Journal of Cosmetics, Dermatological Sciences and Applications, 2016, 6, 24-33
Published Online March 2016 in SciRes. http://www.scirp.org/journal/jcdsa
http://dx.doi.org/10.4236/jcdsa.2016.61004

Loranthus europaeus as an Alternative Medicine in Treatment of Acute Cutaneous Lesihmaniasis: Review Article

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Received 29 November 2015; accepted 7 March 2016; published 10 March 2016

Abstract

***Loranthus europaeus* (LE) is a well-known medical plant that has been used as a folk medicine for long time ago. Recently many different researches have shown that it contains many bioactive compounds like: flavonoids, alkaloids, terpenoides, phenolic acids and others. Cutaneous Leishmaniasisis (CL) is an endemic disease in Iraq since ancient time and now it is running major outbreaks. There are many modalities of treatments but researchers are always seeking for new treatments. Most recently *Loranthus europaeus* has been tried in treatment of CL in a form of 40% ointment and gives a very encouraging result when compared with other standard treatments.**

Keywords

Cutaneous Leishmaniasisis, *Loranthus europaeus*, Alternative Medicine

1. Introduction

Cutaneous Leishmaniasisis (CL), is a parasitic disease caused by 20 Leishmania species, and it is considered a major public health issue as it currently affects 12 million people [1]. Iraq is considered as endemic country and the most common causative species are *L. major* (60%) and *L. tropica* (40%) that approved recently by PCR technique which considered as the most sensitive and specific technique [2] [3]. Iraq is suffering from an ongoing outbreak of the disease, due to floods that occurred because of heavy rains and by terrorist people that close

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How to cite this paper: Sharquie, K.E., Noaimi, A.A. and Saleh, B.A. (2016) *Loranthus europaeus* as an Alternative Medicine in Treatment of Acute Cutaneous Lesihmaniasis: Review Article. *Journal of Cosmetics, Dermatological Sciences and Applications*, **6**, 24-33. http://dx.doi.org/10.4236/jcdsa.2016.61004

the gates on the rivers that result in rise of water level and sank of many towns and villages and this leads to displaced and spread of rodents; the reservoir of leishmaniasias, and also due to continuous wars, heavy displacement of thousands of peoples from their place and living in bad conditions and poor housing led to more exposures to sand fly. Although it is a self-limiting disease however spontaneous cure may took several months or even years, and if left untreated, CL leaves permanent ugly scars and may cause disfigurement [4]. Many different treatment modalities are used for treatment; they are either systemically used including pentavalent antimonial compounds (sodium stebogluconate and meglumie antimoniate); which have been used sixth decade ago, but due to its intramuscular use, long treatment periods, a serious side effects, not always available and the emergence of antimonial-resistant [5]-[7], for these reasons antimonial drugs have been replaced by other drugs such as antifungal (azole & amphotericin B [8]-[11]), dapsone [12], and oral zinc sulfate [4]. While local treatment had been effectively used either itralesionally used like pentavalent antimony compounds [13], hypertonic saline [14], 2% zinc sulfate solution [15] and metronidazole [16], or topically applied such as paromomycin [17] and recently the encouraging result obtained with 25% podophyllin solution [18] and microwave therapy [19].

The reason for seeking an alternative medicine is increasing because the modern drugs are simply not available, expensive or due to resistance to the treatment and emergence of new species of parasite. Perhaps 80% of the world's populations rely solely upon medicinal plants as the source of remedies for treatment of the disease. Herbal remedies have been used for long period of time in both traditional and modern medicine around world, where different plants of medical value are traditionally used worldwide for treatment of leishmaniasis [20]-[22].

Many *in vitro* studies done about natural product from plants for treatment of leishmaniasis with the excellent activity against leishmania parasite, and the most common bioactive natural compounds are: Alkaloids, quinones, terpenes (monoterpens and triterpenes), saponins, flavonoids especially quercetin [23] [24] and phenolic compound including caffiec acid [25] that showed antileishmanial activity.

