOD in reduction of inflammatory cytokines such as CD4 and TNF-α in the immune system of HIV patients (Mohraz *et al*., 2009) and improvement of severe sepsis patients (Mahmoodpoor *et al*., 2010) are reported. Agha-Hosseini *et al*. (2011) showed that IMOD is an effective alternative treatment for human Oral Lichen Planus (OLP) but TNF-α may not be a good indicator for monitoring therapeutic response in this disease.

When IMOD was examined in management of severe sepsis patients, among oxidative stress parameters, a significant elevation in Total Thiol Molecules (TMM) was found (Mahmoodpoor *et al*., 2010).

Preclinical and phase 1 clinical safety of IMOD: The pre-clinical safety studies of IMOD in animal and phases 1 trials have been successfully conducted showing optimistic results. In this regard, Khairandish *et al*. (2009) have tested IMOD in animal acute and chronic toxicities and continued phase 1 clinical trial in HIV-infected patients to determine Maximum Tolerated Dose (MTD) and Dose Limiting Toxicity (DLT). Final conclusion of these studies was that IMOD is safe and can be used in treatment of immunologic disorders.

Table 1: Human studies conducted on IMOD

Results	Type of administration	Dose and duration of study	Type of study	Disease	Study
TNF-α ~	Oral	400 mg/days for 90 days	Before-after clinical trial (30 patients)	Oral lichen Planus	Agha-Hosseini *et al*. (2011)
APACHE score↓, SAPS↓, SOFA↓, IL-1~, IL-2~, IL-6~, PAI-1~, TNF-α↓ TTM↑, NO~, TAP~, LPO~	IV infusion	Loading dose: 125 mg Maintenance dose: 62.5 mg/day for 14 cousecutive days	Clinical trial (20 patients)	Severe sepsis	Mahmoodpoor *et al*. (2010)
CD4 count~	IV infusion	2, 4, 6.7, 10 ml/day for 28 days	Phase I clinical trial (12 patients)	HIV infection	Khairandish *et al*. (2009)
CD4 count↑	IV infusion	4 ml day^{-1} for 90 days	HIV patients	HIV infection	Mohraz *et al*. (2009)

APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; SAPS: Simplified acute physiology score; IL-1, IL-2, IL-6: Interleukin- 1,2,6; TNF-α: Tumor necrosis factor-α; TTM: Total thiol molecule; HIV: Human immunodeficiency syndrome; NO: Nitric oxide; LPO: Lipid peroxidation; TAP: Total antioxidant power; ↓: Decreased; ↑: Increased; ~: No change

Efficacy of IMOD in the treatment of human OLP: OLP is a chronic, immunologically mediated, mucocutaneous disorder. Administration of IMOD (400 mg day^{-1}) for three months was found an effective alternative treatment for OLP while investigators believed salivary TNF-α is not a good indicator for monitoring therapeutic response to OLP. The study showed higher effectiveness of IMOD as compared to ordinary therapies in human OLP lesions (Agha-Hosseini *et al*., 2011).

Efficacy of IMOD in the treatment of severe sepsis: Analysis of current immunomodulating strategies indicates that monovalent approaches are unlikely to restore immunostasis or achieve complete therapy of sepsis. IMOD was significantly effective in improving of SAPS (Simplified Acute Physiology Score), SOFA (Sequential Organ Failure Assessment) and APACHE (Acute Physiologic And Chronic Health Evaluation) score as quantitative indices of clinical status and reduction of mortality rate in critically ill severe sepsis patients. The study showed potential of IMOD in alleviation of severity of disease and dynamics. Also, among tested inflammatory biomarkers, IMOD significantly improved TTM (total thiol molecules) and TNF-α values (Mahmoodpoor *et al*., 2010).

Efficacy of IMOD in the treatment of AIDS patients: A phase 2 (safety and efficacy) and 3 (double-blind multi-center randomized clinical trial) tests were designed to explore the therapeutic effects of IMOD. There was a significant improvement in the immune system of HIV patients receiving IMOD therapy by increase in the CD4 count to the higher and more protective level in most subjects. Considering results of the safety tests and reports of the efficacy, the use of IMOD in HIV patients, especially at the pre-AIDS period, as a therapeutic vaccine was recommended due to slowing down the progress of the disease (Mohraz *et al*., 2009).

Animal studies: The detail of the animal studies that investigated the beneficial effects of IMOD are summarized in Table 2. The results suggest that IMOD most probably acts through induction of anti oxidative stress either direct or indirect by reducing free radicals especially via inhibition of involved cytokines in different organs such as pancreas (Mohseni-Salehi-Monfared *et al*., 2010), colon (Baghaei *et al*., 2010), ovary (Rezvanfar *et al*., 2011) and plasma of rat and in liver of rabbit (Azonov *et al*., 2008).

