



Contents lists available at ScienceDirect

# Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: [www.elsevier.com/locate/jomsmmp](http://www.elsevier.com/locate/jomsmmp)

## Review article

## Understanding molecular mechanisms in multivariant actions of levamisole as an anti-helminthic, anti-inflammatory, antioxidant, anti-neoplastic and immunomodulatory drug



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## ARTICLE INFO

## Article history:

Received 17 August 2015

Received in revised form 20 February 2016

Accepted 15 March 2016

Available online 23 April 2016

## Keywords:

Levamisole

Antioxidant

Anti-inflammatory agent

Anti-helminthic

Anti-neoplastic agent

## ABSTRACT

Levamisole is an imidothiazole derivative with a wide variety of applications in medical field. It has long been used as an anti-helminthic where its primary action is through the opening of acetyl choline receptor channels. It is widely used as an immunomodulatory drug through its action on dendritic cells and by enhancing the release of cytokines like interleukins 12 and 10. The antioxidant action of levamisole is by the enhancing effect on the major cellular redox systems like glutathione, enzymes like superoxide dismutase, catalase and also possible effects on glutathione related enzymes. On the other hand, the anti-inflammatory action is by the inhibition of TNF-alpha (tumor necrosis factor) and interleukin 6. Anti-neoplastic action of levamisole is by two ways that is, through its apoptotic action causing cell cycle inhibition and increased endothelial cell adhesion and the second action is through its anti-angiogenic property. This article enlightens upon the various mechanisms of action of levamisole at molecular level describing its diverse uses as an anti-helminthic, immunomodulatory, anti-neoplastic, anti-inflammatory and antioxidant drug.

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**Abbreviations:** IL-2, interleukin 2; AchR, acetylcholine receptor; Ca<sup>2+</sup>, calcium ions; ATP, adenosine triphosphate; IL-6, interleukin 6; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; TNF-R<sub>1</sub>, tumor necrosis factor receptor 1; TNF-R<sub>2</sub>, tumor necrosis factor receptor 2; MCP-1, monocyte chemoattractant protein-1; ROS, reactive oxygen species; GSH, glutathione; GSTs, glutathione transferases; GPx, glutathione peroxidases; GSSG, glutathione disulfide; SOD, superoxide dismutase; CAT, catalase; GSSG-R, glutathione reductase; TAC, total antioxidant capacity; DC, dendritic cell; IL-10, interleukin 10; IL-12, interleukin 12; *pRb*, retinoblastoma protein; *E2F*, group of genes required for transcription of genes; *p21*, cyclin dependent kinases inhibitor.

\* AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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**1. Introduction**

Levamisole, a more active synthetic levo-isomer of tetramisole was first used as an anti-helminthic during the 1960s [1,2]. Later, its immunostimulatory properties were reported in 1971 [3]. It has also been recognized as an effective adjuvant therapeutic agent for cancer during 1990s [2]. This imidazothiazole derivative has a thiol group and an imidazole ring. The imidazole ring with its cholinergic properties helps in interleukin 2 [IL-2] induced lymphocyte proliferation which is responsible for its immunomodulatory effect [3]. As a cholinergic anti-helminthic drug, levamisole exerts its actions by targeting the parasitic ion channels [4]. It also has an anti-carcinogenic effect by inducing apoptosis and growth arrest in endothelial cells [5]. Although the anti-helminthic action of this drug is well known, this article mainly focuses on the immunomodulatory, anti-inflammatory, anti-neoplastic and antioxidant properties of levamisole.