In this review we selected the medicinal plant *Loranthus europaeus* based on the fact that this plant was not previously used as antileishmanial agent, and because it contains many of the bioactive compound that had been extracted from many plants and investigated in many *in vitro* studies and showed a well antileishmanial activity.

1.1. *Loranthus europaeus* (LE)

***Synonoms*:** (Latin name [26]: *Loranthus europaeus Jacquin*, in Europe [27]: European yellow mistelotoe, Summer mistletoe, in Italy [28]: *Vischio* quercino, in Arabic [29]: Hib el-debgh, Habet pukour, Fulful Hawa and Balaw-Demoke in kirdish [30]).

1.2. Classification [31]

Loranthus is a genus of parasitic plants that grow on the branches of woody trees. It belongs to the family *Loranthaceae* (the showy mistletoe family) and this genus has 1253 species (**Figure 1**) [32] [33].

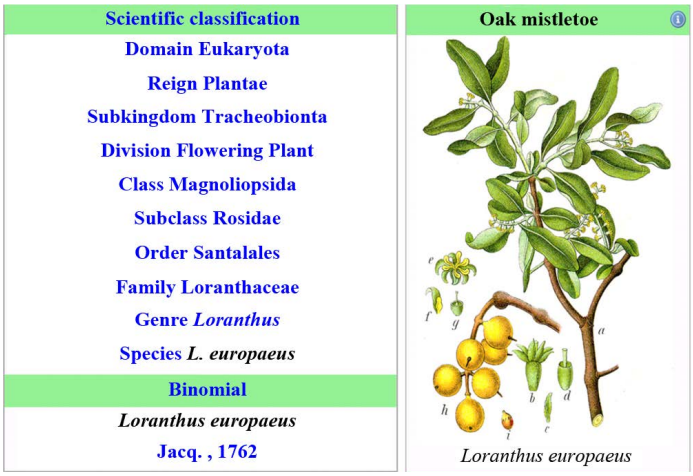


Figure 1. *Loranthus europaeus* plant and classification [31].

LE is a hemi-parasite mistletoe, it is a deciduous plant (flower are produced in May and June) with dull brown twinges, the fruit is yellow roundish berry, which remain sticky even after dried, the fruits ripen in late autumn and gradually fall off in late winter, the plant grows vigorously on aging trees mostly on branches of oak, and chestnut as host trees and once established, the mistletoe take minerals and water from the host tree, and block sunlight through its dense foliage, the most important vectors of yellow mistletoe are birds [34].

LE is widely distributed in south-west Europe, south Russia, Anatolia, Iran and Iraq [35]. In Iraq, *LE* distributed in the north of country especially in Ammadia, Roundoze and Sulymania (**Figures 2-4**) [29] [30].

1.3. *Loranthus europaeus* in the Folk Medicine

LE had a known importance in Iraqi folk medicine for long time ago, for treating boils and abscesses, where a dry fruit used in form of poultice after mastication and moisture in the mouth, it is claimed that the poultice cause maturation and acceleration in the drain of pus from the boils, however the mechanism of action was unknown, until 2006, a study from Iraq done to evaluate the anti-inflammatory effect of the plant in animals, which explained the effect of *LE* oil extract in pyogenic inflammation and concluded that the oil extract may act as immunomodulator during bacterial infection and may contain substance act as a chemotactic agent for neutrophile and promote macrophage activity [29].