Also, studies indicated that biochemical assays including blood glucose, serum lipid levels and liver function tests were reduced by IMOD (Khorram-Khorshid *et al*., 2008a).

Anti-diabetic effect of IMOD: The administration of IMODameliorated oxidative stress indicators and proinflammatory cytokines in pancreas of type 1 diabetic mice. However, this effect did not lead to decrease in blood glucose or histological benefit (Mohseni-Salehi-Monfared *et al*., 2010).

Hepatoprotective effect of IMOD: IMOD showed the protective activity against CCL4-induced hepatotoxicity in rats. Administration of IMOD to rats ameliorated the toxic effects of CCL4 on body weight gain, liver histology or function (Khorram-Khorshid *et al*., 2008b).

Efficacy of IMOD in inflammatory bowel disease: The effect of IMOD was investigated in experimental colitis in rats in comparison to dexamethasone and infliximab. The results were promising and demonstrated that IMOD exerts protective effects in murine model of colitis by improvement of inflammatory mediators, neutrophil infiltration, toxic stress and colonic damage (Baghaei *et al*., 2010).

Table 2: Animal studies conducted on IMOD

Results	IMOD dose and route of administration	Model	Disease	Study
Glucose~, LPO↓, MPO↓, IL-1β↓, TNF-α↓, TAP↑ AST↓, ALT↓, ALP↓,	20 mg kg^{-1} for 21 days; ip	Rat pancreas	Diabetes (induced by STZ 40 mg/kg for 5 days)	Mohseni-Salehi-Monfared*et al.*(2010)
Cholesterol↓, Triglyceride↓, Fibrosis↓, Necrosis↓	20 and 40 mg kg^{-1} for 30 days; ip	Rat liver	Acute liver injury (induced by CCL4 2 ml/kg for 30 days)	Khorram-Khorshid *et al.* (2008a)
Macroscopic and microscopic improvement LPO↓, MPO↓, IL-1β↓, TNF-α↓, TAP↑	13.3, 20 and 30 mg/kg for 14 days; ip	Rat colon	Colitis (induced by TNBS 5%)	Baghaei *et al.* (2010)
AST↓, ALT↓, ALP↓, Cholesterol↓, Triglyceride↓, LDL↓, HDL↓, VLDL↓, Total protein↓, Albumin↓ Blood sugar↓, Bilirubin↓ Atherogenic index↓	20 and 40 mg kg^{-1} 30 days; oral	Rabbit liver and plasma	Hypercholesterolemia	Azonov *et al.* (2008)
Estradiol↑, Progesterone↑ Testosterone↑, Prostaglandin↓ GPX↑, Peroxynitrite↓, TNF-α↓, LPO↓, SOD↑, CAT↑	30 mg/kg/day for 21 days; ip	Rat ovary	PCO (induced by Letrozol 1 mg/kg for 21 days)	Rezvanfar *et al.* (2011)
Post-implantation	21 mg kg^{-1} for 21 days; ip	Mouse germ cell	Dominant lethal mutation	Khorram-Khorshid *et al.* (2008b)

LPO: Lipid peroxidation; MPO: Myeloperoxidase; IL-1β: Interlukine-1β; IL-1, IL-2, IL-6: Interleukin- 1,2,6; TNF-α: Tumor necrosis factor-α; TAP: Total antioxidant power; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; ROS: Reactive oxygen spices; GPX; Glutathione peroxidase; SOD: Superoxide dismutase; CAT: Catalase; TTM: Total thiol molecule; NO: Nitric oxide; ↓: Decreased; ↑: Iucreased; ~: No change

Anti-hypercholesterolemic effect of IMOD: The study by Azonov *et al.* (2008) showed effectiveness of IMOD in reducing the risk of development of diet-induced hypercholesterolemia in rabbits. IMOD showed dose-dependent positive effects on liver and lipid metabolism and the drug was active as an anti-hyperlipidemic agent. Conclusion is that IMOD should be supplemented for detoxification and improvement of liver function.

Protective effect of IMOD in polycystic ovary syndrome: The effect of IMOD was assessed on letrozole-induced experimental PCO rats using biochemical, inflammatory and pathological markers. Administration of IMOD improved letrozole-induced PCO by inhibition of the synthesis or release of inflammatory mediators, reduction of oxidative stress and maintaining steroid status (Rezvanfar *et al.*, 2011).

Safety of IMOD in mutagenic and genotoxic tests: In the study of Khorram-Khorshid *et al.* (2008b), the mutagenic potential of IMOD was evaluated by the Ames test. Under experimental conditions which were employed, the drug was not found mutagenic or genotoxic. In the Ames test, the drug did not cause a significant increase in the number of revertant bacterial colonies as compared with negative control meaning that IMOD within the tested range did not exhibit mutagenic activity. The level of post-implantation losses and as a result the number of lethal mutation in germ cells at different stages of spermatogenesis in mice treated with IMOD was not statistically higher than that of control.