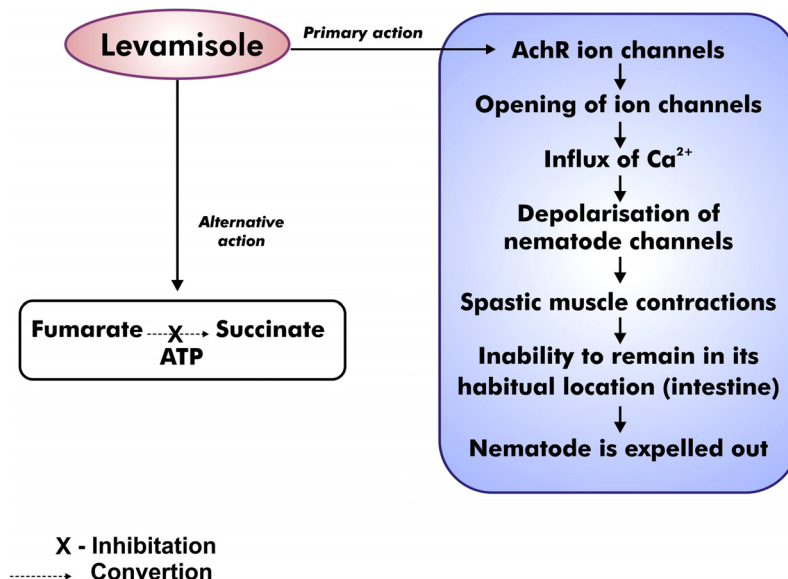
**2. Mechanism of action**

Levamisole is used in a wide array of disease entities owing to its varied actions on different cell types. In depth knowledge of the various mechanisms of actions of levamisole is important for understanding its unrecognized beneficial effects.

*2.1. Anti-helminthic action of levamisole (Fig. 1)*

Ligand gated ion channels are present in most of the animal groups including the parasitic forms and bacteria that depend upon eukaryotes for its survival [6]. Levamisole has got diverse modes of action on different groups of parasites. The primary mode of action of levamisole is on the parasitic ion channels [4]. Levamisole being a cholinergic anti-helminthic drug opens acetylcholine receptor [AChR] ion channels of nematode nerves and muscles, thereby facilitating the entry of calcium ions [Ca<sup>2+</sup>]. It also causes depolarization of nematode nerve [7]. This leads to spastic muscle contraction [8]. The net effect is that the parasite will be unable to remain in its habitual location and will be expelled out [6].

Another mode of action is by blocking the succinate dehydrogenase fumarate system. When fumarate gets reduced to succinate, adenosine triphosphate [ATP] is formed which is the main source of energy for the parasites. Levamisole blocks

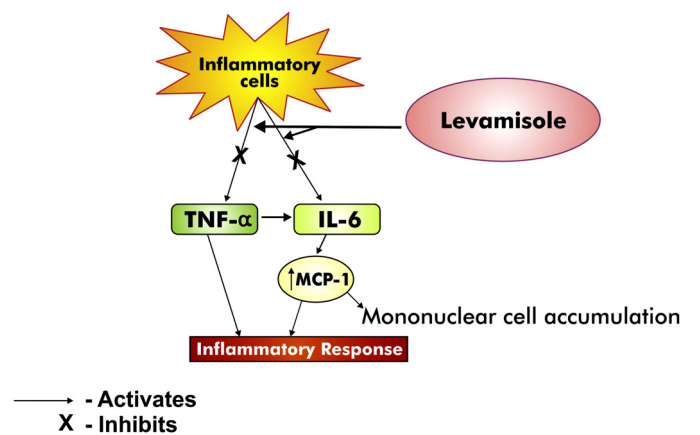


**Fig. 1.** Anti-helminthic action of levamisole.

the conversion of fumarate to succinate thereby inhibiting ATP production [3,9].

*2.2. Anti-inflammatory action of levamisole (Fig. 2)*

Serum TNF-α [tumor necrosis factor α] and interleukin 6 [IL-6] levels may be associated with severity of inflammation [10–13]. TNF-α and IL-6 levels are found to be elevated in acute and chronic inflammatory conditions (e.g., trauma, sepsis, infection, ulcerative conditions, rheumatoid arthritis, etc.) [10–14]. IL-6 is also induced by the activity of TNF-α [15,16]. When the activity of the IL-6 persists after acute inflammation, this proinflammatory cytokine turns the acute stage into a chronic inflammation. In chronic stage, IL-6 activates the mononuclear cell accumulation at the site of injury by increasing the levels of monocyte chemoattractant protein-1 [MCP-1], increasing vascularity by angioproliferation and by inhibitory effect of apoptotic function of T-cells. This in turn can lead to increased levels of IL-6 thus increasing the chronic inflammatory process [16–18].



**Fig. 2.** Anti-inflammatory action of levamisole.

Levamisole exerts its anti-inflammatory action because of its regulatory action on inflammatory cytokine TNF-α and the proinflammatory cytokine IL-6, which are critical inflammatory mediators of humoral and cellular immunity [10,11,19].

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