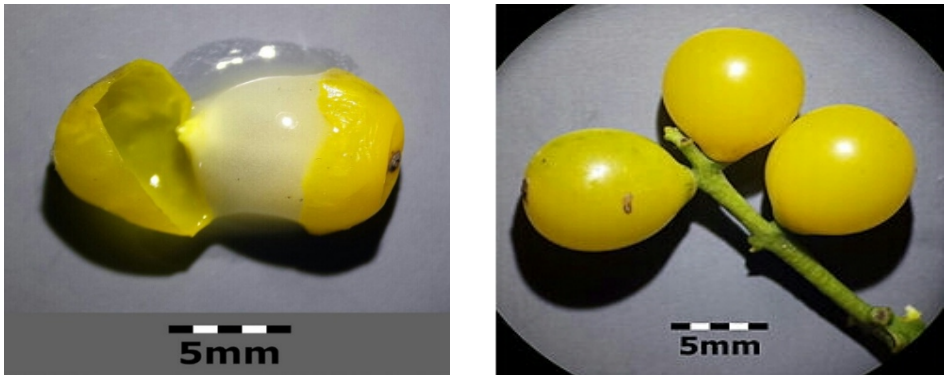
1.4. Active Constituents of *Loranthus* Genus

Loranthus species are known to produce a variety of bioactive compounds and some of them used in a variety of disease such as:

1) Sesquiterpene lactones from *L. parasiticus* used for the treatment of schizophrenia [38].

2) (+)-catechin, 3,4-dimethoxycinnamylalcohol and 3,4,5-trimethoxycinnamyl alcohol extracted from *L. globosus* for antimicrobial and antifungal properties [39].

Figure 2. *Loranthus europaeus* plant [36].



(a) (b)

Figure 3. Freshfruit of *Loranthus europaeus* [37].

Figure 4. Dry fruit of *Loranthus europaeus.*

3) Triterpenoids from *L. grewinkii* and *L. falcatus* [40] [41].

4) Kaempferol 3-*O*-*α*-D-rhamnoside, kaempferol 3,7-di-*O*-*β*-D-glucoside, quercetin 3-*O*-*α*-D-rhamnoside and quercetin 3-*O*-*β*-D-glucoside from *L. kaoi* and *L. europaeus* [42] [43].

5) A cytotoxin from *L. parasiticus* [44], and phenolics from *L. longiflorus* [45].

6) Flavonol rhmnoside from *L. tanakae* and cytoxic effects on the human tumour cell line [46].

Many of these compound have a biological activities such as antihypertensive and anti-diabetic effect of *L. bengwensis* [47] [48], and antiviral activity of *L. parasiticus* [49].

Loranthus europaeus is one species of Loranthecеae, and many studies showed that *LE* contain many biological compounds including: Flavonoids (kaempherol, quercetin [43] and rutin [50]), alkaloids [51], glycosides, carbohydrate, aldehyde, ketones, protein, polysaccharide [52], terpenes (monoterpens and triterpenes [52] [53]), phenolic acid (caffeic and gallic acid) [54], lipid include Palmitic acid, paraffin $C_{30}H_{62}$ and wax alcohol and sugar (sucrose) [55].

Many of these active ingredients had been extracted from different plants and investigated in many *in vitro* studies for antileishmanial activity, such as: Alkaloids that are able to intercalate DNA or interfere with the metabolism of aromatic amino acids in the parasite [56].

As the iron (Fe^{2+}) are essential for organism growth and replication inside macrophage, a chelator effect of the quercetin had been evaluated in interference of parasite's iron metabolism and showed leishmanicidal action [57]-[59]. Quercetin also can induce the production of reactive oxygen species (ROS), that leading to mitochondrial dysfunction and ultimately causing parasite death [60] [61].

The leishmanicidal activity of caffeic acid may attribute to the interaction of with iron and it could cause change in the structure of cytoplasmic proteins that inhibit cell division [25].

In addition to the above antileishmanial effect, the *LE* contain polysaccharide and Aldehyde that showed action in an accelerate wound healing [52], this might contribute to rapid ulcer healing of CL and decrease scar formation which is the main target in CL treatment, and also the antimicrobial effect that prevent secondary bacterial infection [30].

2. Pharmacological Effects of *Loranthus europaeus* According to *in Vitro* Studies

2.1. Antioxidant Effect

In one study revealed that the presence of monoterpene in oily extract of *LE* seeds account for antioxidative action [53]. While other study showed that the pure antioxidant including gallic acid, caffeic acid and quercetin account for this action [54].