Table 3: *In vitro* studies conducted on IMOD

Study	Disease/Model	IMOD dose	Results
Larijani *et al.* (2011)	Survival of isolated Langerhans islets from rat	1, 10, 100, 1000 μl L^{-1}	Best results in dose of 1 μl L^{-1}; Insulin↑, Cell-viability↑, ROS↓
Shirazi *et al.* (2011)	Human B lymphocytes	1/5000 and 1/10000	Viability↑,TLR↓,Ig↓,IL-10↓,CD86↓

ROS: Reactive oxygen spices; TLR: Toll-like receptor; Ig: Immunoglobulin; IL-10: Interleukin 10, ↓: Decreased; ↑: Increased

***In vitro* studies:** Of publications in the initial database search, 2 *in vitro* studies on the beneficial effects of IMOD were reviewed. Information of these *in vitro* studies are summarized in Table 3. The *in vitro* effects of IMOD were investigated for its potential on different biological function of normal human B lymphocytes (Shirazi *et al.*, 2011) and of isolated rat pancreatic islets (Larijani *et al.*, 2011).

Protective effect of IMOD on isolated rat pancreatic islet: IMOD was tested for its potential on the function and level of Reactive Oxygen Species (ROS) in isolated rat pancreatic islets. IMOD showed significant anti-oxidant effects at low doses and improved viability and secretion of insulin from isolated islets in both basic and stimulation levels of glucose (Larijani *et al.*, 2011). IMOD at 1 ppm increased insulin secretion in stimulation levels of glucose and at 10, 100 and 1000 ppm decreased insulin secretion in both levels of glucose.

Immunoinhibitory effects of IMOD on human B lymphocyte: The *in vitro* effects of IMOD were investigated on different biological functions of normal human B lymphocytes. Human B lymphocytes were isolated from peripheral blood and stimulated with Toll-like receptor (TLR) 7/8 (R848) and TLR9 (CpG) agonists in presence or absence of different dilutions of IMOD. The dose-dependent inhibitory effect of IMOD on TLR-stimulated B lymphocytes implies its potential therapeutic implication in B lymphocyte-mediated autoimmune diseases and B-cell malignancies (Shirazi *et al.*, 2011).

Taken all evaluated studies in this review together, it is clear that IMOD may have more beneficial effects if tested in other diseases in which oxidative stress plays a pathophysiological role. Immune-based therapy is a new concept in the treatment of HIV-infected patients which has been developed in the past few years. Immune therapy using vaccines, cytokines and hormones is based on stimulation of immune response in HIV-1 infected individuals to control replication of virus (Hunt and Deeks, 2006). Many drugs from this class of agents are being assessed in clinical trials but none have yet been approved for use in HIV infected patients.

IMOD composes of three herbal extracts, *Rosa canina*, *Tanacetum vulgare* and *Urtica dioica*. All of these herbs have beneficial effects because of their active anti-oxidant and anti-inflammatory potentials (Babaie *et al.*, 2007; Hasani-Ranjbar *et al.*, 2008, 2009a, b; Mehri *et al.*, 2011). Selenium, another constituent of IMOD has many positive effects as an antioxidant and immunomodulator metallo-enzyme (Miroliaee *et al.*, 2011).

Oxidative stress is known responsible in pathogenesis of various diseases like hyperlipidemia (Hasani-Ranjbar *et al.*, 2010), hepatotoxicity (Hoseini *et al.*, 2006), osteoporosis (Abdollahi *et al.*, 2005; Yousefzadeh *et al.*, 2006) and exposure to xenobiotics (Abdollahi *et al.*, 2004; Mohammadirad and Abdollahi, 2011). In most of these conditions, use of antioxidants have been beneficial in ameliorating or even reversing the disease and various herbs have shown promising role against oxidative-stress-related diseases (Abu-Zaiton, 2010; Abuelgassim, 2010;

Abdelmeguid *et al.*, 2010; Oyagbemi and Odetola, 2010; Karou *et al.*, 2011). Therefore, IMOD most probably acts through induction of anti-toxic processes either directly or indirectly mainly through reducing free radicals and inhibition of inflammatory cytokines.

It is concluded that IMOD has positive effects on oxidative stress and pro-inflammatory status in various studies which most probably are due to combinational effects of herbs and the elements present in the mixture of IMOD. The immunomodulatory mechanism of IMOD are not clearly understood yet. Considering the strength, safety and immunologic effects, it could be used in treatment of many immunologic disorders.

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