2.2. Wound and Burn Healing Effect

The efficacy of topical oily extract of *LE* seeds was investigated in wound healing on excision wound in 18 rabbits [52]. After a preparation of ointment from plant seeds and many preliminary biochemical analysis were carried out to find the chemical contents of oily extract which found the presence of glycosides, carbohydrate, aldehyde, ketones, tritrpenoides, protein and polysaccharide, then the wound evaluated daily macroscopically to measure contraction rate, hyperemia, exudate and scab formation, while microscopically for neutrophil, macro-

phage infiltration, re-epithelzation, fibroblast proliferation with collagen production and new blood capillary formation [52].

The study showed that macrophage activated by polysaccharide which stimulates the fibroblast proliferation with subsequent of myoproliferation at periphery of the wound which has important role in wound contraction [62] [63]. The daily contraction rate of wound treated by topical ointment of *LE* was 1.8 mm/ day. The presence of polysaccharides also has a role in activate macrophage to secrete cytokines such platelet derived activating factor (PDAF), transforming growth beta factor (TGβF), interleukin (IL), fibroblast growth factor (FGF), insulin growth factor (IGF-1), epidermal growth factor (EGF), these cytokines are essential for fibroblast proliferation, angiogenesis, and chemotactic of neutrophil [64] and may explained the high infiltration of neutrophil in wound treated by *LE* oil extract particularly in early inflammatory phase. Since oxygen is required for the synthesis of collagen by fibroblast, the extract might improve angiogenesis or vascular supply and make more oxygen available to improve collagen formation for wound healing [65]. During wound healing process, epithelial cells proliferate and migrate from the edge of the wound and eventually cover the wound with new skin [66], by lysing collagen enzyme, the epithelial cells move across the wound and attach to viable tissue, the proliferation and migration of the epithelial cells is dependent on adequate supply of oxygen (O_2) [67], therefore, the increased presence of O_2 caused by *LE* oil extract. There was also a relationship between healing process and scab formation [68], the appearance of scab layer in treated wound by *LE* oil extract can behave like semi-occlusive dressing that protect the wound and promote of migration of epithelium and provide more cosmetic results. Aldehyde in addition to polysaccharide also reported to induce healing properties by increase cellular proliferation and collagen synthesis at wound edge [69].

In other study, when a hot watery and alcoholic extract of seeds of *LE* with different concentration used topically in treatment of burns in mice showed complete cure of burns [70].

2.3. Antimicrobial Effect

The effects of topical *LE* seeds oil extract had been investigated on pyogenic inflammation in excision wound created in the 24 rabbits were the wound of the animals contaminated by *staphylococcus aurous* bacteria, then the wound evaluated macroscopically which showed increase in hyperemia and exudation in the first days and then gradually disappearance, while microscopically show significant neutrophil and macrophage infiltration. During bacterial infection there was a massive production of pro-inflammatory cytokines including IL1 and IL 6 [71], which mediate for chemotactic of neutrophils [64], that responsible for eradicating of invasive bacteria and necrotic tissue from wound site [72], many authors emphasized that polysaccharide promote macrophage activity through binding to glycoprotein surface receptor [73] and these activated macrophage play a role in phagocytosis of killed bacteria and damaged tissue and stimulate the chemotaxis, proliferation of fibroblast, collagen synthesis and induce angiogenesis. On basis of this study one can concluded that the oil extract of *LE* seeds may acts as immuomoduialtors during bacterial infection and contain substance that act as chemotactic agent for neutrophil and promote macrophage activity [29].

2.4. Anti-Inflammatory Effect

The inflammatory effect of ethyl acetate and methanol extract of *LE* were evaluated in the acute inflammation in rats when the extract given intraperitoneal, preliminary phytochemical investigated revealed the presence of Flavonoids (quercetin, kaempherol and rutin) and trace of alkaloids plays a crucial role in the ability of suppression of acute inflammation [50].

2.5. Antitumor Effect

Mistletoe extract have been widely used in complementary cancer therapy in Europe [74], in a retrospective study with 700 lymphoma patients whose received mistletoe extract suggest this therapy to be beneficial [75]. In one study the effect of high concentration *LE* ethyl acetate and chloroform extract show to have cytotoxic effects on the growth of rhabdomyosarcoma (RD) and rat embryo fibroblast (REF) cell lines [51]. The phytochemical evaluation of extract show that the flavonoid are the major constituents and produced many biological activities when administrated both in pure form or within extract these include immune regulation, antioxidant, antibacterial and play important role in modulating cell proliferation in addition to alkaloids, the antitumor effect showed formation of variable adducts with DNA, proteins and other macromolecules and consequently affecting

cells divisions by affecting the time of S and/or G2 phases, while in the same study the low consecration of extract produced proliferative activity in RD and REF cells, so careful should take when using such extract in traditional medicine especially for treatment of tumors [76].

2.6. Immunomodulator Effect

When the flavonoids and terpenoides isolated from *LE* and tested on mouse spleen lymphocyte proliferation, both compounds show activation of unstimulated lymphocytes in dose dependent manner, so considered as potential immunomodulators [77].

2.7. Neuroprotective Effect

In vitro study *LE* fruits show antioxidant and neuroprotective effect in whom Ibn Sian described it in Cannon of Medicine in management of stroke [78].

2.8. Side Effects of *Loranthus europaeus*

Topical poultice of dry fruit of *LE* after mastication in mouth used in treatment of boils and abscess which cause maturation and drain of pus from it and this way used for long time ago in folk medicine in Iraq and no any topical and systemic sides effects had been mentioned in medical literatures from use it topically.

In recent years many *in vitro* studies showed sides effects from used it systemically including:

LE chloroform extract was prepared and used orally for investigation of genotoxic effects in different doses, on bone marrow and peripheral blood cells of mice. Result showed large dose of extract decrease mitotic index and increase chromosomal aberration and significantly decrease the total and different white blood cell counts when compared with lower dose [79].

In other study, gene toxicity of chloroform and ethyl acetate extract of *LE* fruits evaluated with different doses on bone marrow and spleen cells of mice in comparable with methotrexate, the extracts contain different amount of alkaloids and flavonoid, showed increasing the amount of alkaloids leads to increase clastogenicity effect while increasing in the amount of flavonoids offer anti-clastogenic effect, and the genotoxic effect after seven successive days was less toxic than methotrexate [80].

Most recently [81] we used *LE* as topical 40% ointment in the treatment of acute CL as alternative medicine through case therapeutic, comparative study and compared with topical 25% podophillyn solution [18], when thirty-five patients with 86 lesions enrolled in this study. The total number of lesions that treated were 76 lesions, 46 (60.53%) were ulcerated and 30 (39.47%) lesions were dry, while 10 dry lesions in the covered area were left untreated as a control. Lesions were divided into two groups with matching of type and size of lesions. In group one including 33 (43.42%) lesions were treated by topical 25% podophyllin solution once weekly for maximum 6 weeks, while group two consisting 43 (56.58%) lesions treated with topical 40% *Loranthus europaeus* ointment applied daily for maximum 6 weeks. The response to the treatment was assessed by using the modified Sharquie Leishmania score to assess the objective response to the topical or systemic therapy. Follow up was done every 2 weeks for 8 weeks during therapy then monthly for next 3 months. After 6 weeks the cure rate was 84.84% for lesions treated with podophyllin and 79.07% for lesions treated with *Loranthus europaeus.*

When the 2 groups compared with each other there was no statistical significant difference where the *p* value after 6 weeks was 0.648.

3. Conclusion

As *Loranthus europeaus* contains many active bioactive agents, further studies are highly recommended for assessing these active medicinal agents for treatment other skin disease as this plant is safe to be used on the skin.

Disclosure

This study was an independent study and not funded by any drug companies.

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